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CLINICAL REVIEWS

Body Mass Index and Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis

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BACKGROUND: Gastroesophageal reflux disease (GERD) is a common cause of morbidity and health-care utilization in many countries. Obesity is a potentially modifiable risk factor, but existing studies have conflicting results, possibly due to differences in study design, definitions, or populations.

METHODS: We performed a systematic review and meta-analysis of studies identified using MEDLINE, the Web of Science electronic database, manual literature review, and a review of expert bibliographies. Studies were included if they: (1) evaluated obesity, body mass index (BMI), or another measure of body size; (2) included data on reflux symptoms, esophagitis, or a GERD-related hospitalization; and (3) reported a relative risk or odds ratio (OR) with confidence intervals or provided sufficient data to permit their calculation.

RESULTS: We identified 20 studies that included 18,346 patients with GERD. Studies from the United States demonstrated an association between increasing BMI and the presence of GERD (95% confidence interval [CI] = 1.36–1.80, overweight, OR = 1.57, *P* value homogeneity = 0.51, 95% CI = 1.89–2.45, obese, OR = 2.15, *P* = 0.10). Studies from Europe provided heterogeneous results despite stratification for several factors; individual studies demonstrated both positive associations and no association.

CONCLUSIONS: This analysis demonstrates a positive association between increasing BMI and the presence of GERD within the United States; this relationship became apparent only after stratification by country and level of BMI. These results support the evaluation of weight reduction as a potential therapy for GERD. Further studies are needed to evaluate potential mechanisms and any differences in this relationship among different study populations.

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INTRODUCTION

Gastroesophageal reflux disease (GERD), the presence of symptoms or mucosal damage from gastroesophageal reflux, is a common, morbid, and costly medical condition in many countries (1). The prevalence of at least weekly heartburn or acid regurgitation ranges between 10–20% in Western countries, GERD treatments are costly (2–4), and GERD is associated with substantial morbidity, including esophageal adenocarcinoma (3, 5, 6–14). The identification of modifiable risk factors for GERD could potentially have a substantial public health impact. One potential major risk factor is obesity, the prevalence of which has increased markedly in recent decades (15).

Obesity is a postulated risk factor for GERD, although individual studies have conflicting results (16–27). Some studies suggest that an increased body mass index (BMI) is associated with increased esophageal acid exposure (28) and with an increased risk of hospitalization for esophagitis (29). In contrast, other studies, including one of the largest population-based studies to date, have found no association between BMI and GERD (30–33). Potential explanations for the disparate results include a true lack of an association between BMI and GERD, differences in definitions or methodology, dissimilar study populations, or a lack of power to detect an effect in some studies.

We evaluated the relationship between BMI and GERD using a systematic review and statistical synthesis; these methods can be valuable tools for the investigation of disease associations. Data pooling can help evaluate the influence of different study definitions, study designs, or study populations on the exposure-disease association. It can also help explore associations that individual studies may lack the power to investigate such as the influence of gender, levels of BMI, or the presence of confounding factors on disease risk. We thus performed an analysis of observational studies for the association between BMI and GERD with an emphasis on the evaluation of differences in study definitions, study design, and study populations and the creation of more standardized exposure definitions to better compare results among studies.

Methods

Search Strategy

We performed a systematic search for published manuscripts and abstracts that evaluated the association between BMI and GERD-related symptoms or complications. First, we searched MEDLINE (using PubMed, an electronic search engine for published manuscripts) for the years 1966 to June, 2005. Medical subject headings (MeSH) or keywords used for the Medline search utilized the following strategy: ([GERD] OR [gastroesophageal reflux disease] OR [esophagitis]) combined with ([body mass index] OR [BMI] OR [obesity]). Second, we searched the ISI Web of Science, an international electronic database that includes manuscripts from 8,700 journals and abstracts of meetings from several professional societies (34). Search terms for the Web of Science search were similar to those for MEDLINE. Third, we manually searched the bibliographies of retrieved articles. Fourth, we manually searched expert opinion review articles and examined bibliographies from subject experts.

Study Selection

Studies were included if they met all the following inclusion criteria: evaluated obesity (1), high BMI, or other measure of body size; included data on reflux symptoms (2), the presence of esophagitis, or a GERD-related hospitalization; and reported a relative risk or odds ratio (OR) with confidence intervals or provided sufficient data to permit their calculation (3). The inclusion criteria were not otherwise restricted by study size, publication type, or language of publication.

Data Abstraction

Data abstracted included: exposure measurement method (self-report *vs* measured BMI *vs* diagnosis of "obesity"); exposure definitions (*e.g.*, BMI definitions of overweight or obese); outcome definitions (GERD diagnosis, GERD hospitalization, GERD symptoms, or other measures of GERD such as endoscopy); total number of persons or person years in each comparison group; odds ratios or risk ratios with and without adjustment for potential confounders; potential confounders used for adjustment; study design (cohort *vs* case control); and the source of the study population. Two investigators (AK and DAC) independently abstracted the primary outcome and exposure data; discordant results were resolved by consensus. Data reporting conforms to the Meta-Analysis of Observational Studies in Epidemiology Study Group guidelines (35).

Exposure Definition

We defined body mass categories using the following BMI categories (BMI = weight [in kilograms]/height [in meters]^2): "normal" (BMI between 18.5 and 25), "overweight" (BMI between 25 and 28), and "obese" (BMI $\geq$28); these groupings represented the divisions or quartiles most frequently reported in the manuscripts and they differ somewhat from BMI categories in common use (overweight, BMI 25–29.9; obese, BMI $\geq$30) (36). We also created a category that included both overweight and obese (BMI $\geq$25). For each study, we selected the BMI classification that most closely approximated each of these categories. We included more than one estimate from some studies (*e.g.*, if a study reported an odds ratio for persons with a BMI 25–28 and an odds ratio for persons with a BMI $\geq$28, both odds ratios were included in the summary estimate for a BMI $\geq$25). Some studies provided the mean BMI and standard deviation, or the odds ratio per unit BMI, instead of explicit BMI categories (*e.g.*, a BMI category of 25–28) (20, 33). For these studies, we grouped the population into categories of BMI from the data provided; these calculations assumed that the BMI was normally distributed in the population. We then compared the risk of GERD among the BMI categories.

We utilized estimates adjusted for potential confounders whenever they were available; if no adjusted estimates were provided, unadjusted estimates were utilized or calculated from the data.

Outcome Definition

An outcome was defined as any of the following events: the presence of GERD symptoms (either clinician reported, self-reported, or measured by a questionnaire), the documentation of a GERD-related diagnosis such as esophagitis, or the development of a GERD-related hospitalization.

Statistical Analysis

All analyses used the STATA statistical package using the *meta, metainf,* and *metabias* commands (version 8, STATA Corporation, College Station, Texas). Summary OR estimates were calculated using either relative risks (for cohort studies) or odds ratios (for case-control studies). We assumed that an odds ratio was a valid approximation of the risk ratio.

Summary OR estimates were calculated based on the assumption of fixed effects and heterogeneity was tested using the Mantel-Haenszel method (37). We also evaluated for heterogeneity by comparing the results between the fixed effects model and a random effects model (37). As statistical tests for heterogeneity lack substantial power, heterogeneity was considered present if $P \leq 0.1$ (rather than $P < 0.05$) or if there was a greater than 20% difference in the summary estimates between the fixed effects and random effects models. If these tests suggested heterogeneity, we explored potential causes (see below) (37–40).

Qualitative Assessment/Assessment of Heterogeneity

The use of quality scoring in meta-analyses is controversial. Numerous criteria have been suggested for evaluating study quality; however, different scoring systems may yield substantially different results, raising concerns about validity (38, 41, 42). The adequacy of randomization and blinded allocation to study groups have been demonstrated to influence study outcome in randomized trials, but little information is available for observational studies (43–46).

Table 1. Study Characteristics

Authors	Year	Design	Location	Population Size	Case Population	Reference Population	Confounders Adjusted
Chang (62)	1997	Cross-sectional	China	N = 346 (GERD) N = 1,698 (non-GERD)	Single hospital	Hospital controls	
Diaz-Rubio (59)	2003	Cross-sectional	Spain	N = 791 (GERD) N = 1,709 (controls)	General population	General population	A, B, C, E, F, G, S, T
El-Serag (19)	2005	Cross-sectional	USA	N = 118 (GERD) N = 305 (non-GERD)	Veterans hospital employees	Veterans hospital employees	A, F, G, R, S, T
Furukawa (60)	1999	Cross-sectional	Japan	N = 977 (GERD) N = 5,033 (non-GERD)	Single hospital	Hospital controls	
Incarbone (33)	2000	Case-control	Italy	N = 138 (GERD) N = 262 (controls)	Single hospital	Hospital controls	
Kotzan (16)	2001	Cross-sectional	USA	N = 886 (GERD) N = 162,199 (non-GERD)	Medicaid population	Medicaid population	A, E, G, H, I, T
Lagergren (30)	2000	Cross-sectional	Sweden	N = 135 (GERD) N = 685 (non-GERD)	Population register	Population register	A, G. T, D, E, P
Locke (21)	1999	Cross-sectional	USA	N = 872 (GERD) N = 652 (non-GERD)	Population sample in Olmsted County, MN	Olmsted County, MN	A, G, Q, T, E, C, B, F
Mohammed (20)	2005	Cross-sectional	UK	N = 706 (GERD) N = 3,214 (non-GERD)	Population twin registry	Population twin registry	A, E, F, G, T, W, Z
Murray (22)	2003	Cross-sectional	UK	N = 654 (heartburn) N = 3,841 (non-GERD)	Multiple hospital registration	Multiple hospital registration	A, G, T, E, C, H, S, B
Nandurkar (23)	2004	Case-control	USA	N = 95 reflux N = 114 no reflux	Population sample in Olmsted county, MN	Population sample in Olmsted county, MN	A, G, O, X
Nilsson (31)	2002	Case-control	Sweden	N = 224 (GERD) N = 179 (controls)	Multiple hospital	Population register	I
Nilsson (24)	2003	Case-control	Norway	N = 3113 (GERD) N = 39,871 (controls)	General population	General population	A, T, I, Z
Ruhl (29)	1999	Cohort	USA	N = 714 (esophagitis) N = 11,630 (no esophagitis)	NHANES population*	NHANES population*	A, R, P, M, S, V
Ruigomez (17)	2004	Case-control	UK	N = 7159 (GERD) N = 10,000 (non-GERD)	General practice research database	General practice research database	A, E, G, K, T, V
Stanghellini (61)	1999	Cross-sectional	Multi-country	N = 530 (GERD) N = 5,251 (non-GERD)	General population	General population	
Talley (18)	2004	Cross-sectional	Australia	N = 101 (heartburn) N = 676 (no heartburn)	General population	General population	A, E, G, S, T
Wang (26)	2004	Cross-sectional	China	N = 430 (GERD) N = 2,101 (no GERD)	General population	General population	
Wilson (27)	1990	Case-control	USA	N = 189 (esophagitis) N = 1,024 (controls)	Single hospital	Single hospital	A, G, R, J
Wu (32)	2003	Cross-sectional	USA	N = 168 (GERD) N = 1,187 (no GERD)	General population	General population	A, G, R, Y, S

*National Health and Nutrition Evaluation Survey.
A = Age; B = aspirin or NSAID intake; C = coffee; D = meal size; E = alcohol/ethanol; F = family history; G = gender; H = *H. pylori* infection; I = asthma or asthma medication; J = hiatal hernia; K = hospital visit or hospitalization; M = marital status; O = symptom checklist-90 score; P = physical activity; Q = psychosomatic symptoms; R = race; S = socioeconomic status, education; T = tobacco; W = right handedness; V = comorbidity; X = case control status; Y = birthplace; Z = hormone replacement therapy.

Table 2. Exposure and Outcome Definitions

			Exposure (Definitions)				
Authors	Exposure (Source)	BMI Reference*	BMI Overweight	BMI Obese	BMI Overweight + Obese	Outcome (Source)	Outcome (Definitions)
Chang (62)	Measured BMI	<25	25–28	≥28	≥25	Interview	GERD symptoms
Diaz-Rubio (59)	Self-report BMI	<25	25–29.9	≥30	≥25	Self-administered GERD questionnaire	GERD symptoms
El-Serag (19)	Self-report BMI	<25	25–30	≥30	≥25	Self-administered GERD questionnaire	Frequency and severity of heartburn and acid regurgitation
Furukawa (60)	Measured BMI	<25			≥25	Endoscopy	Esophagitis
Incarbone (33)	Measured BMI	<25	25–28	≥28	≥25	GERD confirmed by 24 h pH monitoring	GERD symptoms
Kotzan (16)	Obesity diagnosis			Obesity diagnosis	Obesity diagnosis	Medicaid record	GERD diagnosis
Lagergren (30)	Self-report BMI 20 yrs prior	<25	25–30	≥30	≥25	Interview	Heartburn, regurgitation
Locke (21)	Self-report BMI	<24	27–30	≥30	≥27	Self-administered GERD questionnaire	GERD symptom score
Mohammed (20)	Self-report BMI	<25	25–28	≥28	≥25	Self-administered questionnaire	Weekly heartburn or acid regurgitation
Murray (22)	Measured BMI	<25	25–30	≥30	≥25	Self-administered questionnaire	Frequency and severity of heartburn and acid regurgitation
Nandurkar (23)	Self-report BMI	<25	25–28	≥28	≥25	Medical record & bowel disease questionnaire	Symptoms of heartburn/regurgitation
Nilsson (31)	Self-report BMI	<25		≥30	≥25	Endoscopy	Reflux esophagitis
Nilsson (24)	Measured BMI	<25	25–30	≥30	≥25	Self-administered questionnaire	Severe symptoms of reflux
Ruhl (29)	Measured BMI	<22		≥28.2	≥25	Medical record	Esophagitis hospitalization
Ruigomez (17)	Medical record	<25	25–30	≥30	≥25	General practice research database (GPRD)	Diagnosis of GERD
Stanghellini (61)	Self-report BMI	<25	25–28	≥28	≥25	Interview	GERD symptoms
Talley (18)	Self-report BMI	<25		≥30	≥25	Self-administered questionnaire	GERD symptoms ≥1/month
Wang (26)	Obesity			≥30		Interview	Heartburn and acid/food regurgitation
Wilson (27)	Measured BMI	<25		≥30	≥25	Endoscopy	Reflux esophagitis
Wu (32)	Self-report BMI	<23	25–28	≥28	≥25	Interview	Esophagitis/GERD diagnosis or symptoms

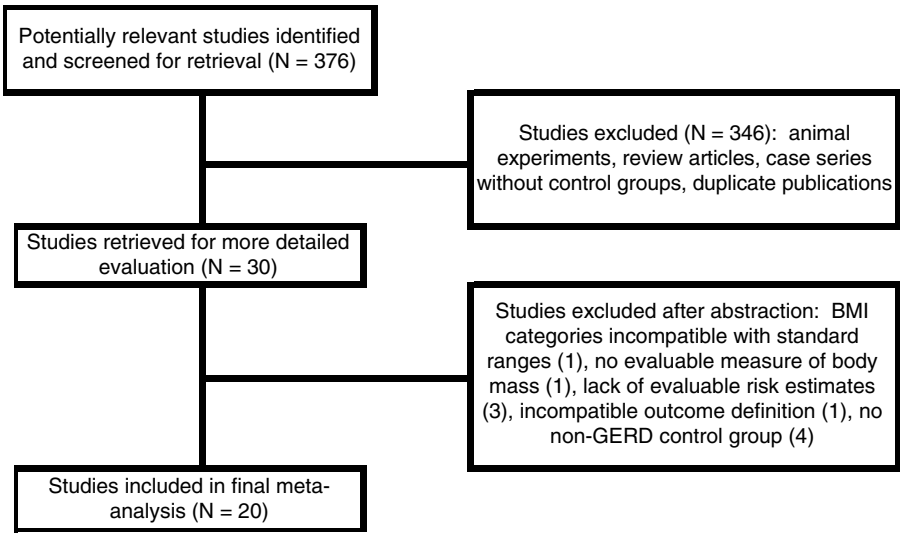

Figure 1. Flow diagram.

We assessed study quality and potential heterogeneity using several methods and evaluated the consistency of our results by performing sensitivity analyses. First, we assessed the statistical heterogeneity among trials for the primary summary estimates (see above). Second, to exclude an excessive influence of any single study, we evaluated whether exclusion of any single study substantially altered the magnitude or heterogeneity of the summary estimate, compared with the summary estimate containing all the studies. Third, because different study designs and populations may incorporate different biases or study quality, we stratified analyses by several factors (43–49).

Stratifying factors were established *a priori* (*i.e.*, prior to data analysis) and included: level of BMI (see exposure definitions), gender, study design (case-control *vs* cross-sectional), type of study population (hospital-based *vs* population-based), source of study population (country of origin), and adjustment for confounders. Studies not providing data for the stratifying factor of interest were excluded from any given analysis (*e.g.*, studies not reporting gender-specific data were excluded from summary estimates stratified by gender).

The presence of bias (including publication bias) was assessed using quantitative and qualitative methods. First, we calculated a correlation coefficient between the effect estimates and their variances (a surrogate for sample size); publication bias was considered present if $P \leq 0.1$ (50). Second, we evaluated for unusual publication patterns by qualitatively assessing funnel plots of the odds ratios *versus* their standard errors (37). Both of these methods evaluate whether there is an association between the size of the study and its final outcome. Publication bias is considered present when there is a disproportionate number of small studies with "positive" results; this suggests that smaller "negative" studies exist, but were not published (37).

RESULTS

Electronic and manual searching identified a total of 376 published manuscripts and meeting abstracts (Tables 1 and 2, Fig. 1). A manual review of the titles and abstracts provided 30 publications and one abstract that appeared to meet the initial inclusion criteria. The excluded studies consisted of review articles, animal experiments, case series that lacked appropriate comparison groups, studies that did not report on the subject of interest, or duplicate publications of the same study population. If more than one publication existed for the same population, we used the most recent or most relevant paper. These 30 studies underwent a complete data abstraction; ten additional studies were excluded after data abstraction for the following reasons: BMI categories that were incompatible with the proposed reference ranges (51), incompatible units to measure adiposity (25), lack of evaluable risk estimates within the proposed categories (52–54), incompatible outcome definition (use of several types of benign esophageal disease rather than only GERD) (55), or the lack of an appropriate comparison group (no control subjects without GERD symptoms) (4, 56–58). The remaining 20 studies, which included 18,346 patients with GERD, were included in the primary analyses (Tables 1 and 2) (16–24, 26, 27, 29–33, 59–62).

Summary Results

The summary estimates (pooling all studies) for the association between an increased BMI ($\geq$25) and GERD were heterogeneous (Table 3, Fig. 2). The presence of heterogeneity suggests that the study results differed by more than random chance; this finding implies differences in study design, population, or other factors and makes a single summary estimate less meaningful as it does not represent a true combination of similar studies. None of the individual estimates

Table 3. Meta-Analysis Results for BMI-GERD Associations, Men and Women

	BMI Category (*vs* Normal Weight)	OR (95% CI)	*P* Value for Homogeneity	Number of Studies
Overall				
Both genders	Overweight	1.49 (1.43–1.55)	<0.01	16
	Obese	2.16 (2.05–2.28)	<0.01	18
	Overweight + obese	1.66 (1.61–1.71)	<0.01	20
U.S. study only				
Both genders	Overweight	1.57 (1.36–1.80)	0.51	6
	Obese	2.15 (1.89–2.45)	0.10	7
	Overweight + obese	1.85 (1.68–2.03)	0.01	7
European study only				
Both genders	Overweight	1.49 (1.43–1.55)	<0.01	8
	Obese	2.21 (2.08–2.35)	<0.01	8
	Overweight + obese	1.69 (1.63–1.75)	<0.01	8

See Table 2 and the "Methods" section for category definitions.

demonstrated a negative association, but several demonstrated no association.

U.S. Studies

Stratification by country of origin and BMI categories provided homogeneous results for the seven studies from the United States (Table 3, Figs. 3 and 4) and demonstrated an association between BMI and GERD. The strength of the association increased with increasing BMI categories (95% confidence intervals [CI] = 1.36–1.80, overweight [OR] = 1.57, *P* value for homogeneity = 0.51; 95% CI = 1.89–2.45, obese OR = 2.15, *P* = 0.10).

European Studies

The results of studies from Europe were heterogeneous (95% CI = 1.63–1.75, overweight + obese OR = 1.69, *P* value for homogeneity <0.01) (Table 3, Fig. 2); a qualitative analysis demonstrated studies with positive associations and no association, but no study had a negative association.

Evaluation of Heterogeneity and Sensitivity Analyses

Heterogeneity was evaluated by using a statistical test for homogeneity (37). There were no substantial differences between the fixed and random effects models for any estimate. Stratification of the European studies using the following factors did not adequately resolve the heterogeneity of the main summary estimates within the strata: level of BMI (Table 3); study design (case control [95% CI = 1.72–1.89, overweight + obese OR = 1.80, *P* value for homogeneity <0.01] *vs* [cross-sectional 95% CI =1.49–1.65, overweight + obese OR = 1.57, $P < 0.01$]); or the inclusion only of studies that adjusted for potential confounders. Only three studies reported

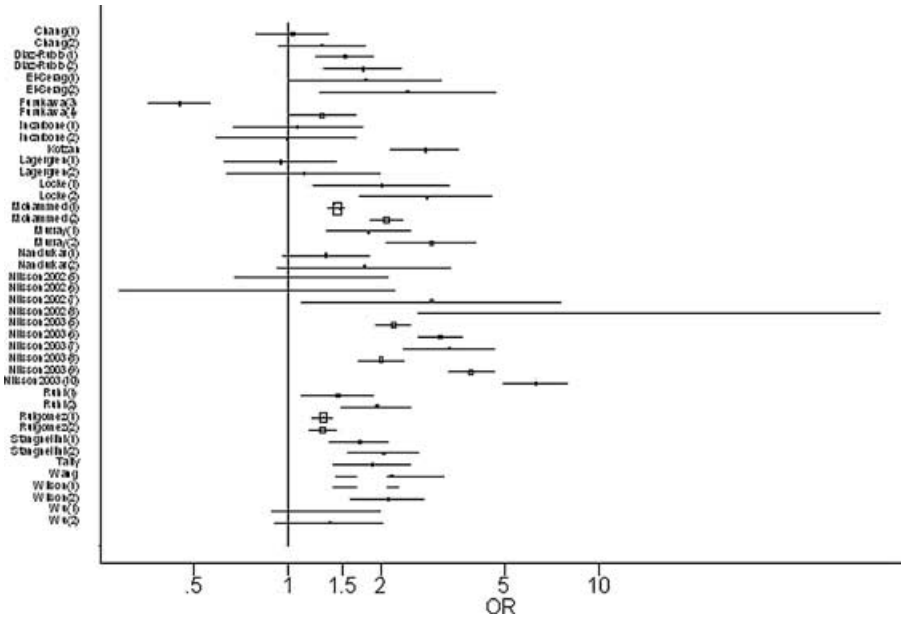

Figure 2. GERD *versus* high BMI (overweight + obese): Individual study estimates (all studies). No summary estimate is reported given heterogeneity. (1) overweight (male + female), (2) obese (male + female), (3) BMI >25 males, (4) BMI >25 females, (5) overweight males, (6) obese males, (7) overweight females, (8) obese females, (9) BMI >35 males (10) BMI >35 females.

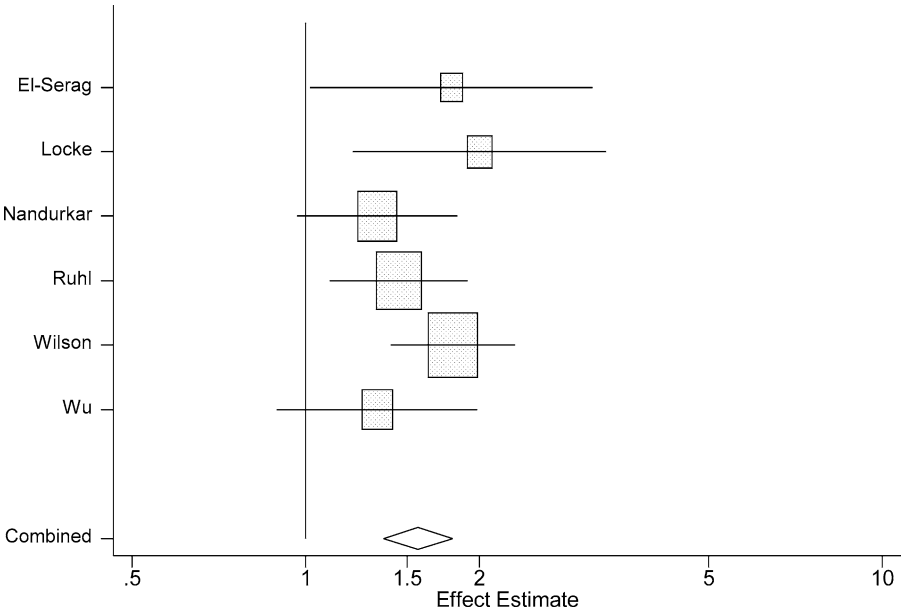

Figure 3. GERD *versus* overweight (BMI 25–28, see methods), U.S. studies, males and females. Shaded box sizes reflect the relative statistical weights each study contributed to the summary estimate.

gender-specific effect estimates (24, 31, 60); stratification by gender using these studies suggested a potentially stronger association in females (95% CI 2.57–3.14, overweight + obese OR 2.84, P value for homogeneity <0.01) than for males (95% CI 1.79–2.14, overweight + obese OR 1.95, $P < 0.01$). Although the summary estimate for all these studies combined was heterogeneous, each of these study's individual results also suggested a similar stronger association in females than in males (Fig. 2).

We also assessed the influence of the method for outcome measurement (*e.g.*, self-reported GERD symptoms using an interview or questionnaire *vs* clinical GERD diagnosis) on the BMI-GERD association (Table 2). The strength of the association for the five European studies using a self-reported GERD diagnosis (95% CI 1.84–2.00, overweight + obese OR 1.91, P value for homogeneity <0.01) was stronger than for the three European studies using a clinical GERD diagnosis (95% CI 1.22–1.38, overweight + obese OR 1.30, P value for

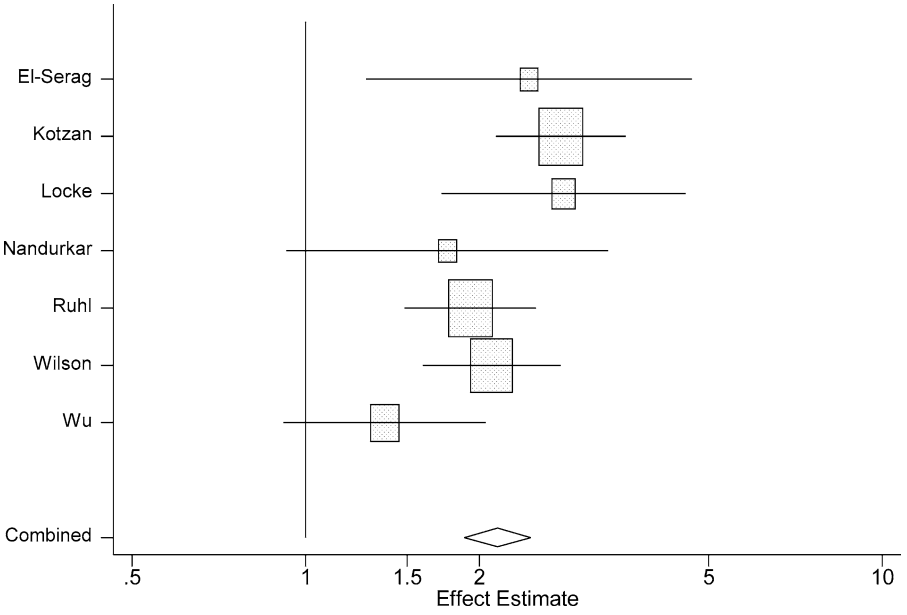

Figure 4. GERD *versus* obese (BMI >28, see methods), U.S. studies, males and females. Shaded box sizes reflect the relative statistical weights each study contributed to the summary estimate.

homogeneity <0.08); however, the results were still heterogeneous within these strata, making these estimates difficult to interpret.

Five studies were in populations outside the United States or Europe (Table 1). An evaluation of a young Australian cohort demonstrated a positive association between an increased BMI and GERD symptoms (95% CI 1.40–2.48, OR 1.87;) (18). A large population-based questionnaire survey in Xi'an, China demonstrated a similar association (95% CI 1.43–3.19, OR 2.15, (26); however, another Chinese study showed no association (62). The Japanese study reported a significant inverse association between BMI and GERD among males (60).

Lastly, we evaluated the possibility that a single, dominant study influenced the main results by systematically excluding each study and evaluating its influence on the main summary estimates for all the studies together and for the countries stratified by geographic location; no study markedly influenced the magnitude or significance of the summary estimate or the degree of heterogeneity for either the United States or the European studies.

Publication Bias

The rank correlation test did not suggest the presence of publication bias for the main summary estimates for either the U.S. ($P = 0.90$) or the European ($P = 0.96$) studies. A review of funnel plots also did not demonstrate patterns strongly suggestive of publication bias.

DISCUSSION

An evaluation of all studies did not demonstrate a consistent association between GERD and elevated BMI; however, stratification by level of BMI and country of origin suggested there is a moderate positive association between elevated BMI and GERD within studies from the United States and that the prevalence of GERD rises with increasing BMI.

These results extend the findings of existing studies by helping to identify factors responsible for the disparate results between current studies: differences based on BMI categories and the location of the study population. A recent meta-analysis of BMI and GERD complications found heterogeneous results and it was not able to identify strata with homogeneous results (63). This may have been due to their methods of stratification, the utilization of estimates with markedly different measures of BMI association (*e.g.,* risk per unit BMI not converted to other measures), the absence of several studies included in the current analysis, and the inclusion of studies that lacked a non-GERD comparison group. In contrast, in the current study, stratification by country of origin demonstrated that the U.S. studies demonstrated a homogeneous increase in GERD prevalence with increasing BMI, after the creation of more comparable categories of BMI between the studies. The overall qualitative assessment indicated there may also be a positive association between BMI and GERD within the European studies, but this is less clear: many of the individual European estimates have positive associations although several also had no association, including a large population-based study (30). It is unclear why there was a difference between the studies from the United States and those from Europe. The average BMI is higher in the United States (64), but our analysis created BMI categories that would be expected to make comparisons more similar. The residual heterogeneity for the European studies suggests that there were persistent differences in the study designs, measurements, or populations that were not captured in the abstracted data. One potential explanation is that the interpretation of the BMI may differ in different populations. The BMI calculation implies a certain relationship between height and weight such that a regression of a function of weight on height produces a similar slope across populations; however, this relationship differs between different countries, between genders, and by age, even in genetically similar populations in different locales (65, 66). In part, this may be due to differences in body composition between groups.

The biological mechanism between any potential BMI-GERD associations is unknown. Abdominal obesity has been hypothesized to cause reflux through an increase in abdominal pressure (67); however, we could not identify any published studies that clearly demonstrated an association between body fat distribution and GERD. Alternative mechanisms might include an association between body fat and metabolically active compounds (68); it is possible that such compounds might alter the lower esophageal sphincter pressure or impact esophageal clearance of refluxate, although minimal data exist.

Strengths of this analysis include the consistency of the BMI-GERD association within the U.S. population despite different patient populations and different study designs, its ability to evaluate the effect of "dose" through the examination of different BMI categories, its ability to stratify by study design, location, and source population, and its ability to assess the influence of including only estimates adjusted for potential confounders.

There are potential limitations of this analysis. First, only observational studies are available; study results may be influenced by the presence of measured or unmeasured confounding factors. BMI is associated with lifestyle in general and a high BMI may be a proxy for some other factors such as diet or physical activity. Few studies controlled for such lifestyle factors; however, analyses that stratified by adjustment for confounders suggested no substantial differences between summary estimates that included all the studies *versus* those that included only studies with adjusted estimates (data not shown). Second, the exposure definitions (obese and overweight) differed somewhat among the studies (Table 2). We addressed this by creating more comparable categories (*e.g.*, BMI <25, ≥25, ≥28), although some residual classification differences may remain. Third, the design of the cross-sectional studies and most of the case-control studies could not definitively establish which came first, the exposure

(high BMI) or the outcome (GERD). This lack of clear temporal association impedes the ability to infer causation from observational studies.

In summary, a systematic review and statistical synthesis of observational studies suggest a positive association between increasing BMI and the presence of GERD within the United States and possibly within other countries as well. The heterogeneity of study results in Europe, including studies that demonstrated no association, suggest that important differences in study populations or study design may influence the investigation of the BMI-GERD association. Considering the prevalence of both GERD and obesity, there is a paucity of studies that evaluate the influence of gender, ethnicity, or age on GERD; similarly, there are few data on potential mechanistic links between GERD and increased body mass. Further studies are needed to evaluate if the relationship between GERD and increased BMI is influenced by demographic variables and the body mass distribution.

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