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Prevalence of Gastroesophageal Reflux Disease and Proton Pump Inhibitor-Refractory Symptoms

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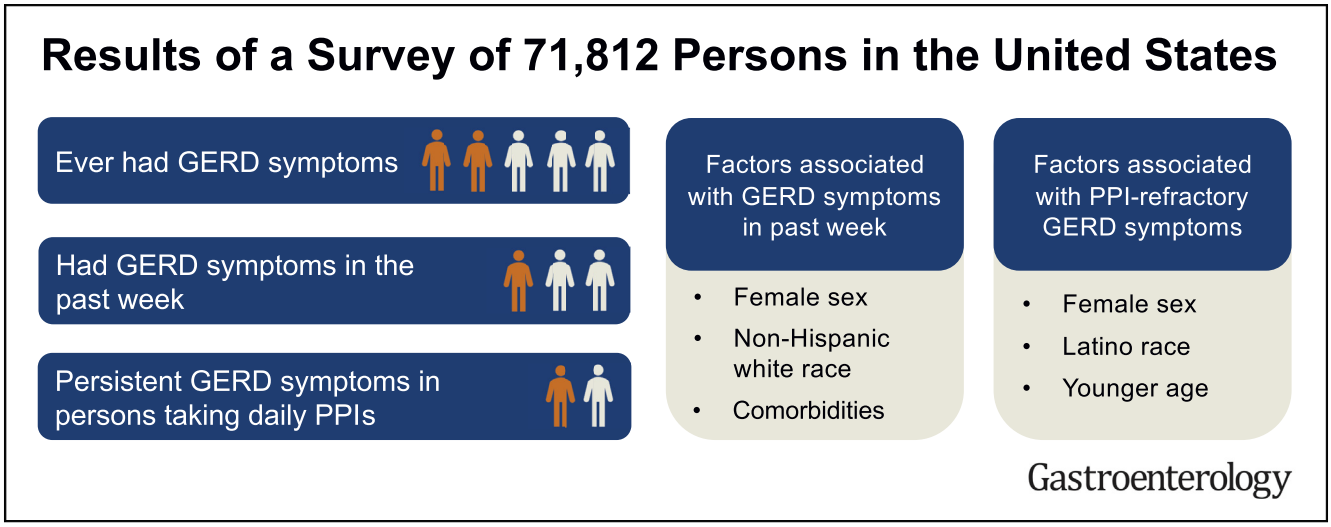

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BACKGROUND & AIMS: There are few data on the prevalence of gastroesophageal reflux disease (GERD) in the United States. We performed a population-based study to determine the prevalence of GERD symptoms and persistent GERD symptoms despite use of proton pump inhibitors (PPIs). **METHODS:** We conducted the National Gastrointestinal Survey in 2015 using MyGiHealth, an app that guides participants through National Institutes of Health gastrointestinal Patient-Reported Outcomes Measurement Information System surveys. Primary outcomes were prevalence of GERD symptoms in the past and persistence of GERD symptoms (heartburn or regurgitation 2 or more days in past week) among participants taking PPIs. Population weights were applied to the data and multivariable regression was used to adjust for confounding. **RESULTS:** Among 71,812 participants, 32,878 (44.1%) reported having had GERD symptoms in the past and 23,039 (30.9%) reported having GERD symptoms in the past week. We also found that 35.1% of those who had experienced GERD symptoms were currently on therapy (55.2% on PPIs, 24.3% on histamine-2 receptor blockers, and 24.4% on antacids). Among 3229 participants taking daily PPIs, 54.1% had persistent GERD symptoms. Younger individuals, women, Latino individuals, and participants with irritable bowel syndrome or Crohn's disease were more likely to have continued symptoms, even when taking PPIs. **CONCLUSIONS:** Using a population-based survey, we found GERD symptoms to be common: 2 of 5 participants have had GERD symptoms in the past and 1 of 3 had symptoms in the past week. We also found that half of PPI users have persistent symptoms. Given the significant effect of GERD on quality of life, further research and development of new therapies are needed for patients with PPI-refractory GERD symptoms.

Keywords: Heartburn; Regurgitation; Esophagus; North America.

***Authors share co-first authorship.**

Abbreviations used in this paper: **AEGIS, Automated Evaluation of Gastrointestinal Symptoms; CI, confidence interval; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBS, irritable bowel syndrome; NIH, National Institutes of Health; OR, odds ratio; PPI, proton pump inhibitor; PROMIS, Patient-Reported Outcomes Measurement Information System; PW, population-weighted.**

Most current article

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Gastroesophageal reflux disease (GERD) involves classic symptoms of heartburn and/or regurgitation.[1] It is a highly prevalent disease with significant economic impact and reduction in patient health-related quality of life.[2–5] Although there are a number of available effective prescription and over-the-counter therapies, 45% of patients on a proton pump inhibitor (PPI) experience persistent GERD symptoms despite treatment.[6]

Previous estimates of the prevalence of weekly GERD symptoms in the United States range from 18% to 28%.[7] These estimates, however, are based largely on 2 populations: residents of Olmstead County, Minnesota, and employees of the Houston Veterans Affairs Medical Center.[7] Neither group is representative of the current US demographics, as Olmstead County is 90% white[7] and the Houston Veterans Affairs employee population is 43% African American.[8] Another US population-based study of 21,128 adults found that 22% and 16% of Americans experienced heartburn and regurgitation within the past month, respectively.[9] Of note, although this study was conducted nationally, the cohort was 82% non-Hispanic white; data from the US Census Bureau's American Community Survey in 2017 shows that 61% of the population is non-Hispanic white.[10] As GERD prevalence varies with race/ethnicity, these prior studies may provide inaccurate estimates of the current prevalence of GERD symptoms in the United States.[11]

Given the significant impact of heartburn and regurgitation on health-related quality of life and health care utilization, along with the evolving demographics of the United States, it is important to understand the current burden and distribution of GERD symptoms in the US population. Moreover, the high prevalence of persistent GERD symptoms despite PPI therapy (referred to as "PPI-refractory GERD symptoms" in this article) also highlights the need for a better understanding of the predictors of the disease and response to therapies as we aim to reduce its overall burden and maximize benefits from future adjunctive, novel therapies. Therefore, the aims of this study were to determine the prevalence and predictors of GERD and PPI-refractory GERD symptoms in a large, representative sample of community-dwelling Americans.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

There are few data on the prevalence of gastroesophageal reflux disease (GERD) symptoms in the United States.

NEW FINDINGS

A population-based survey found GERD symptoms to be common: 44.1% of participants reported having had GERD symptoms in the past and 30.9% reported having GERD symptoms in the last week. Half of users of proton pump inhibitors have persistent symptoms.

LIMITATIONS

These findings are based on a survey completed by patients; results could be subject to bias.

IMPACT

Given the significant effects of GERD on quality of life, further research and development of new therapies are needed for patients with proton pump inhibitor-refractory GERD symptoms.

Materials and Methods

Study Design, Data Source, and Study Population

In October 2015, our group conducted the "National Gastrointestinal (GI) Survey," a population-based audit of GI symptoms in more than 71,000 community-dwelling Americans.[12–15] The survey was administered via *MyGiHealth*, a mobile app that uses AEGIS (Automated Evaluation of GI Symptoms), an automated algorithm that has previously been described in detail.[16] AEGIS asked users to "Select any symptom(s) you experienced in the past week" and "Please check any of these GI symptom(s) that you have EVER experienced." Answer options included the following 8 symptoms as well as a "none of these" option: heartburn, acid reflux, or gastroesophageal reflux; abdominal pain; bloating/gas; constipation; diarrhea; disrupted swallowing; fecal incontinence; nausea and vomiting. We chose these symptoms based on the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) framework.[17–19] For each reported GI symptom, AEGIS guided respondents through corresponding GI PROMIS questionnaires to measure severity[20]; the GERD PROMIS item bank and other questions related to "heartburn, acid reflux, or gastroesophageal reflux" are presented in the Supplementary Material. Participants also were presented questions regarding demographics, socioeconomic status, and medical comorbidities.

We aimed to recruit a representative sample of Americans for the National GI Survey by enacting quotas for age, sex, and region of country (Northeast, South, Midwest, and West). We partnered with Cint, a survey research firm that uses a reward system to incentivize respondents to participate in surveys. Potential respondents were sent an e-mail through Cint research panels inviting them to complete an online survey. Along with the link to the survey, the e-mail also included the following templated text, which was subject to editing from individual research panels: "Based on the information stored in your [research panel] profile, we believe we have a survey that you will qualify and earn from. The survey takes approximately 15 minutes and if you successfully complete it, your account will be credited with [incentive]." Cint's reward symptom is based on the length of the interview and requires certain thresholds to be met before panelists can redeem rewards. This structure is meant to encourage long-term participation and discourage professional respondents who seek to take surveys only for financial gain.

Participant recruitment for the National GI Survey occurred from October 14, 2015, to November 4, 2015. Survey initiations were distributed by Cint until we reached our sample size goal of approximately 70,000 respondents, allowing us to create a dataset with robust explanatory power and for examining the prevalence and predictors of both common as well as less

common GI symptoms. Users who clicked the survey link in the invitation were brought to a home page asking them to complete a "GI Survey"; no specific mentions of GERD were made on the initial screen. All individuals ≥18 years of age were included in the study.

Outcomes

Our primary outcome was prevalence of having had GERD symptoms (heartburn, acid reflux, or gastroesophageal reflux) in the past, categorized by having ever experienced GERD symptoms, GERD symptoms within the past 7 days, and troublesome GERD symptoms as determined by a modified Montreal definition (heartburn or regurgitation occurring ≥2 days in the past week).[1] To determine whether respondents met the Montreal definition, we leveraged 2 items from PROMIS (Supplementary Material): heartburn: In the past 7 days, how often did you feel burning in the red area shown in the picture (behind the breastbone)?; regurgitation: In the past 7 days, how often did you have regurgitation—that is, food or liquid coming back into your throat or mouth without vomiting? Answer options for both questions included never, 1 day, 2 to 6 days, once a day, or more than once a day. Of note, although the Global Consensus Group states that in population-based studies troublesome GERD symptoms can be determined by the presence of mild symptoms on ≥2 days a week or moderate/severe symptoms occurring ≥1 day a week, our survey only assessed for the former, hence our use of a modified Montreal definition. As a secondary outcome, we assessed for GERD symptom severity as determined by PROMIS in those who reported GERD in the past week.[13,19,20] Another secondary outcome was prevalence of PPI-refractory GERD symptoms, defined as heartburn or regurgitation for ≥2 days in the past week among those currently taking a daily PPI.

Covariates

We also examined participants' medication use, demographics, and past medical history. Respondents were asked which medicines they were currently taking for their GERD symptoms and frequency of use (Supplementary Material): PPI (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole); histamine-2 receptor blocker (cimetidine, famotidine, ranitidine); antacids (eg, Tums, Rolaids, Mylanta, Maalox); other medicine. Demographic information elicited via the survey included age, gender, race/ethnicity, education, marital status, employment status, and income level. Participants also were asked to identify comorbid conditions that had been "diagnosed by a doctor and can affect the GI system," including irritable bowel syndrome (IBS), chronic idiopathic constipation, cancer of the GI tract, celiac disease, cirrhosis, Crohn's disease, ulcerative colitis, diabetes, endometriosis, gallstones, human immunodeficiency virus/acquired immunodeficiency syndrome, pancreatitis, peptic ulcer disease, and thyroid disease.

Statistical Analysis

All statistical analyses were performed in Stata 13.1 (StataCorp LP, College Station, TX). We used data from the 2010 US Census (age, sex) and 2015 US Census Bureau's American Community Survey (race/ethnicity) to create population weights and applied them to the sample data to produce population estimates[10,21]; the actual weights used in the analyses were previously described elsewhere.[13,14] This was done to adjust for over- and undersampling of subgroups in the National GI Survey, thereby decreasing bias due to nonresponse and underrepresented groups in the population.

A 2-tailed *P* value of less than .05 was considered statistically significant. We performed population-weighted (PW) multivariable regression models to adjust for potentially confounding factors and to calculate adjusted *P* values, odds ratios (ORs), and 95% confidence intervals (CIs). These regression models were performed on our primary and secondary outcomes, adjusted by relevant demographic, socioeconomic, medication, and comorbidity variables described previously. We used logistic and linear multivariable regression models for binary and continuous outcomes, respectively. This study was approved by the Cedars-Sinai Institutional Review Board (Pro54744).

Results

Study Cohort

In all, 1.3 million individuals were invited to complete the National GI Survey with the opportunity to participate in the study up until at least 70,000 surveys were completed. Ultimately, 124,674 (9.4%) individuals accessed the survey, of whom 71,812 (57.6%) completed the questionnaires and were included in the study. Table 1 lists the demographic information of the study cohort.

GERD Symptoms Within the Past 7 Days Among Overall Cohort

Among 71,812 participants, we found that 32,878 (PW 44.1%) had ever experienced GERD symptoms in the past and 23,039 (PW 30.9%) reported being symptomatic in the past week. Table 2 summarizes the predictors of having had GERD symptoms in the past week. When compared with individuals aged 18 to 29 years, those 30 to 59 years of age had increased odds for reporting recent esophageal symptoms; no significant difference was seen for the ≥60-year-old group. Women and those who identified as non-Hispanic white were more likely to have had recent GERD symptoms. Increasing levels of education as well as nonsingle marital status were associated with significantly higher odds for having experienced GERD symptoms in the past week. Individuals with income levels from $50,001 to $100,000 were more likely to report recent GERD symptoms as compared with those with income levels ≤$50,000; conversely, those making ≥$200,001 were less likely to have such symptoms. Moreover, those with specific comorbidities, including IBS, Crohn's disease, diabetes, endometriosis, gallstones, peptic ulcer disease, and thyroid disease were also more likely to experience GERD symptoms within the past 7 days.

Troublesome GERD Symptoms (Modified Montreal Definition) Among Overall Cohort

We found that 13,881 (PW 18.0%) out of 71,812 individuals met the modified Montreal definition for troublesome GERD symptoms (heartburn or regurgitation for

Table 1. National GI Survey Participant Demographics (N = 71,812)

Variable	n	Actual %	PW %[a]
Age, *y*			
18–29	23,962	33.4	26.5
30–39	19,284	26.9	20.8
40–49	11,854	16.5	15.5
50–59	10,808	15.1	15.6
≥60	5904	8.2	21.5
Gender			
Female	42,696	59.5	51.0
Male	29,116	40.5	49.0
Race/ethnicity			
Non-Hispanic white	50,943	70.9	62.0
Non-Hispanic black	6353	8.9	12.0
Latino	8255	11.5	18.0
Asian	3914	5.5	6.0
Other	2347	3.3	2.0
Education level			
Did not graduate high school	2862	4.0	4.2
High school graduate	15,295	21.3	21.5
Some college	22,282	31.0	30.9
College graduate	24,020	33.4	32.7
Graduate degree	7353	10.2	10.7
Marital status			
Single	19,120	26.6	24.5
Divorced, separated, or widowed	8592	12.0	16.1
Married or in long-term relationship	44,100	61.4	59.4
Employment status			
Unemployed[b]	24,680	34.4	40.3
Employed or full-time student	47,132	65.6	59.7
Total household income			
$0–50,000	35,725	49.7	50.0
$50,001–100,000	22,226	31.0	30.7
$100,001–200,000	7582	10.6	10.3
≥$200,001	1110	1.5	1.7
Prefer not to say	5169	7.2	7.4
Irritable bowel syndrome	2958	4.1	3.8
Chronic idiopathic constipation	276	0.4	0.4
Gastrointestinal cancer	407	0.6	0.8
Celiac disease	755	1.1	0.9
Cirrhosis	450	0.6	0.7
Crohn's disease	553	0.8	0.8
Ulcerative colitis	627	0.9	1.1
Diabetes	4508	6.3	8.6
Endometriosis	1680	2.3	2.0
Gallstones	3058	4.3	4.5
HIV/AIDS	233	0.3	0.4
Pancreatitis	539	0.8	0.8
Peptic ulcer disease	1172	1.6	1.7
Thyroid disease	3483	4.9	5.2

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a]PWs based on recent US Census data for age, sex, and race/ethnicity were applied to the sample data to produce population estimates; the actual weights used in the analyses were previously described elsewhere.[13,14]
[b]Includes those who reported being unemployed, on disability, on leave of absence from work, retired, or homemaker.

≥2 days in the past week): heartburn only, 6751 (PW 47.5%); both heartburn and regurgitation, 5426 (PW 39.8%); regurgitation only, 1704 (PW 12.6%). Table 2 presents findings from the regression on having Montreal-defined GERD symptoms. Similar to the regression on GERD symptoms in the past 7 days, female gender, nonsingle marital status, and total household income level from $50,001 to $100,000 were associated with increased odds for having Montreal-defined GERD symptoms. However, unlike the prior analysis, only those 30 to 49 years of age had increased odds for troublesome GERD symptoms vs those who were 18 to 29 years old; no difference was seen for the 50- to 59-year-old group. Moreover, we also found that participants who were ≥60 years of age had decreased odds for Montreal-defined GERD symptoms when compared with those 18 to 29 years old. As for race/ethnicity, non-Hispanic blacks and Asians remained at lower odds for having bothersome symptoms vs non-Hispanic whites, whereas no differences were seen for the Latino and other racial/ethnic groups. Education level, although predictive of GERD symptoms in the past week, was largely not associated with Montreal-defined GERD. With respect to specific comorbidities, those that were predictive of GERD in the past week remained positively associated with Montreal-defined GERD symptoms, with cirrhosis being a new addition.

GERD Symptom Severity Among Those Who Were Symptomatic in the Past 7 Days

We show findings from the regression on GERD PROMIS percentile scores among individuals who were symptomatic in the past week in Table 3. Latino and Asian individuals had significantly higher GERD PROMIS scores vs non-Hispanic whites. Those who were nonsingle and had IBS, celiac disease, cirrhosis, Crohn's disease, diabetes, endometriosis, and thyroid disease also had more severe symptoms. Moreover, individuals who reported current PPI, histamine-2 receptor blocker, and antacid use also had worse symptoms. Conversely, increasing age, male gender, and higher education levels were associated with significantly lower GERD PROMIS scores.

GERD Medication Use

Among the 32,878 individuals who reported ever experiencing presumptive GERD, we had data on medication use from 29,274 respondents. Among the 29,274, we found that 9234 individuals (PW 35.1%) were currently taking a medicine to manage their symptoms. Those on therapy reported taking the following: PPI, 4935 (PW 55.2%); histamine-2 receptor blocker, 2286 (PW 24.3%); antacids, 2370 (PW 24.4%); other, 217 (PW 2.6%). Table 4 lists the frequency of use of each medicine class. Most of those on a PPI reported taking it daily (PW 68.1%), whereas more intermittent use was noted among those using histamine-2 receptor blockers and antacids.

Persistent GERD Symptoms While on a Daily PPI

Among those taking a daily PPI (n = 3229), 1858 (PW 54.1%) noted persistent, troublesome GERD symptoms (heartburn or regurgitation for ≥2 days in the past week). Symptomatic individuals reported the following symptoms even while on a PPI: both heartburn and regurgitation, 877

Table 2. Predictors of GERD Symptoms in Past 7 Days and GERD as Determined by a Modified Montreal Definition (N = 71,812)

Variable	Had GERD symptoms in past 7 days (n = 23,039)	OR [95% CI][a]	Had GERD symptoms using modified Montreal definition (n = 13,881)[b]	OR [95% CI][a]
Age, *y*				
18–29	6215 (25.2)	reference	3875 (15.6)	reference
30–39	6660 (33.7)	1.34 [1.28–1.40]	4284 (21.7)	1.33 [1.25–1.40]
40–49	4364 (35.3)	1.40 [1.32–1.49]	2657 (21.4)	1.26 [1.17–1.34]
50–59	3945 (35.3)	1.33 [1.25–1.42]	2180 (19.2)	1.03 [0.95–1.10]
≥60	1855 (28.9)	0.98 [0.86–1.11]	885 (13.9)	0.68 [0.57–0.81]
Gender				
Female	14,575 (33.0)	reference	8979 (19.8)	reference
Male	8464 (28.7)	0.88 [0.83–0.93]	4902 (16.0)	0.84 [0.79–0.90]
Race/ethnicity				
Non-Hispanic white	17,708 (33.8)	reference	10,614 (19.4)	reference
Non-Hispanic black	1413 (22.6)	0.62 [0.57–0.69]	860 (13.0)	0.68 [0.61–0.76]
Latino	2425 (30.8)	0.89 [0.79–1.00]	1569 (19.5)	1.02 [0.89–1.16]
Asian	805 (19.2)	0.53 [0.46–0.60]	411 (9.1)	0.48 [0.41–0.56]
Other	688 (28.2)	0.81 [0.72–0.92]	427 (17.5)	0.94 [0.81–1.10]
Education level				
Did not graduate high school	692 (21.1)	reference	487 (14.6)	reference
High school graduate	4906 (31.0)	1.43 [1.24–1.64]	3078 (18.8)	1.16 [1.00–1.35]
Some college	7526 (33.0)	1.52 [1.32–1.74]	4652 (19.2)	1.15 [1.00–1.33]
College graduate	7779 (30.9)	1.33 [1.16–1.53]	4491 (17.5)	0.99 [0.85–1.15]
Graduate degree	2136 (28.5)	1.20 [1.03–1.41]	1173 (15.6)	0.90 [0.74–1.09]
Marital status				
Single	4619 (23.5)	reference	2665 (13.3)	reference
Divorced, separated, or widowed	2957 (32.2)	1.27 [1.14–1.42]	1828 (18.3)	1.39 [1.23–1.57]
Married or in long-term relationship	15,463 (33.6)	1.35 [1.28–1.43]	9388 (19.8)	1.43 [1.34–1.52]
Employment status				
Unemployed[c]	8390 (31.1)	reference	5165 (17.6)	reference
Employed or full-time student	14,649 (30.8)	1.00 [0.94–1.07]	8716 (18.2)	1.02 [0.94–1.11]
Total household income				
$0–50,000	11,535 (30.4)	reference	7155 (18.2)	reference
$50,001–100,000	7775 (34.5)	1.12 [1.05–1.19]	4661 (20.2)	1.10 [1.02–1.18]
$100,001–200,000	2498 (32.4)	1.01 [0.93–1.10]	1400 (18.1)	0.95 [0.86–1.05]
≥$200,001	276 (25.3)	0.81 [0.66–0.99]	162 (14.1)	0.80 [0.64–0.99]
Prefer not to say	955 (18.6)	0.57 [0.49–0.68]	503 (8.0)	0.43 [0.38–0.50]
Irritable bowel syndrome	1590 (54.7)	2.19 [1.85–2.59]	1103 (36.3)	2.11 [1.76–2.54]
Chronic idiopathic constipation	135 (44.4)	1.24 [0.78–1.99]	110 (35.0)	1.66 [0.99–2.79]
Gastrointestinal cancer	123 (28.9)	0.85 [0.43–1.67]	91 (22.2)	1.17 [0.49–2.78]
Celiac disease	268 (33.8)	1.00 [0.82–1.22]	190 (24.2)	1.11 [0.89–1.39]
Cirrhosis	169 (37.4)	1.22 [0.89–1.69]	132 (29.4)	1.60 [1.11–2.31]
Crohn's disease	232 (42.2)	1.34 [1.05–1.70]	183 (32.6)	1.69 [1.31–2.18]
Ulcerative colitis	257 (43.4)	1.50 [0.89–2.52]	176 (26.3)	1.34 [0.76–2.36]
Diabetes	1806 (35.3)	1.16 [1.04–1.30]	1139 (20.0)	1.14 [1.01–1.29]
Endometriosis	808 (44.6)	1.21 [1.05–1.39]	561 (30.5)	1.31 [1.13–1.51]
Gallstones	1536 (48.4)	1.63 [1.40–1.90]	1031 (31.1)	1.63 [1.37–1.94]
HIV/AIDS	67 (28.5)	0.83 [0.45–1.52]	45 (17.8)	0.77 [0.32–1.81]
Pancreatitis	270 (44.7)	1.20 [0.94–1.53]	194 (30.6)	1.28 [1.00–1.64]
Peptic ulcer disease	743 (57.0)	2.33 [1.76–3.07]	530 (38.1)	2.23 [1.79–2.77]
Thyroid disease	1,500 (40.6)	1.25 [1.10–1.42]	974 (25.0)	1.31 [1.14–1.49]

NOTE. Data are presented as n (PW %).
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a]The logistic regression model included all variables listed in the table above.
[b]Defined as heartburn or regurgitation occurring ≥2 days in the past week.
[c]Includes those who reported being unemployed, on disability, on leave of absence from work, retired, or homemaker.

(PW 48.0%); heartburn only, 792 (PW 42.3%); regurgitation only, 189 (PW 9.7%).

Table 5 presents predictors of PPI-refractory GERD symptoms. Individuals who were younger, female, Latino, divorced, separated, widowed, or married, and had IBS and Crohn's disease had higher odds for remaining symptomatic while on a PPI. Conversely, those with GI cancer and ulcerative colitis were less likely to have PPI-refractory

symptoms. No significant associations were largely seen between persistent symptoms and concomitant use of histamine-2 receptor blockers and antacids.

Discussion

In this population-based survey, we found that GERD symptoms are very common in the community. More than 2 of 5 Americans have experienced heartburn or regurgitation in the past, whereas nearly 1 of 3 experienced these symptoms in the past week. In addition, among those managing their symptoms with a daily PPI, we found that more than half still have persistent, troublesome GERD symptoms.

Our prevalence of presumptive GERD is largely in line with prior estimates from other US cross-sectional and population-based studies. Namely, the prevalence of weekly GERD symptoms from past studies conducted in the 1990s and early 2000s ranged from 18% to 28% with a sample size-weighted mean of 20%,[7] whereas we found that 31% of respondents in our study reported GERD symptoms in the past week. Although it is difficult to make direct comparisons in the prevalence rates given the varying definitions of GERD and different populations,[7] our data suggest that the prevalence of GERD symptoms may be increasing.[22] This increasing burden is likely related in large part to the obesity epidemic. At the time of the National GI Survey in 2015, approximately 40% of Americans were obese (as compared with 30% in 1999),[23,24] and obesity has been shown to increase the odds of GERD up to 3-fold.[25–27] This is problematic, as GERD leads to decrements in quality of life, mental health, and social function.[2–4] It is also associated with significant health care utilization, as GERD is the second leading physician diagnosis among the GI disorders, with more than 5.5 million office and emergency room visits in 2014.[5]

Aside from examining the prevalence of GERD symptoms in the past week, we also determined how many individuals in the community have such symptoms as determined by a modified Montreal definition[1]; this allows for a more precise, criterion-definition of GERD. Here, we found that 18% of individuals reported either heartburn or regurgitation at least 2 days of the week, which the Global Consensus Group considers troublesome. The prevalence of GERD symptoms using the modified Montreal definition is much higher in our study than a previous US population study, which found that 6% and 3% of respondents experienced heartburn and regurgitation, respectively, at least twice per week.[9] To our knowledge, the only other studies that used the Montreal definition examined non-US populations, with prevalence rates of 3% and 16% in China[28] and Japan,[29] respectively. These rates are lower than that noted in our study, and the true difference is likely even more pronounced, as we used a modified Montreal definition that did not include moderate-to-severe symptoms of heartburn or regurgitation occurring $\geq$1 day a week; our study was only able to assess for those who had either symptom to any degree on $\geq$2 days a week.

In our study, we found a number of predictors of GERD symptoms. For instance, men were less likely to have had both GERD symptoms in the past week and Montreal-defined GERD when compared with women. Prior data in the literature has been equivocal on this point, as some studies indicate a higher prevalence of GERD in men, others in women, and others demonstrate no difference at all.[30–32] Similarly, although some studies have demonstrated an association of GERD with increasing age, other studies have not.[30] In our present study, we found that increasing age is associated with increased odds for GERD symptoms up to a point, after which the risk decreases. Namely, when compared to 18- to 29-year-olds, those 30 to 49 years of age have a higher prevalence of troublesome, Montreal-defined GERD symptoms, whereas those aged $\geq$60 years have a lower prevalence. As for race/ethnicity, there are also mixed findings. One study showed that black individuals may experience more heartburn and Asian individuals less heartburn as compared with white individuals,[33] whereas another study demonstrated no difference in GERD prevalence among black and white individuals.[8] Although our study confirmed that Asian individuals have a lower prevalence of GERD symptoms, our finding that GERD is also less common among non-Hispanic black vs non-Hispanic white individuals is counter to prior findings.[8,33] Further research examining the etiologies behind disparities in GERD symptoms with age, gender, and race/ethnicity are needed.

Prior studies have demonstrated a higher prevalence of GERD among those with IBS[34–36] and diabetes,[37–39] which was confirmed with our study. We also found that those with IBS and diabetes have more severe GERD symptoms as measured by NIH PROMIS vs those without the disorders. Moreover, we noted a higher prevalence of GERD symptoms among those with other comorbidities, most of which have not been previously reported or rigorously studied: Crohn's disease, endometriosis, and thyroid disease. Individuals with these diagnoses also have higher GERD PROMIS scores.

Aside from determining the prevalence and predictors of GERD symptoms, we also systematically assessed medication use. For those managing their condition with daily PPIs, we noted that 54% still have persistent GERD symptoms, which is comparable to previous observational estimates in primary care and community-based settings (45%, range 30% to 60%).[6] With respect to independent predictors of PPI-refractory GERD symptoms, we found that Latino individuals are 2.44-times more likely to have persistent symptoms while on PPIs when compared with non-Hispanic white individuals. The reason behind this finding is unclear, but may be secondary to physiologic or even cultural etiologies. Women[6] and those with IBS[40] have been previously noted to be more likely to have PPI-refractory GERD, which our study confirmed. Associations have also been found between PPI-refractory symptoms and stress,[41] anxiety, somatization, and functional GI disorders.[42,43] The increased prevalence of functional and psychosomatic disorders among women may account in part for their increased odds of persistent GERD symptoms while on PPIs, as seen in our study.[43] With regard to age, a Japanese study found that older age was more associated with PPI-resistance,[44] which is contrary to our findings. The higher prevalence of PPI-refractory GERD symptoms among younger individuals in our population may again be explained by the higher

Table 3. Predictors of GERD Severity Among Those Symptomatic in the Past Week (n = 19,435)

Variable	GERD PROMIS percentile score (0–100)[a]	β coefficient[b]	*P* value[b]
Age, *y*			
18–29	56.7 [55.9–57.5]	reference	reference
30–39	55.6 [54.8–56.3]	−2.52	<.001
40–49	53.7 [52.7–54.7]	−5.96	<.001
50–59	48.6 [47.5–49.7]	−11.94	<.001
≥60	44.7 [41.6–47.7]	−16.14	<.001
Gender			
Female	52.9 [51.9–53.8]	reference	reference
Male	50.6 [49.4–51.7]	−1.70	.01
Race/ethnicity			
Non-Hispanic white	50.2 [49.7–50.8]	reference	reference
Non-Hispanic black	50.1 [47.5–52.8]	−0.25	.85
Latino	58.7 [55.5–61.8]	7.34	<.001
Asian	53.3 [50.0–56.6]	3.66	.02
Other	54.0 [51.2–56.9]	2.85	.06
Education level			
Did not graduate high school	58.6 [55.5–61.6]	reference	reference
High school graduate	53.0 [51.5–54.6]	−3.88	.02
Some college	52.1 [50.8–53.3]	−5.53	.001
College graduate	51.2 [50.0–52.4]	−7.10	<.001
Graduate degree	49.0 [46.3–51.7]	−8.35	<.001
Marital status			
Single	51.3 [50.2–52.4]	reference	reference
Divorced, separated, or widowed	49.5 [46.7–52.3]	3.11	.01
Married or in long-term relationship	52.6 [51.8–53.4]	3.12	<.001
Employment status			
Unemployed[c]	50.1 [48.8–51.4]	reference	reference
Employed or full-time student	53.1 [52.2–53.9]	1.20	.15
Total household income			
$0–50,000	52.8 [51.7–53.9]	reference	reference
$50,001–100,000	52.3 [51.1–53.5]	0.28	.70
$100,001–200,000	49.1 [47.6–50.6]	−2.17	.02
≥$200,001	52.1 [45.4–58.7]	1.64	.56
Prefer not to say	44.4 [40.7–48.1]	−6.10	.002
Irritable bowel syndrome	60.5 [57.5–63.5]	7.66	<.001
Chronic idiopathic constipation	69.0 [60.9–77.2]	6.56	.07
Gastrointestinal cancer	73.8 [58.7–88.8]	11.88	.06
Celiac disease	68.7 [62.5–74.9]	5.81	.03
Cirrhosis	73.9 [68.2–79.7]	11.67	<.001
Crohn's disease	69.5 [63.9–75.1]	8.30	<.001
Ulcerative colitis	58.3 [43.6–73.0]	4.09	.49
Diabetes	53.5 [51.3–55.7]	2.76	.02
Endometriosis	59.3 [56.7–61.9]	3.91	.004
Gallstones	55.2 [52.7–57.7]	1.77	.18
HIV/AIDS	57.0 [45.2–68.8]	6.36	.37
Pancreatitis	58.9 [53.7–64.1]	1.61	.50
Peptic ulcer disease	57.3 [54.1–60.5]	2.88	.07
Thyroid disease	54.9 [52.6–57.2]	3.45	.006
PPI use			
Not taking	49.9 [49.1–50.7]	reference	reference
Less than daily use	65.3 [62.5–68.1]	14.21	<.001
Daily use	55.2 [53.1–57.3]	8.84	<.001
Unknown frequency of use	60.2 [43.5–76.9]	−1.82	.81
Histamine-2 receptor blocker use			
Not taking	50.8 [50.0–51.5]	reference	reference
Less than daily use	60.6 [57.3–63.8]	9.35	<.001
Daily use	60.8 [57.1–64.5]	12.46	<.001
Unknown frequency of use	68.4 [58.3–78.6]	14.63	.01

Table 3. Continued

Variable	GERD PROMIS percentile score (0–100)[a]	β coefficient[b]	*P* value[b]
Antacid use			
Not taking	51.5 [50.7–52.2]	reference	reference
Less than daily use	52.6 [49.9–55.2]	4.44	<.001
Daily use	63.2 [59.6–66.8]	14.50	<.001
Unknown frequency of use	59.5 [47.4–71.6]	3.21	.56

NOTE. Data are presented as survey-weighted mean [95% CI]. A total of 3604 of 23,039 individuals with GERD in the past 7 days had missing medication data, so the analyses were performed among 19,435 respondents.
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a]Higher score equals more severe symptoms.
[b]The linear regression model included all variables listed in the table above.
[c]Includes those who reported being unemployed, on disability, on leave of absence from work, retired, or homemaker.

prevalence of somatization and functional disorders among this group,[43] where PPIs are unlikely to improve esophageal symptoms. Although the degree to which our findings reflect inadequate acid suppression from PPIs vs representing a surrogate for true underlying functional disease or non–acid reflux remains unclear, our results nonetheless demonstrate the need for further research and development of novel therapies for those with PPI-refractory GERD symptoms. Preliminary data have shown benefit with the potassium competitive acid blocker vonaprazan,[45,46] as well as gastric-retained bile acid sequestrants.[47,48]

This study has strengths and limitations. The National GI Survey is among the largest US population-based studies focused on GI symptoms. We have information on more than 71,000 participants, with more than 32,000 individuals who reported ever experiencing GERD symptoms and nearly 1900 individuals who reported PPI-refractory GERD symptoms in the past week. Another strength is our use of a novel online digital health tool that uses validated NIH PROMIS item banks and GERD-specific questions to systematically gather comprehensive information from respondents.[16,19,49] This digital platform also allowed us to efficiently recruit a large, highly diverse, representative population in a very short period of time.

However, the online collection of data also can be considered a limitation. As the data were based on individuals' responses to an online survey, there are concerns with regard to generalizability, particularly among middle-aged and elderly individuals with poor access to the Internet and/or limited computer skills. Our study also may have selected for older individuals who were more functional and independent. Of note, though, the Pew Research Institute reports that 82% and 63% of those 50 to 64 and ≥65 years old, respectively, used the Internet in 2015.[50] Nevertheless, our survey may have underestimated the prevalence of GERD and PPI-refractory GERD symptoms among older individuals. Conversely, our description of the study as a "GI Survey" to potential respondents may have led to an overestimation of GERD symptom prevalence, as those without GI issues may have opted to not complete the survey. We attempted to minimize participation bias by incentivizing users through Cint's reward system to fully complete the survey. Our results are also largely consistent with prior population-based studies, supporting the validity of our findings. We also would not have expected this to affect our regression analyses, as it is unlikely that there are systematic differences between survey responders and nonresponders with GERD symptoms.

In addition, we were not able to confirm pathologic reflux with esophageal pH monitoring, but instead relied on cardinal symptoms reported by respondents. Our survey methodology may have therefore led to misclassification of which respondents truly did or did not have objective GERD; however,

Table 4. GERD Medication Frequency of Use (n = 9234)

Frequency of use	PPI (n = 4935)	Histamine-2 receptor blocker (n = 2286)	Antacids (n = 2370)	Other (n = 217)
Every few months	170 (3.2)	138 (6.0)	160 (6.8)	14 (4.9)
Few times a month	266 (5.0)	225 (10.9)	375 (16.0)	17 (8.7)
Once a week	383 (7.4)	249 (10.7)	317 (12.0)	9 (4.1)
2–3 d/wk	521 (9.6)	438 (18.9)	612 (29.6)	37 (15.6)
4–6 d/wk	351 (6.5)	254 (11.3)	355 (13.5)	14 (4.7)
Daily	3,229 (68.1)	956 (41.0)	513 (20.3)	116 (59.3)
Unknown	15 (0.2)	26 (1.4)	38 (1.9)	10 (2.8)

NOTE. Data are presented as n (PW %).

Table 5. Predictors of Persistent GERD Symptoms Among Those Taking a Daily PPI (n = 3229)

Variable	Persistent GERD symptoms while on daily PPI (n = 1858)[a]	OR [95% CI][b]
Age, *y*		
18–29	213 (64.9)	reference
30–39	451 (69.2)	1.18 [0.86–1.63]
40–49	448 (60.3)	0.76 [0.56–1.05]
50–59	481 (52.3)	0.56 [0.40–0.77]
≥60	265 (45.6)	0.46 [0.31–0.69]
Gender		
Female	1270 (57.6)	reference
Male	588 (49.4)	0.78 [0.62–0.99]
Race/ethnicity		
Non-Hispanic white	1544 (51.1)	reference
Non-Hispanic black	92 (45.9)	0.83 [0.51–1.34]
Latino	150 (72.8)	2.44 [1.42–4.20]
Asian	22 (62.8)	1.13 [0.47–2.69]
Other	50 (51.7)	0.92 [0.53–1.59]
Education level		
Did not graduate high school	66 (64.7)	reference
High school graduate	444 (53.9)	0.66 [0.33–1.29]
Some college	634 (55.7)	0.73 [0.37–1.41]
College graduate	550 (51.9)	0.62 [0.32–1.22]
Graduate degree	164 (52.1)	0.67 [0.30–1.46]
Marital status		
Single	245 (52.4)	reference
Divorced, separated, or widowed	349 (55.9)	1.55 [1.05–2.29]
Married or in long-term relationship	1264 (53.7)	1.37 [1.02–1.84]
Employment status		
Unemployed[c]	923 (49.7)	reference
Employed or full-time student	935 (59.9)	1.27 [0.96–1.67]
Total household income		
$0–50,000	1013 (57.5)	reference
$50,001–100,000	584 (53.5)	0.81 [0.61–1.07]
$100,001–200,000	180 (48.7)	0.65 [0.45–0.93]
≥$200,001	24 (57.4)	0.94 [0.40–2.22]
Prefer not to say	57 (33.9)	0.41 [0.24–0.69]
Irritable bowel syndrome	263 (62.8)	1.39 [1.03–1.88]
Chronic idiopathic constipation	41 (64.7)	1.17 [0.45–3.05]
Gastrointestinal cancer	12 (23.7)	0.21 [0.09–0.48]
Celiac disease	25 (64.2)	0.98 [0.39–2.48]
Cirrhosis	20 (44.6)	0.68 [0.31–1.48]
Crohn's disease	47 (86.1)	5.16 [2.22–12.00]
Ulcerative colitis	35 (42.0)	0.49 [0.28–0.87]
Diabetes	254 (48.9)	0.83 [0.61–1.14]
Endometriosis	120 (57.1)	0.95 [0.60–1.51]
Gallstones	226 (54.9)	1.02 [0.68–1.51]
HIV/AIDS	10 (54.9)	2.20 [0.17–28.97]
Pancreatitis	50 (58.7)	1.27 [0.65–2.46]
Peptic ulcer disease	157 (60.1)	1.19 [0.82–1.73]
Thyroid disease	215 (55.3)	1.23 [0.86–1.75]
Histamine-2 receptor blocker use		
Not taking	1789 (53.5)	reference
Less than daily use	21 (71.1)	1.52 [0.57–4.09]
Daily use	32 (74.2)	2.37 [0.96–5.86]
Unknown frequency of use	16 (70.4)	2.06 [0.66–6.41]
Antacid use		
Not taking	1789 (53.6)	reference
Less than daily use	33 (56.7)	1.30 [0.57–2.96]
Daily use	20 (72.4)	1.81 [0.67–4.92]
Unknown frequency of use	16 (97.2)	29.79 [3.46–256.57]

NOTE. Data are presented as n (PW %).
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a]Defined as heartburn or regurgitation occurring ≥2 days in the past week among those on a daily PPI.
[b]The logistic regression model included all variables listed in the table above.
[c]Includes those who reported being unemployed, on disability, on leave of absence from work, retired, or homemaker.

any discrepancies would be consistent with misclassifications made in clinical practice where a diagnosis of GERD is typically based on patient-reported symptoms without confirmatory, objective pH or impedance testing. Along the same lines, there may have been misclassification since our GI symptom screener question solely defined GERD as "heartburn, acid reflux, or gastroesophageal reflux" and did not specifically mention regurgitation. Although some respondents may have equated "gastroesophageal reflux" with regurgitation, we nonetheless may have underestimated the prevalence of GERD, particularly for those who only experience regurgitation symptoms. Another limitation is that we did not assess whether respondents were taking PPIs correctly (ie, 30–60 minutes before a meal), whether use of the PPI was guided by a physician or was self-administered (ie, over-the-counter), or if they engaged in lifestyle modifications; this may have led to an overestimation of PPI-refractory symptoms. Finally, our study did not collect data on some demographic and lifestyle factors that can affect GERD symptom prevalence, such as body mass index, waist circumference, and alcohol and tobacco use; this will be addressed in our forthcoming National GI Survey 2. We also did not examine the impact of GERD symptoms on quality of life or health care utilization, as the primary goal of the National GI Survey was to assess the prevalence and distribution of the 8 cardinal GI symptoms. Further research updating our understanding of the burden imposed by GERD is warranted.

In conclusion, in this large population-based survey of community-dwelling Americans, we found that GERD

symptoms are very common, with 2 of 5 having ever had such symptoms in the past and 1 of 3 experiencing symptoms in the past week. We also found an uneven distribution of GERD symptoms, as women, non-Hispanic white individuals, and those with comorbidities such as IBS, Crohn's disease, diabetes, and endometriosis, among others, are more likely to be symptomatic. In addition, we noted that more than half of those on daily PPI therapy continue to experience persistent heartburn and/or regurgitation symptoms. Because of the significant impact of GERD on quality of life and its considerable economic burden, further research is needed to further explore these associations, as well as guide the development of novel therapies for those with PPI-refractory GERD symptoms.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.12.014.

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Conflicts of interest

Brennan M.R. Spiegel and William D. Chey are consultants for Ironwood Pharmaceuticals and patent holders and principals at My Total Health. Christopher V. Almario has a stock option grant in My Total Health. Sean D. Delshad discloses no conflicts.

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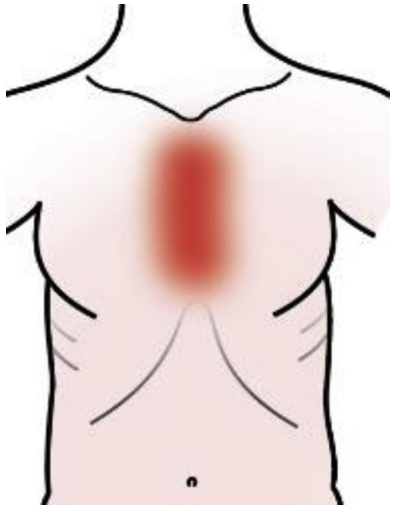
Supplementary Material

National GI Survey questions related to heartburn, acid reflux, or gastroesophageal reflux.

NIH GERD PROMIS questions

1. In the past 7 days, how often did you have regurgitation—that is, food or liquid coming back into your throat or mouth without vomiting?
   - o Never → If Never, go to #5
   - o One day
   - o 2–6 days
   - o Once a day
   - o More than once a day
2. In the past 7 days, what was the most liquid or food that came back up into your mouth at one time?
   - o None came into my mouth
   - o Enough to fill a little of my mouth
   - o Enough to fill some of my mouth
   - o Enough to fill most of my mouth
   - o So much that it filled my entire mouth
3. In the past 7 days, after eating a meal, how often did food or liquid come back into your throat or mouth without vomiting?
   - o Never
   - o Rarely
   - o Sometimes
   - o Often
   - o Always
4. In the past 7 days, how often did you re-swallow food that came back into your throat?
   - o Never
   - o Rarely
   - o Sometimes
   - o Often
   - o Always
5. In the past 7 days, how often did you feel like you were going to burp but food or liquid came up instead?
   - o Never
   - o One day
   - o 2–6 days
   - o Once a day
   - o More than once a day
6. In the past 7 days, how often did you feel like there was too much saliva in your mouth?
   - o Never
   - o Rarely
   - o Sometimes
   - o Often
   - o Always
7. In the past 7 days, how often did you feel burning in the red area shown in the picture (behind the breastbone)?



   - o Never
   - o One day
   - o 2–6 days
   - o Once a day
   - o More than once a day
8. In the past 7 days, how often did you feel burning in your throat?
   - o Never
   - o Rarely
   - o Sometimes
   - o Often
   - o Always
9. In the past 7 days, how often did you burp?
   - o Never → If Never, go to #11
   - o One day
   - o 2–6 days
   - o Once a day
   - o More than once a day

10. In the past 7 days, how much did burping bother you?
    - o Not at all
    - o A little bit
    - o Somewhat
    - o Quite a bit
    - o Very much
11. In the past 7 days, how often did you have hiccups?
    - o Never
    - o Rarely
    - o Sometimes
    - o Often
    - o Very often
12. In the past 7 days, how often did you feel like there was a lump in your throat?
    - o Never → If Never, finish questionnaire
    - o Rarely
    - o Sometimes
    - o Often
    - o Very often
13. In the past 7 days, how much did having a lump in your throat bother you?
    - o Not at all
    - o A little bit
    - o Somewhat
    - o Quite a bit
    - o Very much

GERD medication questions

1. Please select the names of any medications you are CURRENTLY taking for your heartburn/reflux symptoms. Please select all that apply.
    - o Prilosec (omeprazole)
    - o Protonix (pantoprazole)
    - o Prevacid (lansoprazole)
    - o Nexium (esomeprazole)
    - o Dexilant (dexlansoprazole)
    - o Aciphex (rabeprazole)
    - o Tagamet (cimetidine)
    - o Pepcid AC (famotidine)
    - o Zantac (ranitidine)
    - o Antacids (Tums, Rolaids, Mylanta, Maalox)
    - o Other (please specify)
    - o I am not currently taking any medications for heartburn/reflux
2. For each of the following medication(s) that you are taking for heartburn/reflux how frequently do you take each one?
    - o Every few months
    - o Few times a month
    - o Once a week
    - o 2 to 3 days per week
    - o 4 to 6 days per week
    - o Daily