Published in final edited form as:

Am J Gastroenterol. 2010 April ; 105(4): 822–832. doi:10.1038/ajg.2010.40.

Impact of Functional Gastrointestinal Disorders on Survival in the Community

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Abstract

OBJECTIVES—Functional gastrointestinal disorders (FGIDs) comprise a constellation of symptoms that have no identifiable structural or biochemical abnormality. In view of the lack of data from large-scale population-based studies evaluating the effects of these disorders on survival, we aimed to examine whether FGIDs are associated with impaired survival.

METHODS—Between 1988 and 1993, valid self-report questionnaires that recorded gastrointestinal symptoms required for the diagnosis of irritable bowel syndrome (IBS), chronic constipation, chronic diarrhea, dyspepsia, and abdominal pain were mailed to randomly selected cohorts of Olmsted County, Minnesota residents. Minnesota administrative death records were used to identify which of the survey respondents had died over the follow-up period (through April 2008). The association between survival and each FGID was assessed using proportional hazards regression models with univariate and adjusted hazard ratios (HRs, 95% confidence intervals (CIs)), adjusting for age at time of survey, gender, smoking, alcohol, marital status, and Charlson Comorbidity Index (CCI).

RESULTS—Of the 5,262 randomly selected eligible subjects who received a questionnaire, a total of 4,176 responded to the surveys (overall response rate 79%). From these respondents, 243 subjects were excluded because of lack of research authorization (or were registered solely at a different medical institution in Olmsted County, MN), resulting in 3,933 eligible subjects for analysis (eligible response rate 75%); 10% reported symptoms of IBS; 16% chronic constipation; 18% chronic diarrhea; 2% dyspepsia; and 15% abdominal pain. At baseline, the mean (s.d.) age was 54 (18) years, and 52% were female. No association with overall survival was detected for IBS (HR = 1.06 (95% CI: 0.86–1.32)), chronic diarrhea (HR = 1.03 (95% CI: 0.90–1.19)), abdominal pain (HR = 1.09 (95%

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CONFLICT OF INTEREST

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Specific author contributions: Data collection, drafting of the manuscript, data interpretation, critical review, and revision of manuscript: Joseph Y. Chang; study conception, design and oversight, data interpretation, critical review, and revision of manuscript: G. Richard Locke; data collection: Meredythe A. McNally; data collection: Smita L. Halder; data analysis, critical review, and revision of the manuscript: Cathy D. Schleck; data analysis and interpretation, critical review, and revision of the manuscript: Alan R. Zinsmeister; study conception, design and oversight, data interpretation, critical review, and revision of manuscript: Nicholas J. Talley.

Financial support: None.

Potential competing interests: None.

CI: 0.92–1.30)), or dyspepsia (HR = 1.08 (95% CI: 0.58–2.02)). Reporting symptoms of chronic constipation was associated with poorer survival (HR = 1.23 (95% CI: 1.07–1.42)). This association remained significant after adjusting for the CCI (HR = 1.19 (95% CI: 1.03–1.37)).

CONCLUSIONS—In this large population-based cohort study with over 30,000 person-years of follow-up, no significant association was observed between survival and IBS, chronic diarrhea, dyspepsia, or abdominal pain. Furthermore, no association was found between increasing burden of FGIDs and survival. However, in contrast to these other FGIDs, subjects with symptoms of chronic constipation were found to be at increased risk of poorer survival. Further investigation is required to determine the cause of this observed association.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are common in the community with a prevalence reported as high as 40% (1). Although most patients do not seek medical evaluation for their symptoms, FGIDs have still been estimated to account for up to half of the patient care time for gastroenterologists (2–5). Seen by some physicians as predominantly forms of psychological disorders, FGIDs have historically carried potentially harmful stigmas for patients and have even had their existence denied by some physicians (6,7). However, the recent recognition of the complex relationships between genetic, environmental, psychosocial, and physiological factors in the FGIDs has resulted in the wide acceptance of these disorders as clinical outcomes of a dysregulated brain–gut axis (8,9).

With this change in the paradigm, there has been increased interest in the epidemiology and natural history of these functional disorders (1). However, investigation has been hampered in the past by the various and differing diagnostic criteria that have been used for these disorders. The Rome process has played a critical role in bringing consistency to research with categorization and dissemination of evolving knowledge (8). Despite the use of differing diagnostic definitions and criteria, FGIDs have been found to be very common in the community. Estimates of prevalence for symptoms of irritable bowel syndrome (IBS) ranges from 3 to 20%; chronic constipation up to 27%; chronic diarrhea as high as 27%; and dyspepsia has ranged from 2.5% to as high as 41% (10–14). The economic burden of these functional disorders has also been found to be considerable; in 1998, IBS was estimated to have a total cost of \$1.6 billion, and chronic diarrhea had an estimated total cost of \$621 million (15). This tremendous economic burden has also been mirrored by the impact of FGIDs on health-care usage; in 1998, there were close to 6 million physician office visits for IBS and chronic diarrhea, and IBS accounted for almost 500,000 inpatient hospital stays (15). In addition to these concerns, patients with FGIDs, including those in the clinic and community, have been found to have an impaired health-related quality of life (16–18). All of these factors contradict the traditional view of FGIDs as relatively benign disorders.

Despite the above findings, it has been generally assumed that FGIDs do not have an adverse long-term impact on health. However, this assumption occurs in the absence of any substantiating data in the literature, and without investigations from a population-based approach. Community-based investigation of the epidemiology of FGIDs is crucial given that the majority of patients with FGIDs do not seek care for their symptoms (4,5). These disorders do drive medication use, invasive testing, and lead to excess surgery (19); depression (and suicidal ideation) is also associated (20). Hence, it has been speculated that a small but significant excess mortality may accompany these conditions (21). Therefore, this study sought to examine the association of FGIDs with survival in a large population-based cohort study.

METHODS

This is a population-based historical cohort study of randomly selected subjects from Olmsted County, MN. This research was approved by the Mayo Foundation Institutional Review Board.

Subjects

The Olmsted County population comprises ~120,000 persons of whom 89% are Caucasian. Although the education level is slightly higher as well as the proportion employed in the health-related services industry, this community otherwise is sociodemographically similar to the US white population (22). Approximately 80% of the local population resides within 5 miles of Rochester, MN and virtually all residents receive their medical care almost exclusively from two group practices: Mayo Medical Center and Olmsted Medical Center. The Mayo Clinic has maintained a common medical records system with its two affiliated hospitals (St Marys and Rochester Methodist) for over 100 years. All diagnoses and surgical procedures are recorded and indexed, including all diagnoses made from outpatients seen in the office or clinic consultations, emergency room visits, or nursing home care. Diagnoses are also recorded for hospital inpatients, at autopsy examination, or on death certificates. The Rochester Epidemiology Project further developed this system by creating similar indices for the records of other providers to local residents, most notably the Olmsted Medical Center (Olmsted Medical Group and its affiliated Olmsted Community Hospital). This medical records linkage system allows access to details of the medical care provided to Olmsted County residents for research as long as subjects provide research authorization. Annually, over 80% of the entire population is attended by one or both of these two practices, and ~96% of the population is seen at least once during a 4-year period (22). Thus, this medical records linkage system by the Rochester Epidemiology Project provides essentially a true enumeration of this population from which random samples can be drawn.

Sampling, inclusion, and exclusion criteria

Using data resources of the Rochester Epidemiology Project, a series of age- and gender-stratified random samples of Olmsted County residents were drawn between 1988 and 1993. Subjects in these samples were mailed validated gastrointestinal (GI) symptom questionnaires (discussed below) from November 1988 to June 1994 representing an initial, or baseline, survey. The cohort of subjects that returned questionnaires, which contained criteria for defining specific FGID, was identified and consisted of subjects 20 years of age and greater at the time of mailing. Results based on these surveys have been reported earlier (23–30). The complete medical records of subjects listed in the samples were reviewed.

Subjects were excluded from the mailings if they had significant illnesses that might cause GI symptoms; impair their ability to complete the questionnaire (e.g., metastatic cancer, major stroke) ($n = 91$); had a history of major abdominal surgery ($n = 37$); had a major psychotic episode, mental retardation, or dementia ($n = 46$). Incarcerated individuals in the local Federal Medical Center ($n = 8$), and subjects for whom contact was prohibited for legal reasons were also excluded ($n = 190$). Residency confirmation was also performed and excluded subjects no longer residing within the county ($n = 551$) or deceased ($n = 17$).

For these surveys, a study questionnaire and an explanatory letter were mailed to all eligible subjects. Reminder letters were typically mailed as needed at 2, 4, and 7 weeks. The remaining non-responders were typically then contacted by telephone at 10 weeks to request their participation and verify their residency within the county. Subjects were assumed to no longer reside within the county if the questionnaire was not delivered and no new address was known. Although subsets of these subjects received subsequent follow-up surveys between 1998 and 2004, these responses were not included in this study.

A total of 5,262 randomly selected subjects were sent questionnaires that included questions necessary to define specific FGIDs that included dyspepsia, functional constipation, IBS, abdominal pain, and functional diarrhea. Of the 4,176 that responded, 243 were removed after declining research authorization (or were registered solely at a different medical institution in Olmsted County, MN). This left 3,933 subjects for the analysis.

Questionnaire

The original Bowel Disease Questionnaire (BDQ) was designed as a self-report instrument to measure symptoms experienced over the prior year and to collect the past medical history (31). Previous testing has shown the symptom assessment of the BDQ to have adequate reliability and validity with a median statistic (chance corrected measure of agreement) of 0.78 (range 0.52–1.00) (31,32). The BDQ has also been assessed in the outpatient setting and was demonstrated to have adequate content and construct as well as discriminatory validity (31). The original BDQ contained 46 GI symptom-related items; 25 items that measured past illness, health-care use, and sociodemographic data; and the Somatic Symptom Checklist, which was a valid measure of somatic complaints. The Somatic Symptom Checklist is a self-report scale that contains 17 somatic complaints and asks respondents to rate each item on frequency and occurrence; frequency indicated on a scale from 0 (indicating not a problem) to 4 (indicating daily), and intensity also scaled from 0 (indicated not a problem) to 4 (indicating extremely bothersome when symptom occurs) (33). The Somatic Symptom Checklist was adapted to yield a composite score derived by summing the cross-product of each item's frequency by intensity. Derivatives of the original BDQ have also been created for specific conditions or populations, such as the Gastroesophageal Reflux Questionnaire and the Elderly BDQ (34, 35). Reliability testing was also performed on these derivatives before implementation (34, 35). All subjects received either the BDQ or a validated derivative. Of the 3,933 eligible subjects, 1,599 responded to the BDQ, 852 responded to the Gastroesophageal Reflux Questionnaire, and 1,482 responded to the Elderly BDQ.

Definition of symptom categories

For this study, subjects were classified into *a priori* symptom groups based on their responses to each of the questionnaires. Attempts were made so that definitions for each symptom category were modifications based on Rome classification (36). Of note, subjects with IBS were excluded from inclusion in the other FGID categories including functional constipation, functional diarrhea, dyspepsia, and abdominal pain.

Irritable bowel syndrome—IBS was defined as a combination of frequent (more than six times per year) abdominal pain and alteration in bowel habit in the past year. The abdominal pain had to have two of the following characteristics consistent with Rome criteria: (i) relieved by defecation; (ii) associated with a change in stool frequency; or (iii) associated with a change in stool form (8). The original BDQ did not ask the questions “do you often have less bowel movements with abdominal pain?” or “do you often have harder stools with abdominal pain?” but these were included in later versions. Notably, the definition applied has been tested and applied in previous investigations (1,24,26).

Functional constipation—Subjects with symptoms of IBS (as defined above) were excluded. Functional constipation was defined as having two or more of the following symptoms, with each occurring more than 25% of the time in the past year: (i) fewer than three bowel movements per week; (ii) straining during a bowel movement; (iii) passing hard or lumpy stools; and (4) feeling of incomplete evacuation after a bowel movement (24).

Functional diarrhea—Subjects with symptoms of IBS (as defined above) were excluded. Functional diarrhea was defined as having one or more of the following symptoms, with each

occurring more than 25% of the time in the past year: (i) reporting more than three bowel movements a day; (ii) having loose or watery stools; and (iii) fecal urgency or urgency to have a bowel movement (24).

Dyspepsia—Subjects with symptoms of IBS (as defined above) were excluded. Dyspepsia was defined as having two or more of the following: (i) frequent upper abdominal pain (> 6 times per year); (ii) nausea (at least three or more episodes per week); (iii) vomiting (≥ 3 episodes per week); (iv) early satiety; and (v) loss of appetite (23,24). The original BDQ did not ask the questions “early satiety” or “loss of appetite” but these were included in later versions.

Abdominal pain—Subjects with symptoms of IBS (as defined above) were excluded. Abdominal pain was defined as having more than six episodes of abdominal pain in the prior year.

Follow-up and causes of death

Mayo Clinic maintains an institutional database (or “Registration”) that periodically updates routine patient follow-up (e.g., correspondence with patients or next of kin or local providers of medical care), this includes clinic visits. This database is up-to-date for all Olmsted County residents. From this database, vital status (and if deceased, the date of death) was determined for all subjects in this analysis. All remaining subjects assumed at this point to still be alive were cross-checked with the responders to more recent surveys from 2002 to 2004. Through this, a small subset of subjects were identified that had not responded and had a last contact date in the database of more than 2 years before the onset of this study. A list of this group of subjects was sent to the Mayo Survey Research Center, which used the Accurint database to track down addresses, phone numbers, and vital status (37). These methods were used to identify which of the survey respondents had died over the 15-year follow-up period (through April 2008). For deceased subjects, cause of death was obtained through use of Minnesota Death Tapes. For deceased subjects not found on the Minnesota Death Tapes, the Accurint system was used to request death certificates; causes of death were then obtained through review of these certificates. On the basis of previous cohort studies from Olmsted County, the methods applied have been demonstrated to be exhaustive with near complete ascertainment of deaths (38–40).

Charlson Comorbidity Index and other risk factors

Developed in 1987 from a cohort of 559 medical patients, the Charlson Comorbidity Index (CCI) encompasses 19 weighted categories of comorbidity, including myocardial infarction, congestive heart failure, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, hemiplegia, liver disease (including mild vs. moderate or severe), diabetes mellitus, diabetes with end organ damage, AIDS, tumor, metastatic tumor, leukemia, lymphoma, ulcer disease, renal disease, dementia, and connective tissue disease (41). The CCI has demonstrated good predictive validity and reliability for a variety of clinical outcomes similar to that of other comorbidity indices (42). Deyo *et al.* further developed the CCI for use with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) administrative databases and codes (43). The Rochester Epidemiology Project adapted the CCI for use based on the electronic medical index using ICD-9-CM codes. As the overall distribution in the total sample indicated that few subjects had more than two of the diseases included in the CCI, the proportional hazards regression analysis incorporated the morbidity index categorized as none vs. one or more.

Notable risk factors collected at baseline included alcohol use, smoking, and socioeconomic status. Alcohol use was categorized as none vs. one to six standard drinks per week vs. seven

or more drinks per week. Smoking was recorded as yes/no regarding current status. Socioeconomic status was measured by education level and this was categorized as college graduate/professional training vs. high school/some college vs. less than high school.

Statistical analysis

The association between survival and each of the FGID (dyspepsia, functional constipation, IBS, abdominal pain, and functional diarrhea) was assessed using proportional hazards regression models to compute hazard ratios (HRs) with 95% confidence intervals (CIs). To account for potential confounding factors, HRs were also estimated adjusting for age at time of survey, gender, education level, CCI, alcohol use, and smoking. Kaplan–Meier estimates of overall survival, separately for each FGID analysis subset, were plotted and an overall observed vs. expected survival for the whole cohort was constructed. Expected survival was based on the age- and gender-specific features of the whole cohort using the survival characteristics of the Minnesota Caucasian population.

The association between survival and burden of FGIDs (e.g., number of FGIDs) was also assessed using proportional hazards regression models to compute HRs with 95% CIs. Multiple variable analyses, adjusting for the same factors used for each FGIDs and survival, were also examined.

Study power

On the basis of the distribution of subjects for a specific FGID (e.g., 10% with IBS vs. 90% without), the univariate hazards ratios that could be detected with ~80% power (two-sided $\alpha = 0.05$) assuming 1,100 events (“deaths”) were estimated.

Irritable bowel syndrome—With 397 subjects reporting symptoms of IBS, there was 80% power to detect an HR of 1.33, or greater (corresponding to a 33% increase in risk relative to those without symptoms of IBS).

Functional. constipation—With 622 subjects reporting symptoms of functional constipation, there was 80% power to detect an HR of 1.27.

Functional diarrhea—With 694 subjects reporting symptoms of functional diarrhea, there was 80% power to detect an HR of 1.26.

Dyspepsia—With 68 subjects reporting symptoms of dyspepsia, there was 80% power to detect an HR of 1.91.

Abdominal pain—With 596 subjects reporting symptoms of frequent abdominal pain, there was 80% power to detect an HR of 1.28.

Thus, this study had adequate power to detect a clinically relevant survival disadvantage for each of the disorders. If an adjustment for multiple FGIDs analyzed is used, a Bonferroni-adjusted α level of 0.01 (i.e., 0.05 divided by 5 FGIDs) would provide an overall Type 1 error rate of at most 5%.

RESULTS

Demographics

A total of 4,176 subjects responded to the surveys (overall response rate of 79%), and the response rates for each survey were over 70%. From these respondents, 243 subjects were excluded because of lack of research authorization (or were registered solely at a different

medical institution in Olmsted County, MN), resulting in 3,933 eligible subjects for analysis (eligible response rate 75%). The mean (s.d.) age of the respondents at baseline was 54 (18) years and 52% were women.

Overall, 10% of the population reported symptoms of IBS, 16% reported constipation, 18% diarrhea, 2% dyspepsia, and 15% abdominal pain. The sociodemographic factors and CCI are summarized in Table 1.

Survival

There were 1,101 deaths observed in the cohort through the last follow-up point of April 2008. Table 2 provides the results from the univariate proportional hazards regression models, which indicated poorer survival with increasing baseline age, male gender, smokers, and worsening CCI scores. Overall observed vs expected survival for the whole set of respondents is illustrated in Figure 1, which suggested slightly better survival in respondents ($P = 0.09$, log rank test).

Irritable bowel syndrome—At 10 years, the estimated survival was 87% among those reporting IBS (95% CI: 84, 90) vs. 83% in subjects not reporting IBS (95% CI: 81, 84) (Figure 2a). After adjusting for just age and gender, IBS was not associated with worse survival (HR = 1.06 (95% CI: 0.86–1.32), Table 2). This association was not appreciably altered when adjusted for smoking, education, alcohol use, and CCI (Table 3).

Functional constipation—At 10 years, the estimated survival was 73% among those reporting constipation (95% CI: 69, 76) vs. 85% in subjects not reporting constipation (95% CI: 84, 86) (Figure 2b). After adjusting for age and gender, constipation was associated with worse survival (HR = 1.23 (95% CI: 1.07–1.42), $P = 0.005$, Table 2). This association remained significant ($P = 0.01$) when adjusted for smoking, education, alcohol use, and CCI (Table 3). Restricting the analysis to subjects without any of the comorbidities in the CCI, the 10-year survival rates were 85% (95% CI: 82, 88) and 93% (95% CI: 92, 94) for those with and without constipation, respectively ($P < 0.001$, log rank test for overall survival in this restricted subset). In addition, the association of constipation with overall survival was examined based on the severity of constipation. Severity was categorized using the number of constipation symptoms endorsed by each subject (e.g., none, one out of four, two out of four, three or greater out of four). Using no reported symptoms as the reference category, a consistent “dose response” association was not observed, although those with two symptoms did have an increased HR (HR = 1.3 (95% CI: 1.1, 1.6), $P < 0.005$) relative to no symptoms reported, whereas those reporting three or four symptoms did not, adjusted for age, gender, and CCI.

Functional diarrhea—At 10 years, the estimated survival was 77% among those reporting chronic diarrhea (95% CI: 74, 80) vs. 84% in subjects not reporting chronic diarrhea (95% CI: 83, 86) (Figure 2c). After adjusting for age and gender, chronic diarrhea was not associated with survival (HR = 1.03 (95% CI: 0.90–1.19), Table 2). This association was not appreciably altered when adjusted for smoking, education, alcohol use, and CCI (Table 3).

Dyspepsia—At 10 years, the estimated survival was 93% among those reporting dyspepsia (95% CI: 87, 99) vs. 83% in subjects not reporting dyspepsia (95% CI: 82, 84) (Figure 2d). After adjusting for age and gender, dyspepsia was not associated with survival (HR = 1.08 (95% CI: 0.58–2.02), Table 2). This association was not appreciably altered when adjusted for smoking, education, alcohol use, and CCI (Table 3).

Abdominal pain—At 10 years, the estimated survival was 83% among those reporting abdominal pain (95% CI: 80, 86) vs. 83% in subjects not reporting chronic abdominal pain (95% CI: 82, 84) (Figure 2e). After adjusting for age and gender, abdominal pain was not

associated with survival (HR = 1.09 (95% CI: 0.92–1.30), Table 2). This association was not appreciably altered when adjusted for smoking, education, alcohol use, and CCI (Table 3).

Causes of death

The causes of death for each FGID are given in Table 4. No association between specific cause of death and each specific FGID was detected. The number of GI cancers occurring within each FGID group during the follow-up period is presented in Table 5; no significant associations were detected.

Burden of FGIDs and survival

The association between burden of FGIDs and survival was evaluated and decreased survival was significant in the univariate analysis for those with two (HR = 1.23 (95% CI 1.04, 1.44)) and four (HR = 3.18 (95% CI 1.02, 9.98)) FGID. However, these associations for two (HR = 1.15 (95% CI 0.97, 1.36)) and four (HR = 2.64 (95% CI 0.83, 8.38)) FGIDs were attenuated and did not remain significant in the multiple variables model adjusting for age, gender, smoking, education level, alcohol use, and CCI. Having one or three FGIDs was not associated with survival in either the univariate (one FGID: HR = 1.03 (95% CI 0.90, 1.18); three FGIDs: HR = 1.10 (95% CI 0.75, 1.62)) or multiple variables (one FGID: HR = 1.05 (95% CI 0.91, 1.20); three FGIDs: HR = 1.01 (95% CI 0.67, 1.52)) models.

DISCUSSION

FGIDs are common in the community and despite significant impact on health-care usage and resultant economic burden have been traditionally perceived as relatively benign disorders without adverse prognoses. However, this assumption is made despite a paucity of data from large-scale population-based studies evaluating whether FGIDs have an actual impact on survival. Community-based investigations of FGIDs is crucial given that the majority of patients with FGIDs do not seek care for their symptoms (4,5). In this population-based cohort study with over 30,000 person-years of follow-up, no significant association was observed between survival and IBS, chronic diarrhea, dyspepsia, or abdominal pain. Furthermore, no association was found between an increasing burden of FGIDs and survival. However, in contrast to these other FGIDs, subjects with symptoms of chronic constipation were found to be at increased risk of poorer survival.

IBS is one of the most common FGIDs in the community with a prevalence in North America reported as high as 20%, with most estimates ranging between 10 to 20% (44). This translates into ~30 million people with symptoms meeting the criteria for IBS. The economic burden posed by IBS is considerable and appears to not only arise from its high prevalence in the community, but also from a disproportionately high consumption of health-care resources (45–47). This disparate usage of resources often involves various invasive procedures as well as surgeries such as cholecystectomy, appendectomy, and hysterectomy (45,48). The willingness of patients with IBS to undergo the risks of invasive testing and surgeries is not surprising, given other data suggesting that these patients are willing to expose themselves to considerable risk, and even death, for a therapy that may potentially resolve their symptoms (49). Despite these considerations, we did not find any association with IBS and poorer survival. Of note, better survival was not observed either, despite the increased usage of health-care resources seen in this group. Whether this lack of either association reflects a balance between excess risk exposure and benefits of frequent health-care visits is uncertain. Nonetheless, the findings of this study for IBS are reassuring.

Dyspepsia and abdominal pain are two upper GI symptoms that are commonly seen in the general population. Similar to IBS, subjects with symptoms of dyspepsia or abdominal pain

have greater health seeking behavior over the general population (50). Unlike abdominal pain, dyspepsia has been reported earlier to be associated with poorer survival in a study from the United Kingdom (51). However, the study had various limitations that include subjects with dyspepsia who were obtained from the general practice setting were identified solely based on diagnosis codes from the Oxford Medical Information System and subjects with dyspepsia were more likely to be diagnosed with angina or chest pain, which raises the question of excess mortality from overlooked cardiac causes. In contrast to the UK findings, the subjects with dyspepsia from our study were identified by symptom-based criteria in a population-based setting; comorbidities, including myocardial infarction and congestive heart failure, were adjusted for in the multiple variable analyses with the CCI. Therefore, our results showing no association between dyspepsia and survival may more accurately reflect the community perspective than has been reported earlier. Although the percent of our population reporting symptoms of dyspepsia was unexpectedly low at 2%, this may reflect (1) our exclusion of subjects with IBS and the overlap that is commonly seen between these two groups and (2) a more stringent definition used here in terms of requirements for how frequent symptoms occurred (e.g., nausea and vomiting both required episodes occurring at least three or more times per week). Given the population-based setting of our study and more stringent definition used, our findings for dyspepsia are felt to be both reassuring and more reflective of patients with dyspepsia in the community.

Subjects with lower GI symptoms often complain of a spectrum of symptoms that often include both diarrhea and constipation. Chronic diarrhea can be a manifestation of various disorders including inflammatory bowel disease, malabsorption syndromes, and chronic infections. In contrast, functional diarrhea occurs in the absence of obvious biochemical or structural etiologies. In this study, we found no association between functional diarrhea and survival. We made multiple efforts to ensure that other causes of chronic diarrhea were excluded from the diarrhea group; subjects with IBS were also excluded.

However, despite the lack of association found between survival and the multiple FGIDs described above, we found that subjects with symptoms of chronic constipation had poorer survival. This finding was significant in both the univariate and multiple variable analyses, which adjusted for smoking, education level, alcohol use, and the CCI. Explaining this finding is difficult, especially in light of the lack of associations found for the other FGIDs. Given the data from multiple studies suggesting that constipation is associated with an increase risk for colorectal adenocarcinoma (52–56), we explored whether the observed excess mortality may be secondary to deaths from colorectal cancer. Although not a primary endpoint of this study, we found no association between symptoms of constipation and colorectal cancer or any other GI malignancy. Another possible explanation for our finding is that symptoms of constipation may be a surrogate for general health status and reflective of underlying comorbidities, and poorer survival is actually secondary to these factors and not the constipation itself. However, it may be difficult to apply this argument to our results given that (i) individuals with any significant illnesses were excluded at baseline from the mailings, (ii) the association found remained significant despite adjusting for comorbidities through the CCI, and (iii) the 10-year survival rates were still significantly lower in those with constipation even when comparing subjects without any of the comorbidities. Despite our careful analyses, caution is recommended regarding this finding given the lack of association found between survival and the other FGIDs included in this study. An increased mortality in constipation not only contradicts the majority of findings of this study, but also we could not account for the excess mortality despite examining causes of death and frequency of GI malignancies. Further investigation is clearly needed to explore whether these findings are spurious or indeed meaningful.

One limitation of our study is that the racial majority (at ~90%) of our Olmsted County study population was Caucasian. Thus, these data may be only applicable to the Caucasian population and not other ethnic groups. Response bias is possible, but this seems less likely given the reasonable response rate and lack of differences between responders and nonresponders that is now well documented in this population (57). Although an earlier validated symptom questionnaire was applied, it is possible that measurement bias influenced the results. Recall bias may have been increased because symptoms were assessed over the previous year, although in validation testing locally this has not been an issue (31). The power calculations performed were also *post hoc*. Referral bias is a remote consideration given that although subjects were recruited randomly from a population-based setting, subjects were limited to those who had received care at some time from the Mayo Clinic, given the use of the earlier discussed institutional database (or “Registration”) as part of the methods for determination of vital status. The transition between FGIDs over time may result in misclassification bias (1). However, as misclassification bias often results in an underestimation of a true association, our findings for constipation despite this bias is notable.

In summary, FGIDs are common in the community and pose a significant health-care burden. Although commonly assumed to be benign, there has been a lack of large-scale population-based studies examining whether or not FGIDs are associated with increased mortality. The results from this population-based cohort study are largely reassuring in that no association was found between survival and symptoms of IBS, functional diarrhea, dyspepsia, or abdominal pain. In light of these findings, caution should be applied regarding our observation that chronic constipation is associated with poorer survival. Whether this finding is spurious or secondary to an underlying process requires further investigation.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Functional gastrointestinal disorders (FGIDs) are common in the community.
- It is generally assumed that FGIDs do not have an adverse long-term impact on health.
- There is a lack of population-based investigation into the long-term impact on health by FGIDs.

WHAT IS NEW HERE

- This is a population-based cohort study, with over 30,000 person-years of follow-up, examining the association of FGIDs with survival.
- No significant association was observed between survival and irritable bowel syndrome, chronic diarrhea, dyspepsia, or abdominal pain.
- Subjects with symptoms of chronic constipation had poorer survival. This finding was significant in both the univariate and multiple variable analyses, which adjusted for smoking, education level, alcohol use, and the Charlson Comorbidity Index.

REFERENCES

1. Halder SL, Locke GR III, Schleck CD, et al. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. *Gastroenterology* 2007;133:799–807. [PubMed: 17678917]

2. Switz DM. What the gastroenterologist does all day. A survey of a state society's practice. *Gastroenterology* 1976;70:1048–1050. [PubMed: 1269864]
3. Mitchell CM, Drossman DA. Survey of the AGA membership relating to patients with functional gastrointestinal disorders. *Gastroenterology* 1987;92:1282–1284. [PubMed: 3557021]
4. Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993;38:1569–1580. [PubMed: 8359066]
5. Talley NJ, Zinsmeister AR, Melton LJ III. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. *Am J Epidemiol* 1995;142:76–83. [PubMed: 7785677]
6. Drossman DA. Functional GI disorders: what's in a name? *Gastroenterology* 2005;128:1771–1772. [PubMed: 15940609]
7. Christensen J. Heraclides or the physician. *Gastroenterol Int* 1990;3:45–48.
8. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;130:1377–1390. [PubMed: 16678553]
9. Jones MP, Dilley JB, Drossman D, et al. Brain-gut connections in functional GI disorders: anatomic and physiologic relationships. *Neurogastroenterol Motil* 2006;18:91–103. [PubMed: 16420287]
10. Johnanson JF, Sonnenberg A, Koch TR. Clinical epidemiology of chronic constipation. *J Clin Gastroenterol* 1989;11:525–536. [PubMed: 2551954]
11. Brandt LJ, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002;97:S7–S26. [PubMed: 12425586]
12. Stewart WF, Liberman JN, Sandler RS, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. *Am J Gastroenterol* 1999;94:3530–3540. [PubMed: 10606315]
13. Sandler RS, Stewart WF, Liberman JN, et al. Abdominal pain, bloating, and diarrhea in the United States: prevalence and impact. *Dig Dis Sci* 2000;45:1166–1171. [PubMed: 10877233]
14. El-Serag HB, Talley NJ. Systemic review: the prevalence and clinical course of functional dyspepsia. *Aliment Pharmacol Ther* 2004;19:643–654. [PubMed: 15023166]
15. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002;122:1500–1511. [PubMed: 11984534]
16. El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment Pharmacol Ther* 2002;16:1171–1185. [PubMed: 12030961]
17. Akehurst RL, Brazier JE, Mathers N, et al. Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting. *Pharmacoeconomics* 2002;20:455–462. [PubMed: 12093301]
18. Halder SL, Locke GR III, Talley NJ, et al. Impact of functional gastrointestinal disorders on health-related quality of life: a population-based case-control study. *Aliment Pharmacol Ther* 2004;19:233–242. [PubMed: 14723614]
19. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. *Gastroenterology* 2004;126:1665–1673. [PubMed: 15188159]
20. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002;122:1140–1156. [PubMed: 11910364]
21. Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil* 2008;20 Suppl 1:121–129. [PubMed: 18402649]
22. Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996;71:266–274. [PubMed: 8594285]
23. Talley NJ, Zinsmeister AR, Schleck CD, et al. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology* 1992;102:1259–1268. [PubMed: 1551533]
24. Talley NJ, Weaver AL, Zinsmeister AR, et al. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol* 1992;136:165–177. [PubMed: 1415139]

25. Talley NJ, Weaver AL, Zinsmeister AR. Smoking, alcohol, and nonsteroidal anti-inflammatory drugs in outpatients with functional dyspepsia and among dyspepsia subgroups. *Am J Gastroenterol* 1994;89:524–528. [PubMed: 8147354]
26. Talley NJ, Fett SL, Zinsmeister AR, et al. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. *Gastroenterology* 1994;107:1040–1049. [PubMed: 7926457]
27. Locke GR III, Zinsmeister AR, Talley NJ, et al. Familial association in adults with functional gastrointestinal disorders. *Mayo Clin Proc* 2000;75:907–912. [PubMed: 10994826]
28. Locke GR III, Weaver AL, Melton LJ III, et al. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004;99:350–357. [PubMed: 15046228]
29. Vege SS, Locke GR III, Weaver AL, et al. Functional gastrointestinal disorders among people with sleep disturbances: a population-based study. *Mayo Clin Proc* 2004;79:1501–1506. [PubMed: 15595333]
30. Delgado-Aros S, Locke GR III, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. *Am J Gastroenterol* 2004;99:1801–1806. [PubMed: 15330922]
31. Talley NJ, Phillips SF, Wiltgen CM, et al. Assessment of functional gastrointestinal disease: the Bowel Disease Questionnaire. *Mayo Clin Proc* 1990;65:1456–1479. [PubMed: 2232900]
32. Talley NJ, Phillips SF, Melton J III, et al. A patient questionnaire to identify bowel disease. *Ann Intern Med* 1989;111:671–674. [PubMed: 2679285]
33. Attanasio V, Andrasik F, Blanchard EB, et al. Psychometric properties of the SUNYA revision of the Psychosomatic Symptom Checklist. *J Behav Med* 1984;7:247–257. [PubMed: 6748072]
34. Locke GR, Talley NJ, Weaver AL, et al. A new questionnaire for gastroesophageal reflux disease. *Mayo Clin Proc* 1994;69:539–547. [PubMed: 8189759]
35. O’Keefe EA, Talley NJ, Tangalos EG, et al. A bowel symptom questionnaire for the elderly. *J Gerontol* 1992;47:M116–M121. [PubMed: 1624694]
36. Drossman, D.; Corazziari, E.; Talley, NJ., et al. *The Functional Gastrointestinal Disorders Rome III*. 3rd edn. Associates, D., editor. McLean, VA: Degnon Associates, Inc; 2006.
37. Accurint®, a LexisNexis® commercial location and research online service 2005. Retrieved from Accurint® website: <http://www accurint.com>
38. Rocca WA, Grossardt BR, de Andrade M, et al. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006;7:821–828. [PubMed: 17012044]
39. Kyle RA, Therneau TM, Rajkumar SV, et al. Incidence of multiple myeloma in Olmsted County, Minnesota: trend over 6 decades. *Cancer* 2004;101:2667–2674. [PubMed: 15481060]
40. Bambha K, Kim WR, Talwalkar J, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. *Gastroenterology* 2003;125:1364–1369. [PubMed: 14598252]
41. Carlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383. [PubMed: 3558716]
42. Hall WH, Ramachandran R, Narayan S, et al. An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer* 2004;4:94. [PubMed: 15610554]
43. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–619. [PubMed: 1607900]
44. Saito YA, Schoenfeld P, Locke GR III. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol* 2002;91:1910–1915. [PubMed: 12190153]
45. Spiegel BM. The burden of IBS: looking at metrics. *Curr Gastroenterol Rep* 2009;11:265–269. [PubMed: 19615301]
46. Hillila MT, Siivola MT, Farkkila MA. Comorbidity and use of health-care services among irritable bowel syndrome sufferers. *Scand J Gastroenterol* 2007;42:799–806. [PubMed: 17558902]
47. Longstreth GF, Wilson A, Knight K, et al. Irritable bowel syndrome, health care use, and costs: a US managed care perspective. *Am J Gastroenterol* 2003;98:600–607. [PubMed: 12650794]

48. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. *Gastroenterology* 2004;126:1665–1673. [PubMed: 15188159]
49. Drossman DA, Morris CB, Schneck S, et al. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. *J Clin Gastroenterol* 2009;43:541–550. [PubMed: 19384249]
50. Haycox A, Einarson T, Eggleston A. The health economic impact of upper gastrointestinal symptoms in the general population: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl* 1999;231:38–47. [PubMed: 10565622]
51. Wallander MA, Johansson S, Ruigomez A, et al. Dyspepsia in general practice: incidence, risk factors, comorbidity and mortality. *Fam Pract* 2007;10:403–411. [PubMed: 17728288]
52. Jacobs EJ, White E. Constipation, laxative use, and colon cancer among middle-aged adults. *Epidemiology* 1998;9:385–391. [PubMed: 9647901]
53. Kune GA, Kune S, Field B, et al. The role of chronic constipation, diarrhea, and laxative use in the etiology of large-bowel cancer. Data from the Melbourne Colorectal Cancer Study. *Dis Colon Rectum* 1988;31:507–512. [PubMed: 3391059]
54. Vobecky J, Caro J, Devroede G. A case-control study of risk factors for large bowel carcinoma. *Cancer* 1983;51:1958–1963. [PubMed: 6831361]
55. Roberts MC, Millikan RC, Galanko JA, et al. Constipation, laxative use, and colon cancer in a North Carolina population. *Am J Gastroenterol* 2003;98:857–864. [PubMed: 12738468]
56. Watanabe T, Nakaya N, Kurashima K, et al. Constipation, laxative use and risk of colorectal cancer: The Miyagi Cohort Study. *Eur J Cancer* 2004;40:2109–2115. [PubMed: 15341986]
57. Von Blumenthal J, Choung R, Locke GR, et al. Differences between non-respondents and respondents in bowel disease surveys in Olmsted County residents. *Neurogastroenterol Motil* 2008;20:138.

Figure 1.
Overall observed vs. expected survival.

Figure 2.

(a) Overall survival for subjects with vs. without irritable bowel syndrome (IBS). (b) Overall survival for subjects with vs. without chronic constipation. (c) Overall survival for subjects with vs. without diarrhea. (d) Overall survival for subjects with vs. without dyspepsia. (e) Overall survival for subjects with vs. without abdominal pain.

Table 1
Mean age and frequency of gender, smoking, alcohol, education, and comorbidity by GI symptom

	IBS		Constipation		Diarrhea		Dyspepsia		Abdominal pain	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Total										
<i>N</i> = 3,933	397 (10.1%)	3,536 (89.9%)	622 (15.8%)	3,311 (84.2%)	694 (17.6%)	3,239 (82.4%)	68 (1.7%)	3,865 (98.3%)	596 (15.2%)	3,337 (84.8%)
Mean age ($\pm$ s.d.)	51 $\pm$ 18	55 $\pm$ 18	59 $\pm$ 20	53 $\pm$ 18	58 $\pm$ 18	53 $\pm$ 18	46 $\pm$ 14	54 $\pm$ 18	54 $\pm$ 18	52 $\pm$ 18
Male (<i>n</i> =1,913) (48.6%)	163 (41.1%)	1,750 (49.5%)	250 (40.2%)	1,663 (50.2%)	355 (51.2%)	1,558 (48.1%)	30 (44.1%)	1,883 (48.7%)	275 (46.1%)	1,638 (49.1%)
Smoking—yes (<i>n</i> =425)(10.8%)	62 (15.6%)	363 (10.3%)	71 (11.4%)	354 (10.7%)	80 (11.5%)	345 (10.6%)	14 (20.6%)	411 (10.6%)	62 (10.4%)	363 (10.9%)
<i>Education</i>										
College grad/post grad (<i>n</i> =1,238)(31.5%)	107 (27.0%)	1,131 (32.0%)	149 (24.0%)	1,089 (32.9%)	182 (26.2%)	1,056 (32.6%)	21 (30.9%)	1,217 (31.5%)	195 (32.7%)	1,043 (31.3%)
High school/ some college (<i>n</i> =2,172)(55.2%)	248 (62.5%)	1,924 (54.4%)	361 (58.0%)	1,811 (54.7%)	374 (53.9%)	1,798 (55.5%)	40 (58.8%)	2,132 (55.2%)	317 (53.2%)	1,855 (55.6%)
< High school (<i>n</i> =495)(12.6%)	39 (9.8%)	456 (12.9%)	103 (16.6%)	392 (11.8%)	132 (19.0%)	363 (11.2%)	7 (10.3%)	488 (12.6%)	79 (13.3%)	416 (12.5%)
<i>Alcohol</i>										
None (<i>n</i> =1,469) (37.4%)	153 (38.5%)	1,316 (37.2%)	315 (50.6%)	1,154 (34.8%)	298 (42.9%)	1,171 (36.2%)	18 (26.5%)	1,451 (37.5%)	229 (38.4%)	1,240 (37.2%)
1–6 Drinks/week (<i>n</i> =1,192)(30.3%)	128 (32.2%)	1,064 (30.1%)	197 (31.7%)	995 (30.0%)	216 (31.1%)	976 (30.1%)	10 (14.7%)	1,182 (30.6%)	135 (22.6%)	1,057 (31.7%)
$\geq$ 7 Drinks/week (<i>n</i> =395)(10.0%)	45 (11.3%)	350 (9.9%)	60 (9.6%)	335 (10.1%)	95 (13.7%)	300 (9.3%)	10 (14.7%)	385 (10.0%)	61 (10.2%)	334 (10.0%)
<i>Charlson index</i>										
0 (<i>n</i> =2,975) (75.6%)	308 (77.6%)	2,667 (75.4%)	434 (69.8%)	2,543 (76.8%)	493 (71.0%)	2,482 (76.6%)	53 (77.9%)	2,922 (75.6%)	435 (73.0%)	2,540 (76.1%)
1 (<i>n</i> =455)(11.6%)	43 (10.8%)	412 (11.7%)	76 (12.2%)	379 (11.4%)	82 (11.8%)	373 (11.5%)	9 (13.2%)	446 (11.5%)	80 (13.4%)	375 (11.2%)
$\geq$ 2 (<i>n</i> =503)(12.8%)	46 (11.6%)	457 (12.9%)	112 (18.0%)	389 (11.8%)	119 (17.2%)	384 (11.9%)	6 (8.8%)	497 (12.9%)	81 (13.6%)	422 (12.6%)

GI, gastrointestinal; IBS, irritable bowel syndrome.

Table 2

Survival hazard ratios by sociodemographic factor, co-morbidity, and GI symptom

	Hazard ratios (95% CI) ^a
Female	1.0 (ref)
Male	1.6 (0.15,1.8)
Age per 10 years	3.1 (2.9,3.3)
<i>Smoking</i>	
No	1.0 (ref)
Yes	1.7 (1.4,2.1)
<i>Education</i>	
< High school	1.0 (ref)
High school/some college	0.97 (0.8,1.1)
College grad/post grad	0.9 (0.7,1.0)
<i>Alcohol</i>	
None	1.1 (0.99,1.3)
1–6 Drinks/week	1.0 (ref)
≥7 Drinks/week	1.0 (0.8,1.3)
Charlson index	1.3 (1.2,1.3)
<i>IBS</i>	
No	1.0 (ref)
Yes	1.1 (0.9,1.3)
<i>Constipation</i>	
No	1.0 (ref)
Yes	1.2 (1.1,1.4)
<i>Diarrhea</i>	
No	1.0 (ref)
Yes	1.0 (0.9,1.2)
<i>Dyspepsia</i>	
No	1.0 (ref)
Yes	1.1 (1.5,1.8)
<i>Abdominal pain</i>	
No	1.0 (ref)
Yes	1.1 (0.9,1.3)

CI, confidence interval; GI, gastrointestinal; IBS, irritable bowel syndrome.

^aUnivariate hazard ratios adjusted for gender and age.

Table 3

Multiple variable cox proportional hazards models

	Multiple variable hazard ratios (95% CI) ^a				
	IBS	Constipation	Diarrhea	Dyspepsia	Abdominal pain
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.5 (1.3,1.7)	1.5 (1.3,1.7)	1.5 (1.3,1.7)	1.5 (1.3,1.7)	1.5 (1.3,1.7)
Age per 10 years	3.1 (2.8,3.3)	3.0 (2.8,3.3)	3.1 (2.8,3.3)	3.1 (2.8,3.3)	3.1 (2.8,3.3)
Smoking					
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.7 (1.3,2.0)	1.7 (1.3,2.0)	1.7 (1.3,2.0)	1.7 (1.3,2.0)	1.7 (1.3,2.0)
Education					
< High school	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
High school/some college	1.0 (0.9,1.2)	1.0 (0.9,1.2)	1.0 (0.9,1.2)	1.0 (0.9,1.2)	1.0 (0.9,1.2)
College grad/post grad	0.9 (0.7,1.1)	0.9 (0.7,1.0)	0.9 (0.7,1.1)	0.9 (0.7,1.1)	0.9 (0.7,1.1)
Alcohol					
None	1.2 (1.0,1.3)	1.1 (1.0,1.3)	1.1 (1.0,1.3)	1.1 (1.0,1.3)	1.1 (1.0,1.3)
1–6 Drinks/week	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
≥7 Drinks/week	1.1 (0.9,1.3)	1.1 (0.9,1.4)	1.1 (0.9,1.3)	1.1 (0.9,1.3)	1.1 (0.9,1.3)
Charlson index	1.3 (1.2,1.3)	1.3 (1.2,1.3)	1.3 (1.2,1.3)	1.3 (1.2,1.3)	1.3 (1.2,1.3)
FGID ^b					
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.9 (0.8,1.2)	1.2 (1.0,1.4)	1.1 (0.9,1.2)	1.0 (0.5,1.9)	1.1 (0.9,1.3)

CI, confidence interval; FGID, functional gastrointestinal disorder; IBS, irritable bowel syndrome.

^aHazard ratios from separate (each column) multiple variable proportional hazards models incorporating all variables in respective column.

^bFGID as defined by the respective disorder for each specific column.

Table 4
Causes of death by functional gastrointestinal disorder among the study cohorts from Olmsted County, MN

	IBS		Constipation		Diarrhea		Dyspepsia		Abdominal pain	
	Yes	None	Yes	None	Yes	None	Yes	None	Yes	None
Total, <i>n</i>	91	1,010	256	845	243	858	10	1091	148	953
Cancer, <i>n</i> (%)	15 (16.5%)	165 (16.3%)	36 (14.1%)	144 (17.0%)	35 (14.4%)	145 (16.9%)	3 (30.0%)	177 (16.2%)	26 (17.6%)	154 (16.2%)
Central nervous system, <i>n</i> (%)	11 (12.1%)	144 (14.3%)	39 (15.2%)	116 (13.7%)	32 (13.2%)	123 (14.3%)	1 (10.0%)	154 (14.1%)	22 (14.9%)	133 (14.0%)
Cardiovascular, <i>n</i> (%)	19 (20.9%)	264 (26.1%)	65 (25.4%)	218 (25.8%)	69 (28.4%)	214 (24.9%)	2 (20.0%)	281 (25.8%)	41 (27.7%)	242 (25.4%)
Respiratory, <i>n</i> (%)	24 (26.4%)	219 (21.7%)	60 (23.4%)	183 (21.7%)	53 (21.8%)	190 (22.1%)	3 (30.0%)	240 (22.0%)	29 (19.6%)	214 (22.5%)
Miscellaneous, <i>n</i> (%)	18 (19.8%)	149 (14.8%)	38 (14.8%)	129 (15.3%)	42 (17.3%)	125 (14.6%)	0 (0%)	167 (15.3%)	21 (14.2%)	146 (15.3%)
Unknown, <i>n</i> (%)	4 (4.4%)	69 (6.8%)	18 (7.0%)	55 (6.5%)	12 (4.9%)	61 (7.1%)	1 (10.0%)	72 (6.6%)	9 (6.1%)	64 (6.7%)

IBS, irritable bowel syndrome.

Table 5
Gastrointestinal cancers by functional gastrointestinal disorder in the study population

	IBS, <i>n</i> ^a (%)			Constipation, <i>n</i> ^a (%)			Diarrhea, <i>n</i> ^a (%)			Dyspepsia, <i>n</i> ^a (%)			Abdominal pain, <i>n</i> ^a (%)		
	Yes	None		Yes	None		Yes	None		Yes	None		Yes	None	
Esophageal/EGJ/ gastric, <i>n</i> (%)	0	8 (14.8%)		1 (10.0%)	7 (15.2%)		2 (20.0%)	6 (13.0%)		0	8 (14.6%)		1 (11.1%)	7 (14.9%)	
Anal/rectal/colon, <i>n</i> (%)	1 (50.0%)	21 (38.9%)		6 (60.0%)	16 (34.8%)		3 (30.0%)	19 (41.3%)		0	22 (40.0%)		5 (55.6%)	17 (36.2%)	
Liver/biliary/ gallbladder, <i>n</i> (%)	0	6 (11.1%)		0	6 (13.0%)		2 (20.0%)	4 (8.7%)		0	6 (10.9%)		0	6 (12.8%)	
Ampullary/ duodenal, <i>n</i> (%)	0	1 (1.9%)		0	1 (2.2%)		0	1 (2.2%)		0	1 (1.8%)		0	1 (2.1%)	
Pancreas/ neuroendocrine, <i>n</i> (%)	1 (50.0%)	16 (29.6%)		2 (20.0%)	15 (32.6%)		3 (30.0%)	14 (30.4%)		1 (100%)	16 (29.1%)		3 (33.3%)	14 (29.8%)	
Oral, <i>n</i> (%)	0	2 (3.7%)		1 (10.0%)	1 (2.2%)		0	2 (4.4%)		0	2 (3.6%)		0	2 (4.3%)	

EGJ, esophagogastric junction; IBS, irritable bowel syndrome.

^a *n*, number of deaths of indicated types (percentage of column total deaths).