ORIGINAL ARTICLE

Effect of Sex on Symptoms Associated With Gastroesophageal Reflux

Zhen Chen, MD; Sarah K. Thompson, MD, FRCSC, FRACS; Glyn G. Jamieson, MS, FRACS; Peter G. Devitt, MS, FRCS, FRACS; David I. Watson, MD, FRACS

Background: Previous research suggests that females have a poorer outcome than do males after surgery for gastroesophageal reflux.

Objective: To evaluate reflux and esophageal symptoms in males and females in a community sample and in patients undergoing antireflux surgery.

Design: Face-to-face interview.

Setting: A South Australian community.

Participants: Random sample of 2973 individuals from the community and 2153 patients presenting for antireflux surgery.

Main Outcome Measures: In a random sample of 2973 individuals from the community, the prevalence of reflux and other esophageal symptoms was determined and compared with symptoms in 2153 patients presenting for antireflux surgery. Identical questions were used to assess frequency and severity of heartburn and dysphagia and medication use. Analog scales assessed heartburn and dysphagia (0 indicating no symptoms and 10, severe symptoms). Outcomes for males vs females were compared across both groups.

Results: In the community, females were more likely to report heartburn, and when reported, symptom severity was higher. The prevalence of dysphagia was similar for males and females, although females reported higher dysphagia scores for solid foods. A similar proportion of males and females took antireflux medications. Females presenting for antireflux surgery were, on average, 7 years older than males, had a higher body mass index, and had higher heartburn and dysphagia symptom scores. At endoscopy, men were more likely to have ulcerative esophagitis and Barrett esophagus, and at surgery they were less likely to have a hiatal hernia.

Conclusions: Significant differences were noted between males and females in the frequency and severity of gastroesophageal reflux–associated symptoms in the community and in patients presenting for surgery. These might reflect differences in symptom perception, which explain previously reported better outcomes in men undergoing antireflux surgery.

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Author Affiliations:
Department of Surgery, Flinders University, Flinders Medical Centre, Bedford Park, South Australia, Australia (Drs Chen and Watson); and Discipline of Surgery, University of Adelaide, Adelaide, South Australia, Australia (Drs Thompson, Jamieson, and Devitt).

GASTROESOPHAGEAL REflux is common. Up to 40% of adults in the Western world experience at least monthly symptoms of reflux, and 4% to 7% report reflux at least once a day.[1-3] As a result, a substantial proportion of the population of the Western world is consuming proton pump inhibitor medications. We recently reported[4] that 10% of the adult population of the State of South Australia uses these medications either regularly or on an ad hoc basis. Concurrently, since the early 1990s, laparoscopic approaches to the surgical treatment of gastroesophageal reflux disease have also been applied more widely,[5] and good long-term surgical outcomes have been reported.[6-8]

A recent study[9] evaluated the impact of sex on long-term outcomes after laparoscopic fundoplication in a cohort of 703 patients. In this study, women were less satisfied with their overall outcome after surgery and reported more symptoms of heartburn and dysphagia at the 5-year follow-up. Furthermore, revisional surgery was undertaken more often in women. A further study by Oelschlager et al[10] also identified male sex as a predictor of better symptom resolution after antireflux surgery.

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At the population level, epidemiological studies[11-14] suggest that gastroesophageal reflux occurs in equivalent proportions of men and women, and, in general, these studies have not identified an association between sex and gastroesophageal reflux. However, the conclusions of these studies are inconsistent with postsurgical outcomes. Furthermore, sex differences for the severity of reflux symptoms and the clinical presentation of patients who present for surgical treatment have not been well explored. Hence, in this study, we evaluated differences in reflux and esophageal symptoms in males and females in the community and in patients undergoing laparoscopic antireflux surgery.

METHODS

ASSESSMENT OF REFLUX SYMPTOMS IN THE COMMUNITY

Data were collected from individuals in the South Australian community through participation in the 2006 South Australian Spring Health Omnibus Survey. This survey was conducted by Harrison Health Research (Eastwood, South Australia) on behalf of the South Australian Department of Health, and we commissioned a subset of questions within a larger questionnaire. The overall prevalence of reflux and other esophageal symptoms in this data set has been analyzed and reported elsewhere.[4] However, this data set has not been analyzed previously for sex differences.

The full details of the community survey have already been described.[4] Briefly, a population sample of 2973 individuals 15 years or older were surveyed. A random stratified sampling technique was used to identify participants, and questions were asked at a face-to-face interview. The interviewers were familiarized with the questions, and, to minimize the risk of bias, the questions were asked by all interviewers according to a standardized script. The interviewers were independent of the authors of the present article. The population sample was shown to accurately reflect the characteristics of the population of the State of South Australia.[4] Demographic data were obtained, and symptoms specific to reflux, other esophageal symptoms, and antireflux medication use were also assessed. The full questionnaire has been published elsewhere.[4] Questions addressed the frequency and severity of symptoms of heartburn and dysphagia and the frequency and type of medications consumed. These questions were similar to those used previously for the evaluation of patients undergoing antireflux surgery.[6,7,15] Identical visual analog scales were used to assess the severity of heartburn, dysphagia for liquids, and dysphagia for solid foods (0 indicates no symptoms; 10, severe symptoms).

Data were deidentified by Harrison Health Research and were provided to us as a computer file. Data were entered into a spreadsheet program (Microsoft Excel; Microsoft Corp, Redmond, Washington) and were analyzed to determine the frequency of various symptoms and responses to the questions, in particular differences between males and females. The questionnaire and the survey method were approved by the South Australian Department of Health research ethics committee.

ASSESSMENT OF REFLUX SYMPTOMS BEFORE ANTIREFLUX SURGERY

Since 1991, data for patients undergoing laparoscopic surgery for gastroesophageal reflux disease in Flinders Medical Centre, the Royal Adelaide Hospital, and associated private hospitals have been collected prospectively and entered in a computerized database (FileMaker Pro, version 8; FileMaker Inc, Santa Clara, California). This database contains records from more than 2000 patients, and this was the study group for the patient component of the study. Patients were included if the primary indication for surgery was gastroesophageal reflux, and they were excluded if they had a large hiatal hernia containing 50% or more of the stomach or if they had undergone a previous operation for gastroesophageal reflux.

Before surgery, demographic and clinical information was collected from each patient, including age, sex, body weight, and height. Body mass index (BMI) was calculated whenever feasible. The duration of preoperative symptoms was determined. Symptoms of gastroesophageal reflux were assessed using a previously reported, standardized clinical questionnaire.[16] This was applied before surgery and then yearly after surgery. Heartburn, dysphagia for liquids, and dysphagia for solid foods were assessed using visual analog scales (0 indicates none; 10, severe symptoms).

The results of various preoperative clinical investigations were also recorded. Endoscopic esophagitis was graded initially according to the Savary-Miller classification,[17] but for this study, the grading system was reduced to the following 4 groups: no ulcerative esophagitis, ulcerative esophagitis, esophageal stricture, and Barrett esophagus. For patients who underwent more than 1 endoscopy before surgery, the highest grade was used in this study. Esophageal manometry was performed using a standard water-perfused manometry system.[18] The percentage success of primary peristalsis at 10 water swallows and the resting lower esophageal sphincter (LES) pressure were analyzed in this study. Twenty-four–hour pH monitoring was performed selectively for patients who did not have endoscopic evidence of ulcerative esophagitis and for patients with atypical symptoms.

Patients underwent either a Nissen fundoplication or a partial fundoplication. The presence or absence of hiatal hernia was determined at surgery and was classified as absent, small (<2 cm long), medium (2-5 cm), and large (>5-10 cm). All these data were analyzed for differences between males and females. Data collection for this study was approved by the clinical research ethics committees of the Royal Adelaide Hospital and Flinders Medical Centre.

STATISTICAL ANALYSIS

Statistical evaluation was undertaken using a commercially available statistical software package (SPSS, version 18; SPSS Inc, Chicago, Illinois). Data are expressed as mean (range) or as number (percentage) as appropriate. χ^2, Mann-Whitney, and *t* tests were used where applicable to compare variables between the 2 groups of patients. Differences were regarded as significant at $P < .05$.

RESULTS

REFLUX SYMPTOMS IN THE COMMUNITY

A total of 5600 households were selected for the community survey; of 2973 people interviewed between September 1 and December 31, 2006, 1277 (43.0%) were male and 1696 (57.0%) were female. Participants ranged in age from 15 to 95 years (median, 49.0 years; mean, 49.4 years). Answers to questions about the frequency of heartburn and dysphagia are summarized in **Table 1** and **Table 2**. Females were more likely to never report the symptom of heartburn than were males (52.1% vs 46.8%, $P = .005$).

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The severity of heartburn and dysphagia measured by the analog scores are summarized in Table 2. Females were more likely to report a heartburn score of 4 or higher (54.0% vs 44.7%, $P = .01$), and the mean heartburn score was also higher in women. The prevalence of dysphagia for liquids and solid foods was similar for males and females (Table 1), although women also had a higher mean solid food dysphagia score.

A similar proportion of males and females were taking medications for reflux symptoms (16.2% vs 17.4%) (**Table 3**). One hundred twenty-two males (18.0%) and 177 females (21.8%) with heartburn symptoms were taking a proton pump inhibitor ($P = .07$).

Table 1. Frequency of Heartburn and Dysphagia in 2973 Individuals in the Community

	Participants, No. (%)	
	Males (n = 1277)	Females (n = 1696)
Frequency of Heartburn		
Never	598 (46.8)[a]	883 (52.1)[a]
Rarely	281 (22.0)	318 (18.8)
Once every 6 mo	52 (4.1)	56 (3.3)
Once every few months	64 (5.0)	82 (4.8)
Once a month	136 (10.6)	127 (7.5)
Few times a week	97 (7.6)	122 (7.2)
Daily	39 (3.1)	85 (5.0)
Multiple times daily	7 (0.6)	17 (1.0)
Do not know	3 (0.2)	6 (0.4)
Refused to answer	0	0
Frequency of Dysphagia		
For liquids		
Never	1204 (94.3)[b]	1567 (90.0)[c]
Rarely	43 (3.4)	62 (3.7)
Once every 6 mo	5 (0.4)	9 (0.5)
Once every few months	3 (0.2)	15 (0.9)
Once a month	7 (0.6)	24 (1.4)
Few times a week	7 (0.6)	13 (0.8)
Daily	7 (0.6)	4 (0.2)
Multiple times daily	0	2 (0.1)
Do not know	1 (0.08)	0
Refused to answer	0	0
For solid foods		
Never	1149 (89.9)[b]	1504 (88.7)[b]
Rarely	73 (5.7)	95 (5.6)
Once every 6 mo	4 (0.3)	11 (0.6)
Once every few months	11 (0.9)	15 (0.9)
Once a month	18 (1.4)	29 (1.7)
Few times a week	14 (1.1)	24 (1.4)
Daily	7 (0.6)	12 (0.7)
Multiple times daily	1 (0.08)	5 (0.3)
Do not know	0	1 (0.06)
Refused to answer	0	0

[a] $P = .005$ by χ^2 test.
[b] $P = .05$ by χ^2 test.
[c] $P = .32$ by χ^2 test.

PATIENTS UNDERGOING SURGERY FOR REFLUX

Between October 1, 1991, and May 31, 2009, 2153 patients underwent a laparoscopic fundoplication and met the inclusion criteria for this study; 1091 of these patients (50.7%) were male and 1062 (49.3%) were female. The median age of the study cohort was 51 years (age range, 15-95 years).

Table 4 summarizes differences between males and females for various preoperative variables. Females were, on average, 7 years older than males at the time of surgery, had a higher preoperative BMI, and had higher preoperative symptom scores for heartburn and dysphagia. No differences were noted between males and females for average esophageal acid exposure measured by 24-hour pH monitoring and manometrically measured esophageal peristalsis. Males had a significantly lower mean resting LES pressure than did females. At preoperative endoscopy, males were more likely to have ulcerative esophagitis and Barrett esophagus (**Table 5**). At surgery, males were less likely to have a hiatal hernia (**Table 6**). No differences were noted between males and females for the duration of preoperative reflux symptoms before their presentation for surgery.

COMMENT

Although the impact of sex on reflux and its presentation has received attention from researchers and outcomes after surgery for reflux are probably not as good in females,[9,10] differences in the way males and females perceive symptoms of reflux and in the way they present for the surgical treatment of reflux are not well understood. In this study, we showed that males and females in the community describe different levels of reflux symptoms. Females were more likely to report heartburn, and the severity of this symptom was greater in females. However, in the community, medication use for reflux was similar for both sexes, and there were no differences in the symptom of dysphagia.

We also showed that there are differences in the presentations of males and females for antireflux surgery. In particular, females presenting for surgery tend to be older, to have a higher BMI, to be more likely to have a hiatal hernia, and to report more symptoms of heartburn and dysphagia than males. In contrast, at preop-

Table 2. Analog Symptom Scores[a] for Individuals in the Community With Symptoms

	Males		Females		
Symptom	Mean (SD)	No.	Mean (SD)	No.	*P* Value (*t* Test)
Heartburn	3.86 (2.21)	664	4.18 (2.32)	799	.008
Dysphagia for liquids	3.18 (2.27)	67	3.71 (2.55)	117	.16
Dysphagia for solid foods	3.72 (2.50)	116	4.4 (2.75)	164	.03

[a] 0 indicates no symptoms; 10, severe symptoms.

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erative endoscopy, males are more likely to have ulcerative esophagitis or complicated esophagitis, and at esophageal manometry, males have a lower resting LES pressure. These findings suggest that men present for surgery with more advanced reflux disease, although this does not result in men reporting more severe symptoms.

We, and others,[9,10] showed significant differences in outcomes after laparoscopic fundoplication between males and females. In a previous study[9] of 703 patients, we demonstrated higher levels of postoperative heartburn and dysphagia and lower levels of satisfaction with the outcome of laparoscopic fundoplication in females. In addition, the rate of revisional surgery at a minimum 5-year follow-up was almost twice as high in females as in males (15.5% vs 8.4%). Oelschlager et al[10] also showed that female sex was associated with a poorer longer-term outcome after antireflux surgery.

The reasons for lower levels of reflux symptoms in males in the community and in those presenting for antireflux surgery are unclear. The tendency to present with a higher grade of endoscopic esophagitis and lower resting LES pressure actually suggests that men present with more severe reflux disease, at least from the viewpoint of these objective measures of reflux. These differences might be partly explained by males being less preoccupied with their health than females and, therefore, less likely to seek medical attention for a variety of diseases, including gastroesophageal reflux. It is widely recognized that males tend to ignore symptoms of illness and are more reluctant to engage in preventive health measures than are females. Males are probably more tolerant of adverse effects after surgery for reflux, and this might explain why a previous study[9] showed that males are more "satisfied" with surgical outcomes. On the other hand, females probably take more interest in their health and might be more likely to report symptoms that many males might not worry about. These dynamics could explain some of the differences observed in the present study. Supporting this contention are other studies[19-21] that have shown that sex is a confounding factor for clinical outcomes after orthopedic and cardiac surgery. For example, Rosseland and Stubhaug[19] demonstrated higher pain scores in women undergoing arthroscopic surgery. Similarly, Holbrook et al[20] demonstrated poorer functional and psychological outcomes in women after major trauma compared with men, and Vaccarino et al[21] demonstrated poorer early outcomes in women undergoing coronary artery bypass surgery, independent of all identifiable confounding factors.

Furthermore, we previously reported[22] the outcome for 24 pH studies in 76 patients who described postfundoplication reflux symptoms and identified that not all heartburn symptoms after surgery are due to reflux. Although this particular study did not identify a statistically significant difference between male and female patients, there was a trend toward women being more likely to report symptoms that were not associated with objective evidence of reflux. Thirty-six percent of men (12 of 33) vs 19% of women (8 of 43) had abnormal postoperative pH study results, which supported a diagnosis of recurrent reflux.

It is also conceivable that there are other factors that could contribute to differences between males and females. el-Serag and Sonnenberg[23] previously showed that men have higher levels of gastric acid production, and this might contribute to reflux-induced esophageal mucosal damage. However, in the present study, the extent of esophageal acid exposure in the patient group measured by 24-hour pH monitoring was similar for both sexes. Other factors that could contribute to the sex differences are known risk factors for reflux, such as central obesity, smoking, and alcohol consumption in men.[24] These might contribute to worse outcomes in objective tests for reflux but do not explain the apparently more severe symptoms in women. Banki et al[25] also demonstrated that compared with males, females with reflux

Table 3. Frequency of Medication Use for Reflux in Individuals in the Community[a]

Frequency of Medication Use	Participants, No. (%)	
	Males (n = 1276)	Females (n = 1690)
Regularly	111 (8.7)	170 (10.1)
Several times each week	21 (1.6)	25 (1.5)
Less than once a week	27 (2.1)	29 (1.7)
Occasionally	48 (3.8)	70 (4.1)
Not using medication	1069 (83.7)	1396 (82.3)

[a] $P = .45$ by χ^2 test. Due to missing data, the values do not total to the size of the subsample.

Table 4. Preoperative Variables, Scores,[a] and Outcomes From Objective Tests in Patients Undergoing Antireflux Surgery

Variable	Males		Females		*P* Value (*t* Test)
	Mean (SD)	No.	Mean (SD)	No.	
Age, y	48.0 (14.8)	1091	55.4 (14.8)	1062	<.001
BMI	28.3 (4.5)	363	30.0 (6.3)	311	<.001
Heartburn score (0-10)	7.1 (3.4)	896	7.5 (3.4)	903	.01
Dysphagia score for liquids (0-10)	1.3 (2.7)	896	2.2 (3.4)	903	<.001
Dysphagia score for solid foods (0-10)	2.0 (3.1)	896	3.4 (3.8)	903	<.001
Time pH <4 over 24 h, %	12.0 (10.0)	448	11.5 (9.5)	511	.43
Successful primary peristalsis, %	85.0 (25.7)	850	82.0 (26.6)	791	.08
Resting LES pressure, mm Hg	8.9 (8.6)	831	10.8 (9.4)	735	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LES, lower esophageal sphincter.
[a] 0 indicates no symptoms; 10, severe symptoms.

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Table 5. Endoscopy Findings of Esophagitis in Patients Undergoing Antireflux Surgery[a]

Endoscopy Finding	Participants, No. (%) Males (n = 908)	Females (n = 824)
No esophagitis	267 (29.4)	357 (43.3)
Ulcerative esophagitis	448 (49.3)	377 (45.8)
Stricture	26 (2.9)	14 (1.7)
Barrett esophagus	167 (18.4)	76 (9.2)

[a] $P < .001$ by χ^2 test.

Table 6. Length of Hiatal Hernia at Laparoscopic Surgery[a]

Hernia Length, cm	Participants, No. (%) Males (n = 1091)	Females (n = 1062)
<2	231 (21.2)	208 (19.6)
2-5	128 (11.7)	175 (16.5)
>5-10	184 (16.9)	271 (25.5)
No hernia	548 (50.2)	408 (38.4)

[a] $P < .001$ by χ^2 test.

symptoms were less likely to have an abnormal 24-hour pH test result, reduced resting LES pressure, or a hiatus hernia. Some of these outcomes were consistent with the results of the present study. A further factor that might contribute to the higher level of symptoms in women was the higher prevalence of hiatal hernia in women. Note, however, that to minimize the risk of confounding the symptom scores with mechanical symptoms from very large hiatal hernias, we deliberately excluded patients with very large hernias.

Another significant difference between males and females in the present study was BMI. Other studies[26,27] have shown that obesity is strongly related to the frequency of heartburn and acid regurgitation. Obese individuals are almost 3 times more likely to report heartburn than are normal-weight individuals.[26,27] A recent population study[27] from Scandinavia suggests that BMI is an independent risk factor for gastroesophageal reflux symptoms but only in healthy female adults. Similarly, another Scandinavian study[28] demonstrated a strong dose-dependent association between body mass and reflux esophagitis in women but no association in men. This association might be due to increased estrogen activity in overweight and obese females, as it is known that elevated levels of estrogen and progesterone increase gastroesophageal reflux.[29-31] Support for this hypothesis includes the observation that LES pressures decrease during pregnancy.[29] A weakness of BMI data used in this context, however, is that the distribution of adipose tissue differs between males and females, with males tending to have greater amounts of visceral fat, even at lower BMIs. Arguably, a better measure of obesity would be waist circumference. However, such data were not available for this study.

It is uncertain that all symptoms that might be attributed to reflux in the community are actually due to reflux, although the preoperative symptoms in the patients scheduled for antireflux surgery reflect a large group of patients undergoing surgical treatment for objectively proved gastroesophageal reflux disease. We showed significant differences between males and females in their presentations for antireflux surgery and in the frequency and severity of symptoms in the community. It is true that some of the variables that are highly significantly different (eg, heartburn: 7.5 vs 7.1, $P = .01$) do not impress as having much biological significance. However, other differences, such as the presence of Barrett esophagus, look altogether impressively different. Is it possible that females interpret their symptoms as being more severe than do males, particularly because males present with more severe grades of esophagitis and lower resting LES pressures? Differences in symptom perception could contribute to previously reported differences in outcomes after antireflux surgery, with males, on average, being more likely to have a better postsurgical outcome. For now, however, differences between the sexes should not preclude females from antireflux surgery. Instead, this information could help during the process of obtaining informed consent; when explaining surgery to females, the expectations for a good outcome might need to be a bit less optimistic than for males.

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Correspondence: David I. Watson, MD, FRACS, Department of Surgery, Flinders University, Room 3D211, Flinders Medical Centre, Bedford Park, South Australia 5042, Australia (david.watson@flinders.edu.au).
Author Contributions: *Study concept and design:* Chen and Watson. *Acquisition of data:* Chen, Jamieson, Devitt, and Watson. *Analysis and interpretation of data:* Chen, Thompson, Jamieson, Devitt, and Watson. *Drafting of the manuscript:* Chen, Thompson, and Watson. *Critical revision of the manuscript for important intellectual content:* Thompson, Jamieson, Devitt, and Watson. *Administrative, technical, and material support:* Watson. *Study supervision:* Thompson, Jamieson, Devitt, and Watson.
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