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Meta-Analysis

A Systematic Review and Meta-Analysis of the Sex Ratio for Barrett's Esophagus, Erosive Reflux Disease, and Nonerosive Reflux Disease

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Barrett's esophagus is associated with reflux disease and substantially increases the risk of esophageal adenocarcinoma. The authors undertook a systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease (ERD), and nonerosive reflux disease (non-ERD) to compare these results with the sex ratio for esophageal adenocarcinoma. MEDLINE (US National Library of Medicine, Bethesda, Maryland) (1966–2004) and EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands) (1980–2004) were searched for relevant citations with a highly sensitive search strategy. Studies to be included required a sample size of 50 or more patients and consecutive recruitment at an institute accessible by all. Stata, version 8.2, software (StataCorp LP, College Station, Texas) was used to conduct random effects meta-analyses. Excess heterogeneity was investigated by meta-regression. The Barrett's esophagus meta-analysis gave an overall pooled male/female sex ratio of 1.96/1 (95% confidence interval (CI): 1.77, 2.17/1). For ERD, the pooled male/female sex ratio was 1.57/1 (95% CI: 1.40, 1.76/1) and, for non-ERD, 0.72/1 (95% CI: 0.62, 0.84/1). All of these estimates were associated with substantial heterogeneity ($I^2 = 81.1\%$, 92.7%, and 88.8%, respectively). The meta-analysis estimates for ERD and Barrett's esophagus, while showing an excess of males, are substantially lower than similar estimates for esophageal adenocarcinoma. It is important to establish why male Barrett's esophagus and ERD patients are at increased risk of malignancy compared with females.

Barrett esophagus; female; gastroesophageal reflux; male; meta-analysis; sex ratio

Abbreviations: CI, confidence interval; ERD, erosive reflux disease; non-ERD, nonerosive reflux disease.

Barrett's esophagus is a condition whereby the normal distal esophageal squamous epithelium is replaced by a columnar metaplastic epithelium characterized by the presence of mucus-secreting goblet cells. Autopsy data indicate that the prevalence of Barrett's esophagus in a normal Western population is about 0.4 percent (1). There is considerable evidence that the reflux of acid and bile from the stomach into the esophagus is a risk factor for Barrett's esophagus (2–7), and 15–20 percent of Western populations experience reflux on a weekly basis (8–10). Approximately 10 percent of gastroesophageal reflux disease sufferers will go on to develop Barrett's esophagus (11). This condition confers an approximate 0.5 percent per annum risk for esophageal adenocarcinoma (12), a disease which is increasing in incidence in White populations (13).

The three conditions that comprise the majority of the multifaceted spectrum of reflux diseases, which can be distinguished diagnostically among one another with endoscopy, are Barrett's esophagus, erosive reflux disease (ERD), and nonerosive reflux disease (non-ERD). ERD is diagnosed when visible anomalies (erosion, ulcer, perforation, and so on) of the esophagus are associated with self-reported severe reflux.

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Non-ERD is a less distinctive phenotype with no such anomalies being found upon investigation of the esophagus, yet the patient still reports symptoms typical of excessive reflux.

The male/female sex ratio of Barrett's esophagus is often reported to be approximately 2–4/1. However, the evidence is obtained from nonsystematic estimates derived from small populations often recruited at a few selected institutes (14, 15). There are some larger cohorts, for example, from Veteran Affairs hospitals (16, 17), but these studies may also not be truly representative of the general population. Thus, the aforementioned studies individually do not provide an ideal representation of the true sex ratio of Barrett's esophagus. Moreover, they do not provide insights into possible publication bias or differences that may exist between geographic locations or ethnic groups, factors which may affect the ratio. Such differences by geography or ethnic group may also provide novel clues to risk factors that play a crucial role in the etiopathogenesis of Barrett's esophagus.

In contrast to the sex ratio for esophageal adenocarcinoma, which is routinely documented, there has been no systematic consideration of the sex ratio for Barrett's esophagus or reflux disease. We undertook, therefore, a systematic review and meta-analysis of the sex ratio for Barrett's esophagus, ERD, and non-ERD to compare these results with the sex ratio for esophageal adenocarcinoma.

MATERIALS AND METHODS

Sex ratio data were collated for Barrett's esophagus, ERD, and non-ERD. Searches were conducted in the databases MEDLINE (US National Library of Medicine, Bethesda, Maryland) (1966–2004), EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands) (1980–2004), and MEDLINE In-Process (March 16, 2004) and were designed to be highly sensitive by utilizing all possible terms for the disease of interest (a copy of the search strategies is available on request). Duplicate citations were deleted using the reference management software EndNote 7 (The Thomson Corporation, London, England). Studies to be included could be of any design but were required to have a sample size of 50 or more patients, consecutive recruitment at an institute accessible by all of the general population, an age inclusion criterion of at least 18–70 years, and no evident signs of bias in the recruitment process or numbers reported, an example being the inherent selection bias in cohorts recruited from Veteran Affairs institutes that were, therefore, excluded. These selection criteria were designed to find studies that would provide a representative sex ratio of the given diseases, even if this was not a study objective at the outset. Although the search strategies were not restricted to the English language, the inclusion of studies was; thus, if an abstract in English provided all of the above required information, it was included in the meta-analysis. Barrett's esophagus was defined so as to include studies that required both the histochemical identification of specialized intestinal metaplasia and only the endoscopic identification of columnar epithelium-lined esophagus.

Selected references had their citations checked for any articles that may have been missed in the search or may not have been available in the databases utilized. Any possible duplicate data sets, where the recruitment period at the same institute overlapped, were excluded; the paper that adhered most stringently to the selection criteria or was most recent was chosen.

Certain studies met all the selection criteria but failed to report all the necessary data. The authors of these otherwise eligible papers were contacted in a request for additional omitted information.

With regard to statistical analysis, Stata, version 8.2, software (18) was used for statistical analysis. Pooled sex ratios were computed by using the random effects meta-analysis of DerSimonian and Laird with I^2 given as the chosen measure of heterogeneity, as described by Higgins et al. (19). If the I^2 statistic is 0 percent, then this indicates no observed heterogeneity, while larger values indicate increasing heterogeneity. A random effects meta-regression was subsequently used to investigate possible effect modifiers (20).

Funnel plots were produced to inspect publication bias. Forest plots were created to allow studies and their 95 percent confidence intervals to be compared within and between subgroups (from the meta-regression) and with the pooled sex ratios. A sensitivity analysis was also conducted, whereby each study was omitted in turn.

RESULTS

The searches conducted produced a total of 3,602 references after duplicates had been deleted. A total of 91 studies met the full inclusion criteria, with 32 studies providing a sex ratio for Barrett's esophagus, 28 for ERD, and 14 for non-ERD (database can be provided upon request). These numbers include replies from authors whose original publications had omitted required information from their studies. Forty-four authors of such studies were contacted, 23 replied, and 12 provided the requested data.

Funnel plots for the Barrett's esophagus and ERD data sets showed a deficit of small studies with low male/female sex ratios, while the non-ERD data set showed a normal distribution (data not shown but can be provided on request).

Barrett's esophagus

The Barrett's esophagus data set comprised 32 studies that had met the selection criteria and provided information on the male/female sex ratio of their cohort, with the lowest being 1.08/1 and the highest being 4.43/1. A random effects sex ratio meta-analysis gave a pooled male/female sex ratio of 1.96/1 (95 percent confidence interval (CI): 1.77, 2.17/1), with an I^2 of 81.1 percent. The studies within this meta-analysis are shown as a forest plot in figure 1, with accompanying details presented in table 1. A sensitivity analysis was conducted on the Barrett's esophagus data set, and no single study significantly altered the sex ratio (data not shown).

The results of univariate random effects meta-regressions are presented for variables that were thought to potentially act as effect modifiers (table 2). The variables study design (prospective vs. retrospective), study size (less than vs. greater than the median number), and year of study (mean

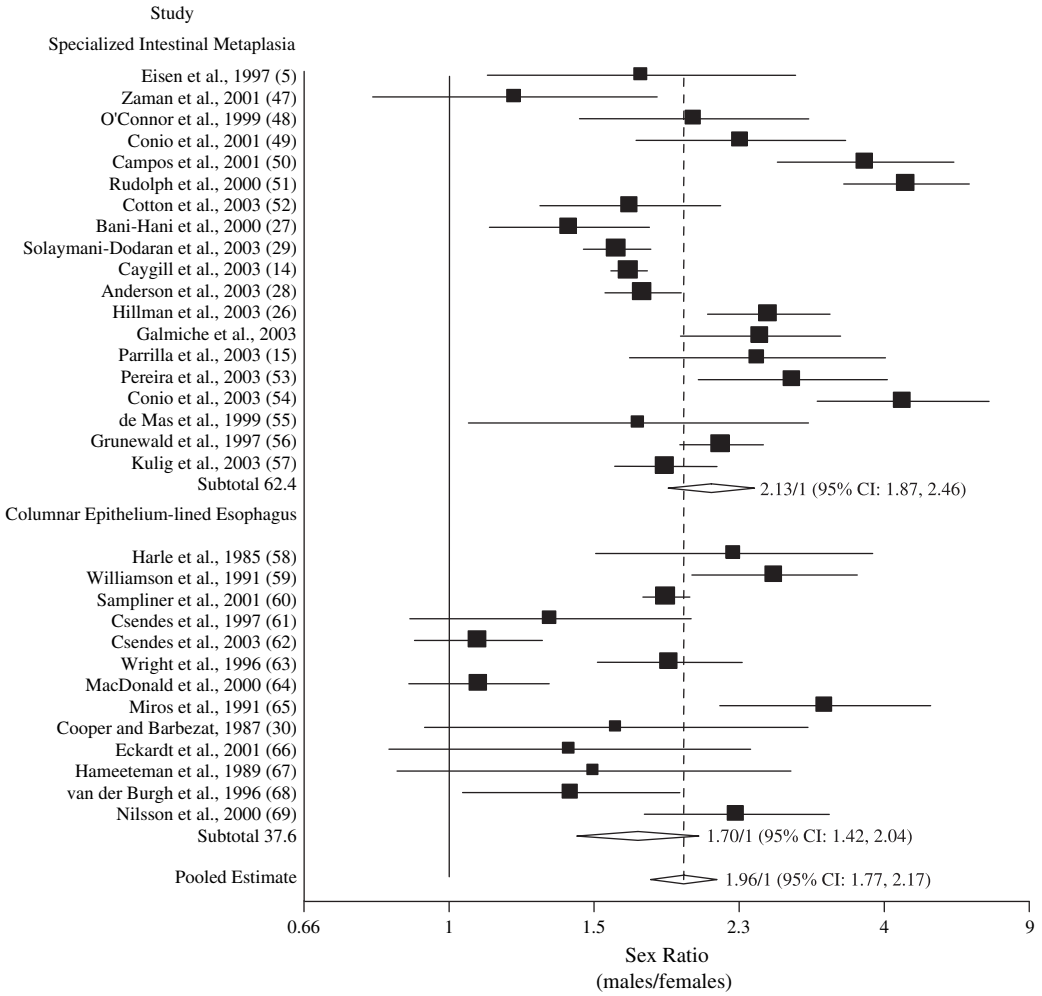

FIGURE 1. Forest plot of Barrett's esophagus random effects meta-analysis by use of a diagnostic marker as the subgrouping variable. Each study's sex ratio is represented by the corresponding black square, with the arms representing 95% confidence intervals (CIs). The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The pooled sex ratio (males/females) subtotals are designated by the unfilled diamonds that follow each subgroup; these are 2.13/1 (95% CI: 1.87, 2.46) and 1.70/1 (95% CI: 1.42, 2.04), respectively, while the last diamond with an ascending dashed line from its upper point is the total pooled sex ratio, which is 1.96/1 (95% CI: 1.77, 2.17). The following information applies to the 13th entry under "specialized intestinal metaplasia": J. P. Galmiche, Centre d'Investigation Clinique (CIC)/Institut National de la Santé et de la Recherche Médicale (INSERM), personal communication, 2003.

year of study recruitment) were found not to have a significant effect upon the heterogeneity. The dichotomous variable diagnostic marker (columnar epithelium-lined esophagus vs. specialized intestinal metaplasia), however, was found to be a statistically significant effect modifier ($p = 0.046$), although the I^2 values of 85.3 percent for the columnar epithelium-lined esophagus and 89.7 percent for the specialized intestinal metaplasia subgroups highlight the substantial additional heterogeneity remaining. A random effects meta-analysis of 19 of the 32 references that used specialized intestinal metaplasia for the diagnosis of Barrett's esophagus was undertaken. The range of male/female sex ratios for this group was from 1.20/1 to 4.43/1, while the pooled sex ratio was 2.13/1 (95 percent CI: 1.87, 2.46/1), with an I^2 value of 89.7 percent. This ratio is higher than in the pooled studies of columnar epithelium-lined esophagus (refer to the subgroups in figure 1).

The random effects meta-regression also included an analysis of geographic location (table 2). The United Kingdom was compared with all continents where three or more studies were available. All comparisons were highly statistically significant, although the I^2 values within geographic subgroups remained high (North America: $I^2 = 89.1$ percent; Europe: $I^2 = 73.5$ percent; United Kingdom: $I^2 = 71.6$ percent; and Australasia: $I^2 = 43.2$ percent). Overall male/female pooled sex ratios were highest in Australasia (2.57/1 (95 percent CI: 1.94, 3.35/1)), followed closely by North America (2.33/1 (95 percent CI: 1.77, 3.00/1)), Europe (excluding United Kingdom) (2.13/1 (95 percent CI: 1.86, 2.57/1)), and finally the United Kingdom (1.56/1 (95 percent CI: 1.44, 1.70/1)).

TABLE 1. Details of the studies included in the Barrett's esophagus random effects meta-analysis

Study (reference)	Location	No. of patients	Percentage contribution to pooled estimate
Specialized intestinal metaplasia			
Eisen et al., 1997 (5)	United States	79	2.21
Zaman et al., 2001 (47)	United States	99	2.38
O'Connor et al., 1999 (48)	United States	136	2.82
Conio et al., 2001 (49)	United States	154	2.98
Campos et al., 2001 (50)	United States	174	3.27
Rudolph et al., 2000 (51)	United States	309	3.69
Cotton et al., 2003 (52)	United Kingdom	232	3.23
Bani-Hani et al., 2000 (27)	United Kingdom	307	3.41
Solaymani-Dodaran et al., 2003 (29)*	United Kingdom	1,677	4.07
Caygill et al., 2003 (14)*	United Kingdom	5,717	4.20
Anderson et al., 2003 (28)	Northern Ireland	1,292	4.02
Hillman et al., 2003 (26)	Australia	433	3.71
Galmiche, 2003†	France	256	3.40
Parrilla et al., 2003 (15)	Spain	101	2.60
Pereira et al., 2003 (53)	Portugal	175	3.16
Conio et al., 2003 (54)	Italy	166	3.30
de Mas et al., 1999 (55)	Germany	65	2.00
Grunewald et al., 1997 (56)	Germany	1,000	3.98
Kulig et al., 2003 (57)	Germany, Austria, and Switzerland	702	3.86
Columnar epithelium-lined esophagus			
Harle et al., 1985 (58)	Canada	89	2.44
Williamson et al., 1991 (59)	United States	236	3.36
Sampliner et al., 2001 (60)	United States	3,357	4.16
Csendes et al., 1997 (61)	Chile	100	2.41
Csendes et al., 2003 (62)	Chile	492	3.67
Wright et al., 1996 (63)	United Kingdom	348	3.53
Macdonald et al., 2000 (64)	United Kingdom	409	3.57
Miros et al., 1991 (65)	Australia	133	2.97
Cooper and Barbezat, 1987 (30)	New Zealand	52	1.75
Eckardt et al., 2001 (66)	Germany	60	1.87
Hameeteman et al., 1989 (67)	Netherlands	50	1.70
van der Burgh et al., 1996 (68)	Netherlands	166	2.92
Nilsson et al., 2000 (69)	Sweden	199	3.19

* These studies cannot verify the method of diagnosis but, in this meta-analysis, were considered to represent the subgroup, specialized intestinal metaplasia; in consideration of the dates of each study and the current practice guidelines in the United Kingdom, the majority of such patients are assumed to have undergone histologic diagnosis.

† J. P. Galmiche, Centre d'Investigation Clinique (CIC)/Institut National de la Santé et de la Recherche Médicale (INSERM), personal communication, 2003.

Erosive reflux disease and nonerosive reflux disease

The ERD random effects meta-analysis comprised 28 studies giving a pooled male/female sex ratio of 1.57/1 (95 percent CI: 1.40, 1.76/1), with an I^2 of 92.7 percent. The ERD data sets are shown as a forest plot in figure 2, with accompanying details of the studies in table 3. Univariate random effects meta-regressions were also undertaken upon this data set, and these are shown in table 4. The variables study design (prospective vs. retrospective), study size (less than and greater than the mean number), and mean year of subject recruitment were all found to be nonsignificant effect modifiers. Geographic location was statistically significant in comparisons between the

TABLE 2. Meta-regression of potential effect modifier variables within the Barrett's esophagus data set

Variable for univariate meta-regression	No. of studies in meta-regression	Proportion of males for each category of the variable (95% confidence interval)*	Difference in the proportion of males	95% confidence interval	*p* value
Diagnostic marker†	32	SIM: 0.68 (0.65, 0.71)	0.05	0.000, 0.100	0.046
		CLE: 0.63 (0.59, 0.72)			
Study design‡	32		0.00	−0.046, 0.059	0.807
Study size§	32		0.03	−0.020, 0.071	0.27
Year of study¶	29#		0.00	−0.003, 0.006	0.42
Geographic location**					
United Kingdom and Northern Ireland vs. rest of Europe	18	United Kingdom and Northern Ireland: 0.61 (0.59, 0.63)	0.07	0.018, 0.059	0.00
		Rest of Europe: 0.68 (0.65, 0.72)			
United Kingdom and Northern Ireland vs. North America	16	United Kingdom and Northern Ireland: 0.61 (0.59, 0.63)	0.09	0.038, 0.145	0.001
		North America: 0.70 (0.64, 0.75)			
United Kingdom and Northern Ireland vs. Australasia	10	United Kingdom and Northern Ireland: 0.61 (0.59, 0.63)	0.11	0.055, 0.162	0.00
		Australasia: 0.72 (0.66, 0.77)			
United Kingdom and Northern Ireland vs. rest of world	32	United Kingdom and Northern Ireland: 0.61 (0.59, 0.63)	0.07	0.006, 0.030	0.004
		Rest of world: 0.68 (0.65, 0.71)			

* Provided only for regressions that were statistically significant.
† "Diagnostic marker" is specialized intestinal metaplasia (SIM) versus columnar epithelium-lined esophagus (CLE).
‡ "Study design" is prospective versus retrospective.
§ "Study size" is large versus small, defined by the median size ($n = 187$).
¶ "Year of study" is the mean year of subject recruitment.
# Unknown for three studies.
** The number of studies within each geographic category is the following: United Kingdom and Northern Ireland = 7; rest of Europe = 11; Australasia = 3; North America = 9; rest of the world = 25. (Note that the coefficient is the percentage points of difference in the *proportion* of males).

United Kingdom and North America and against South America, while against the rest of Europe the result approached significance ($p = 0.067$). Nonsignificant results were found in comparisons against Asia and the rest of the world.

The non-ERD random effects meta-analysis extracted data from 14 studies to give a pooled male/female sex ratio of 0.72/1 (95 percent CI: 0.62, 0.84/1), with an I^2 of 88.8 percent. Studies that make up the non-ERD meta-analysis are depicted as a forest plot in figure 3 and detailed in table 5.

DISCUSSION

Many Barrett's esophagus studies from the 1990s do not specify specialized intestinal metaplasia as a diagnostic criterion; often, the identification of columnar epithelium-lined esophagus alone has been enough to warrant a subject's inclusion in a study. This has been due to the evolving definition of Barrett's esophagus and the practicalities of applying the current definition to large cohorts or registers. Therefore, the Barrett's esophagus data set collated for this analysis included both studies explicit in their diagnosis through the identification of specialized intestinal metaplasia upon histochemistry, as is now the "gold standard," and studies that had diagnosed Barrett's esophagus through endoscopic visualization of columnar epithelium-lined esophagus (figure 1).

The Barrett's esophagus random effects meta-analysis gave a male/female sex ratio of 1.96/1 (95 percent CI: 1.77, 2.17/1). This data set contained substantial heterogeneity ($I^2 = 81.1$ percent), and the variability between studies was also visually apparent in the sensitivity analysis, although no single study significantly skewed the pooled sex ratio (data not shown). Univariate meta-regression analyses were undertaken for study-level variables postulated to be potential effect modifiers. Study design, study size, and year of study were not found to have a significant effect upon the heterogeneity detected. The variable of diagnostic marker was found to be statistically significant ($p = 0.046$), albeit with the caveat of residual heterogeneity's remaining within the two diagnostic subgroups (specialized intestinal metaplasia and columnar epithelium-lined esophagus).

The pooled sex ratios obtained from these meta-analyses should be considered as a systematically derived guide rather than precise estimations of what one would expect in a given population or clinical setting. For example, in figure 1, the sex ratios presented for Barrett's esophagus vary with geographic location, as might be expected if there were within-country shared practices, for example, referral and diagnostic, which may influence the resultant ratio.

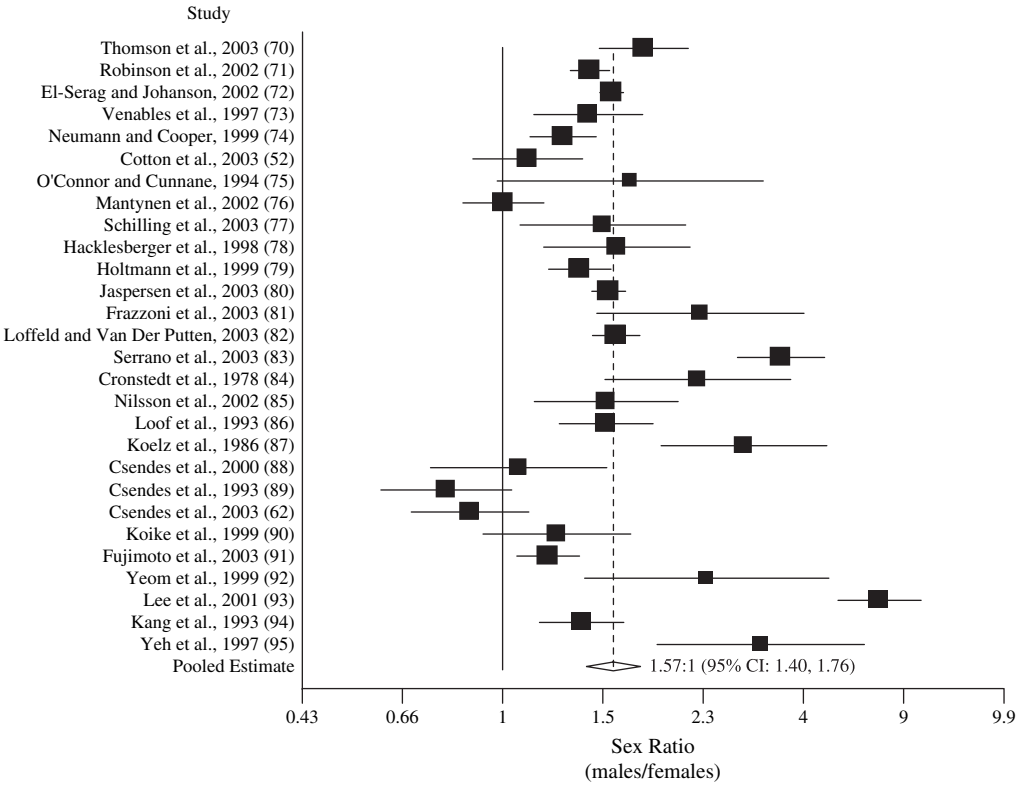

FIGURE 2. Forest plot of erosive reflux disease random effects meta-analysis. Each study's sex ratio is represented by the corresponding black square, with the arms representing 95% confidence intervals (CIs). The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The unfilled diamond with an ascending dashed line from its upper point represents the total pooled male/female sex ratio of 1.57/1 (95% CI: 1.40, 1.76).

These practices were not directly measured in the studies reviewed here, but the meta-regression analyses in table 2 and the forest plot (figure 1) suggest that such variations do exist. In comparisons between the United Kingdom and Northern Ireland and other regions, all comparisons were statistically significant, although it should be noted that Australasia included only three studies. However, even within the subgrouped regions, there was still substantial heterogeneity, with I^2 scores of 89.1, 73.5, and 71.6 percent for North America, Europe, and the United Kingdom, respectively, although this I^2 statistic was reduced within the European and United Kingdom subgroups compared with the 81.1 percent in the total Barrett's esophagus data set. While these levels of heterogeneity are high, a direct comparison with I^2 values in meta-analyses of randomized controlled trials may not be a fair assessment. The data presented here are likely to be prone to many nonquantifiable sources of variation. The levels of heterogeneity for the sex ratios should not detract from the male predominance of the pooled estimate: 25 of 32 studies report a male/female sex ratio of more than 1.5/1.

Possible explanations for the geographic variability of the Barrett's esophagus sex ratio are differences in exposure to risk factors and variable genetic susceptibility/protection across populations. This hypothesis is supported by the incidence and sex ratio of esophageal adenocarcinoma, which has been reported to vary by geographic location (table 6), inferring variable exposures to factors that differentially affect male and female risk (21–24).

The age structure of a cohort could also have an effect upon the Barrett's esophagus sex ratio. Although the age of onset of this disease is understudied, some recent evidence suggests that the rate of prevalence increase in males aged between 30 and 50 years is substantially greater than that in females (25). Furthermore, cohorts almost always present a higher mean for age at diagnosis in females compared with that in males (14, 26–30) (J. P. Galmiche, Centre d'Investigation Clinique (CIC)/Institut National de la Santé et de la Recherche Médicale (INSERM), personal communication, 2003). However, all studies selected for this meta-analysis were required to have an inclusion criterion of at least 18–70 years. Therefore, no study was confined to a specific age group. Age distribution is rarely presented or considered in studies of Barrett's esophagus cohorts, and this prevented any valid statistical analysis of age structure upon sex ratio variability.

The ERD random effects meta-analysis, of 28 studies, gave a pooled male/female sex ratio statistic of 1.57/1 (95 percent CI: 1.40, 1.76/1) and an I^2 of 92.7 percent. Again,

TABLE 3. Details of the studies included in the erosive reflux disease random effects meta-analysis

Study (reference)	Location	No. of patients	Percentage contribution to pooled estimate
Thomson et al., 2003 (70)	Canada	451	3.93
Robinson et al., 2002 (71)	United States	2,449	4.30
El-Serag and Johanson, 2002 (72)	United States	6,709	4.36
Venables et al., 1997 (73)	England	316	3.73
Neumann and Cooper, 1999 (74)	England	869	4.13
Cotton et al., 2003 (52)	Scotland	318	3.72
O'Connor and Cunnane, 1994 (75)	Ireland	51	2.12
Mantynen et al., 2002 (76)	Finland	591	4.00
Schilling et al., 2003 (77)	Germany	135	3.11
Hacklesberger et al., 1998 (78)	Germany	171	3.32
Holtmann et al., 1999 (79)	Germany	967	4.16
Jaspersen et al., 2003 (80)	Germany	3,245	4.33
Frazzoni et al., 2003 (81)	Italy	76	2.67
Loffeld and Van Der Putten, 2003 (82)	Netherlands	1,632	4.26
Serrano et al., 2003 (83)	Spain	351	3.95
Cronstedt et al., 1978 (84)	Sweden	95	2.89
Nilsson et al., 2002 (85)	Sweden	179	3.35
Loof et al., 1993 (86)	Sweden	421	3.88
Koelz et al., 1986 (87)	Switzerland	108	3.11
Csendes et al., 2000 (88)	Chile	124	2.99
Csendes et al., 1993 (89)	Chile	223	3.50
Csendes et al., 2003 (62)	Chile	278	3.64
Koike et al., 1999 (90)	Japan	175	3.31
Fujimoto et al., 2003 (91)	Japan	977	4.15
Yeom et al., 1999 (92)	Korea	54	2.31
Lee et al., 2001 (93)	Korea	242	3.98
Kang et al., 1993 (94)	Singapore	532	3.97
Yeh et al., 1997 (95)	Taiwan	66	2.67

although this heterogeneity is very high, the meta-regression of geographic location (table 4) and the distribution of data in figure 2 are consistent with similarities of practice and differences in exposures and genetic background by geographic region. It should be noted that, in the statistically significant univariate regressions of the data from the United Kingdom against those from North America and South America, each geographic category was composed of only three studies.

Evidence that ERD is a precursor to Barrett's esophagus and esophageal adenocarcinoma (31, 32) supports the male predominance for ERD, although the male/female sex ratio of 1.57/1 is still less disproportionate than that previously given for Barrett's esophagus. Why more men than women appear to proceed to Barrett's esophagus from ERD needs to be considered in the context of the debate as to whether ERD is a true precursor lesion (33, 34). The ERD category represents relatively common lesions with multifaceted causes, some of which may also be risk factors for Barrett's esophagus and some of which may not. Thus, not all ERD patients may be at risk for developing metaplasia, and this may partly explain the greater male/female sex ratio for Barrett's esophagus.

Non-ERD is currently diagnosed through utilization of endoscopy and ambulatory 24-hour pH monitoring (35) in order to avoid inclusion of subjects with hypersensitive esophagus (36, 37), functional dyspepsia (38), and other, as of yet, nonfully characterized symptomatically similar conditions (39–41). Unfortunately, ambulatory 24-hour pH monitoring had been used in very few of the studies that met the selection criteria. As such, the paucity of papers that diagnose non-ERD by use of such pH monitoring did not allow the selective criteria to be any more stringent; even with the diagnostic criteria relaxed, only 14 studies were included in the analysis. The random effects meta-analysis produced a pooled male/female sex ratio of

TABLE 4. Meta-regression of potential effect modifier variables within the erosive reflux disease data set

Variable for univariate meta-regression	No. of studies in meta-regression	Proportion of males for each category of the variable (95% confidence interval)*	Difference in the proportion of males	95% confidence interval	*p* value
Study design†	28		0.02	−0.038, 0.076	0.51
Study size‡	28		0.04	−0.014, 0.093	0.15
Year of study§	28		0.00	−0.003, 0.006	0.57
Geographic location¶					
United Kingdom and Northern Ireland vs. rest of Europe	16		0.04	−0.003, 0.075	0.067
United Kingdom and Northern Ireland vs. North America	6	United Kingdom and Northern Ireland: 0.56 (0.53, 0.59)	0.05	0.011, 0.085	0.012
		North America: 0.61 (0.58, 0.63)			
United Kingdom and Northern Ireland vs. South America	6	United Kingdom and Northern Ireland: 0.56 (0.53, 0.59)	0.09	0.014, 0.045	0.00
		South America: 0.47 (0.43, 0.51)			
United Kingdom and Northern Ireland vs. Asia	9		0.03	−0.018, 0.073	0.24

* Provided only for regressions that were statistically significant.
† "Study design" is prospective versus retrospective.
‡ "Study size" is large versus small, defined by the median size ($n = 297$).
§ "Year of study" is the mean year of subject recruitment.
¶ The number of studies within each geographic location is the following: United Kingdom and Northern Ireland = 3; rest of Europe = 13; North America = 3; South America = 3; Asia = 6. (Note that the coefficient is the percentage points of difference in the *proportion* of males).

0.72/1 (95 percent CI: 0.62, 0.84/1) and an I^2 of 88.8 percent. The high heterogeneity could not be investigated by univariate meta-regression as only 14 studies were included.

The majority of questionnaire studies report that reflux disease symptoms, when pregnancy is excluded from the analysis, are approximately equal in both sexes (8, 9, 42–45), with occasional reports of a slight, but significant, preponderance in females (10, 46). Questionnaires on symptoms obviously place undiagnosed Barrett's esophagus, ERD, and non-ERD subjects together. When considering the Barrett's esophagus and ERD proportions of individuals completing such questionnaires, one would expect, from the sex ratios presented, an excess of males. The remaining

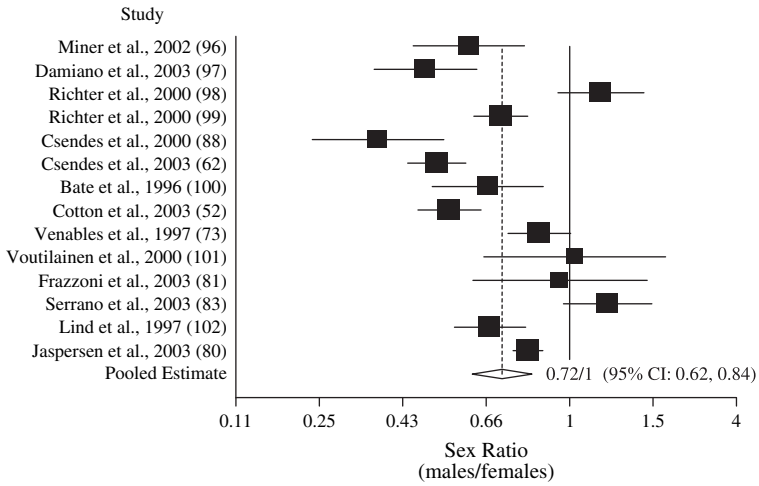

FIGURE 3. Forest plot of nonerosive reflux disease random effects meta-analysis. Each study's sex ratio is represented by the corresponding black square, with the arms representing 95% confidence intervals (CIs). The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The unfilled diamond with an ascending dashed line from its upper point represents the overall pooled male/female sex ratio of 0.72/1 (95% CI: 0.62, 0.84).

TABLE 5. Details of the studies included in the nonerosive reflux disease random effects meta-analysis

Study (reference)	Location	No. of patients	Percentage contribution to pooled estimate
Miner et al., 2002 (96)	United States	203	6.72
Damiano et al., 2003 (97)	United States	223	6.97
Richter et al., 2000 (98)	United States	359	7.43
Richter et al., 2000 (99)	United States	898	8.20
Csendes et al., 2000 (88)	Chile	122	6.15
Csendes et al., 2003 (62)	Chile	710	8.11
Bate et al., 1996 (100)	United Kingdom and Ireland	209	6.73
Cotton et al., 2003 (52)	United Kingdom	615	8.00
Venables et al., 1997 (73)	England	677	8.01
Voutilainen et al., 2000 (101)	Finland	81	4.83
Frazzoni et al., 2003 (81)	Italy	88	5.01
Garrido Serrano et al., 2003 (83)	Spain	339	7.36
Lind et al., 1997 (102)	Denmark and Sweden	509	7.81
Jaspersen et al., 2003 (80)	Germany	2,970	8.60

category of non-ERD would, therefore, be predicted to have more females, and this is confirmed in the male/female sex ratio of 0.72/1 from this meta-analysis.

The male/female sex ratio for Barrett's esophagus of 2.13/1 (95 percent CI: 1.87, 2.46/1) provides some precision to the anecdotal statement of an excess of this condition in males. The difference between Europe (including the United Kingdom) and North America is small, with ratios of 1.85/1 and 2.33/1, respectively, and this similarity contrasts with the sex ratio for esophageal adenocarcinoma. The majority of European countries have a male/female sex ratio of about 3.5/1, while the US ratio is significantly higher at 5.7/1 (table 6). Despite these differences, all countries exhibit a greater male/female sex ratio for esophageal adenocarcinoma than that described for Barrett's esophagus, and the underlying reasons for this difference may well highlight the risk factors for malignancy. In addition, while the sex ratio of esophageal adenocarcinoma is more skewed in the United States, the population incidence of this cancer in White males is highest in the United Kingdom (21). Thus, there may be a geographic variation in both the risk factors that promote carcinogenesis in both sexes and the risk factors that have a differential effect upon the sexes in terms of progression to erosive states, Barrett's esophagus, and esophageal adenocarcinoma.

TABLE 6. Comparison of Barrett's esophagus sex ratios with those for esophageal adenocarcinoma

Country	Barrett's esophagus male/female sex ratio	Esophageal adenocarcinoma male/female sex ratio
United States	2.33/1	5.75/1*
United Kingdom	1.54/1	2.08/1*,†
Denmark	2.12/1‡	3.43/1*
Iceland		3.55/1*
Finland		3.23/1*
Sweden		3.85/1*
Norway		3.93/1*
Netherlands		2.24/1*
Switzerland		3.24/1*
France		5.26/1*
Australia	2.70/1	5.00/1*

* Calculated from the study by Vizcaino et al. (23).
† Calculated from incidence values from Scotland.
‡ Calculated from European studies (excluding the United Kingdom) in the meta-analysis.

In summary, more males appear to suffer pathologic changes following reflux than do females. This meta-analysis highlights the trend of the increasing male/female sex ratio in the progression from reflux to reflux disease to Barrett's esophagus to esophageal adenocarcinoma. Why the sex ratios presented in this paper are disproportionate and why there is disparity between the sex ratios for Barrett's esophagus and esophageal adenocarcinoma are two questions emphasized by this study. The answers to these questions will aid efforts to develop targeted interventions, refined surveillance and screening strategies, and improved diagnostics, ultimately resulting in reductions in the incidence and mortality of esophageal adenocarcinoma.

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