Published in final edited form as:
Clin Gastroenterol Hepatol. 2013 September ; 11(9): 1147–1157. doi:10.1016/j.cgh.2013.03.011.

Type, Rather than Number, of Mental and Physical Comorbidities Increases the Severity of Symptoms in Patients with Irritable Bowel Syndrome

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Abstract

BACKGROUND—Irritable bowel syndrome (IBS) has significant mental and physical comorbidities. However, little is known about the day-to-day burden these comorbidities place on quality of life (QOL), physical and mental function, distress, and symptoms of patients.

METHODS—We collected cross sectional data from 175 patients with IBS, diagnosed based on Rome III criteria (median age, 41 y; 78% women), referred to 2 specialty care clinics. Patients completed psychiatric interviews, a physical comorbidity checklist, the IBS symptom severity scale, the IBS quality of life instrument, the brief symptom inventory, the abdominal pain intensity scale, and the SF-12 health survey.

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Disclosures: None to report

Specific author contributions: Jeffrey Lackner participated in study design, data collection, data analysis, and manuscript preparation; Chang-Xing Ma study design, data analysis and manuscript preparation; Gregory Gudleski data analysis and manuscript preparation, Rebecca Firth, data collection and manuscript preparation, Nikhil Satchidanand, data analysis and manuscript preparation, Laurie Keefer, manuscript preparation and data collection, Darren Brenner, manuscript preparation and data collection, Leonard Katz, data collection and manuscript preparation, Michael Sitrin, data collection and manuscript preparation, Susan Krasner, data collection, Sarah K. Ballou, data collection; Bruce Naliboff, manuscript preparation; Emeran Mayer, manuscript preparation

RESULTS—Patients with IBS reported an average of 5 comorbidities (1 mental, 4 physical). Subjects with more comorbidities reported worse QOL after adjusting for confounding variables. Multiple linear regression analyses indicated that comorbidity type was more consistently and strongly associated with illness burden indicators than disease counts. Of 10, 296 possible physical–mental comorbidity pairs, 6 of the 10 most frequent dyads involved specific conditions (generalized anxiety, depression, back pain, agoraphobia, tension headache, insomnia). These combinations were consistently associated with greater illness and symptom burdens (QOL, mental and physical function, distress, more severe symptoms of IBS, pain).

CONCLUSIONS—Comorbidities are common among patients with IBS. They are associated with distress and reduced QOL. Specific comorbidities are associated with more severe symptoms of IBS.

Keywords

Chronic disease; health related quality of life; comorbidity; transdiagnostic; stress; IBSQOL

Introduction

Irritable bowel syndrome (IBS) is a chronic, often disabling gastrointestinal (GI) disorder characterized by abdominal pain associated with an alteration in bowel habits (diarrhea, constipation, or both in an alternating pattern). In addition to its core GI symptoms, IBS is associated with mental and physical comorbidity (1). While comorbidity lacks an universally accepted definition, it is often operationalized as the co-occurrence of one of more (mental or physical) conditions in the same person with an index disease of interest (e.g., IBS) (2–4). Comorbidity differs from multimorbidity which refers to the co-occurrence of two more chronic medical conditions in one person where one is not necessarily more central than the others (e.g., IBS and low back pain). Comorbidity is important because it may delay accurate diagnosis, influence clinical decision making, confound analyses and interpretability of research findings, undermine the patient-physician relationship, complicate patient presentation of chief complaints, and shed light on common biobehavioral mechanisms underlying multiple disorders

Comorbidity is the rule not the exception in IBS. Up to two-thirds of IBS patients report non-GI symptoms compared to less than 15% of healthy individuals (5). Some comorbid physical disorders include a cluster of benign medical syndromes such as interstitial cystitis, chronic pelvic pain, migraine and/or tension headaches, and fibromyalgia that are disproportionately associated with IBS (6). Others include more well-defined physical illnesses such as hypertension and arthritis (6, 7). IBS is associated with significant mental comorbidity as well. In studies (8) that have administered structured clinical interviews to establish the rate of psychiatric comorbidity per criteria as specified in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM, 9), approximately 60% of treatments seeking IBS patients have a diagnosable psychiatric condition (10) with generalized anxiety disorder and depression the most common disorders. By comparison, approximately 25% of American adults suffers from a diagnosable mental disorder (11, 12).

Few studies have considered the burden comorbidity imposes on IBS patients. Levy et al. (13) studied the economic burden of IBS in patients seen in a HMO and found that the majority of healthcare charges are for non-GI medical conditions. Other research teams (14, 15) found a relationship between health care use and coexisting physical complaints. It is unclear how physical or mental comorbidity contributes to the illness or symptom burden of IBS patients. Symptom burden refers to the magnitude of symptoms that are core parts of the patient's target illness (e.g. more intense abdominal pain for IBS patients). Illness burden

refers to the personal toll (i.e. impact) symptoms exact on patients' lives in terms of quality of life [QOL], physical and mental functioning, and distress. Based on research with other disease populations (16), we would predict that physical comorbidities have strongest impact on physical aspects of QOL (e.g., functional impairment) of IBS patients, while psychiatric comorbidities have strongest impact on psychological aspects of QOL (mental well-being).

Beyond their possible independent effects, we are interested in any burden due to the combination of mental and physical comorbidities. After all, mental and physical illnesses do not occur in isolation. They co-occur at greater than chance levels in the general population (17) and their co-occurrence is associated with elevated symptom burden, functional disability, decreased quality of life, and use of health care services and costs (12). We reasoned that this pattern of data extends to a problem like IBS. Furthermore, we expected that the joint effects of mental and physical comorbidities would be greater than their individual effects. A third goal was to determine which type of diagnosed comorbidities (e.g., fibromyalgia, depression), either separately or in combination, are associated with the greatest illness/symptom burden. The broader comorbidity literature indicates that specific pairs of comorbid illnesses can lead to worsening health problems(18). Specifying the combinations of conditions that impose the greatest burden "is very important for individual patient care" (p. 46, 18) because it can clarify factors that contribute to and maintain comorbidity, target patients for whom disease specific treatments may be insufficient, and guide the development of more robust disease management interventions that, in the absence of a cure, help patients gain control of the day to day burden of IBS. Drawing from earlier research (6, 19–21), we expected that a cluster of physical and mental disorders that occur more frequently in IBS patients (interstitial cystitis, headache, generalized anxiety disorder, major depression, pelvic pain, fibromyalgia, chronic fatigue syndrome) would be more strongly associated with illness and symptom burden in more severe IBS patients.

Materials and Methods

Participants

Participants included 175 individuals between the ages of 18 and 70 (inclusive) years who were recruited to an NIH funded behavioral trial through a variety of sources including from specialists (e.g., gastroenterology) and primary care physicians, media coverage and advertisements in local media. Individuals who passed a brief telephone screening were scheduled for formal medical and psychological evaluations to determine their standing on eligibility criteria. Inclusion criteria included Rome III IBS diagnosis (22) confirmed during a medical examination by a board certified gastroenterologist; IBS symptoms (ie, pain and defecatory symptoms) of at least moderate severity (occur an average of two or more days per week with life interfernece, e.g., 23, 24); ability to provide written consent; and a minimum 6^{th} grade reading level. Exclusion criteria were: presence of a comorbid organic GI disease (e.g., IBD) that would adequately explain GI symptoms; mental retardation; current or past diagnosis of schizophrenia or other psychotic disorders; current diagnosis of unipolar depression with suicidal ideation; current diagnosis of psychoactive substance abuse. Patients' predominant bowel habit was determined after medical examination using Rome III guidelines (22) and clinical impression: 43% were diarrhea-predominant; 26% constipation-predominant, and 31% were alternating or mixed. Additional demographic data are presented in Table 1.

Procedure

As part of screening procedure, respondents underwent psychological testing which for the purposes of this study included the test battery described below. Informed consent was obtained at both institutions from all subjects before participation. This study was carried out as part of the Irritable Bowel Syndrome Outcome Study (IBSOS), an NIH funded multisite clinical trial the details of which can be found elsewhere (25). The testing battery and the experimental procedures of the study were approved by the Health Sciences IRBs of both clinical sites of the IBSOS (University at Buffalo, Northwestern University). Subjects were compensated $50 for completing baseline assessment battery from which data for the current study were obtained.

Measures

Physical Comorbidity—Physical comorbidity was assessed using a modified version of the survey used in the National Health Interview Survey (NHIS) to record the recency of commonly occurring chronic conditions believed to be associated with substantial quality of life impairment (26). We have adapted the NHIS checklist to characterize physical comorbidity of IBS patients in three NIH funded clinical trials (27). The current version (28) has been expanded to cover 112 medical conditions organized around 12 body systems: musculoskeletal (e.g., diagnosis of low back pain, FMS), digestive (e.g., functional dyspepsia), kidney/genitourinary (e.g., interstitial cystitis), endocrine (e.g., diabetes), respiratory (e.g., asthma), circulatory (e.g., mitral valve prolapse), cardiovascular (e.g., hyperlipidemia), oral (e.g. bruxism), CNS (e.g., tension headache), dermatological (e.g., recurrent skin rash), Ear Nose, Throat [ENT, e.g., insomnia], cancer. Respondents were asked whether a doctor had ever diagnosed them with a specific condition and, if so, whether the assigned diagnosis (vs. symptom) was present in the past 3 months. To reduce potential reporting bias (29), persons were counted as current cases if the lifetime medically diagnosed condition was present in the last 3 months. If the subject was diagnosed with a lifetime medical condition that s/he described as “absent” during the 3 months prior to testing, it was not counted as a current medical comorbidity. Establishing the content validity of items of the comorbid physical condition checklist involved assembling a panel of experts who reviewed the frequency of comorbid physical conditions reported in the literature (e.g. (1, 6, 30), those believed to occur frequently in IBS patients, and those regarded as most important in existing comorbidity measures (31). Our goal was to refine a psychometrically sound measure whose items described more appropriately and comprehensively comorbidity in IBS than existing comorbidity measures (e.g., Charlson Comorbidity Index) that were validated on the basis of their ability to predict an outcome (mortality) of questionable clinical relevance for a benign medical condition like IBS. For physical and psychiatric comorbidity, we generated two unweighted scores for each patient: the total number of conditions and the number of categories endorsed (e.g., anxiety disorders, respiratory diseases). Data derived from similar checklists of physical conditions has been found to correspond with information obtained from medical records (32–34). Because self-reported physical conditions better predict quality of life and functional status than data from medical records (35), it was deemed as preferable to information collected though alternative sources (medical records, insurance claims) for a study seeking to establish the illness/symptom burden of comorbidity. The physical conditions were simplified to language that respondents without any prior medical background could understand. The questionnaire was pilot tested with 10 subjects to ensure clarity and comprehension.

Mental Comorbidity—Mental comorbidity was assessed by trained health psychologists who administered the computerized version of the MINI International Neuropsychiatric Interview (MINI). The MINI (36) is a fully structured diagnostic interview that generates

psychiatric diagnoses according to the fourth edition of the DSM (9). The version of the MINI developed for the IBSOS included disorders covering 6 classes of conditions: anxiety disorders (panic, agoraphobia, generalized anxiety disorder, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder), mood disorders (e.g., major depressive disorder, dysthymic disorder), substance use disorders (alcohol and drug abuse with or without dependence); somatization disorders (e.g. hypochondriasis, pain disorder), anxiety-depression, and antisocial personality disorder.

IBS Symptom Severity—The Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS, 37) is a 5-item instrument used to measure severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference with quality of life on a 100-point scale. The five items are summed with the total scores ranging 0 to 500 with higher scores signifying more severe symptoms.

Global Distress—Psychological distress was assessed using the 18-item version of the Brief Symptom Inventory (38). The BSI-18 requires respondents to indicate on a five-point scale (0 = not at all, 4 = extremely) their level of distress of 18 somatic and psychological symptoms for three types of problems (e.g., anxiety, somatization, depression). The average intensity of all items yields a composite index of psychological distress (Global Severity Index [GSI]). The GSI has been used extensively to measure psychological distress in patients with IBS (39).

IBS–specific Quality of Life—The IBS-QOL (40) is a 34-item measure constructed specifically to assess the perceived impact of IBS on quality of life in eight domains (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual dysfunction, and relationships). Each item is scored on a five-point scale (1 = not at all, 5 = a great deal). Items are scored to derive an overall total score of IBS related quality of life ranging from zero (poor quality of life) to 100 (maximum quality of life).

Health Related Quality of Life (HRQOL)—The 12-item Short Form or SF-12 SF-12(41) is a generic HRQOL measure based on the SF-36. The SF-12 captures approximately 90% of the variance of the SF-36(42). The SF-12 provides two summary indices of HRQOL: the Physical Component Summary (PCS) and Mental Component Summary (MCS). Scores on both summary scales have a range of 0 to 100 (M =50, SD = 10) with higher scores indicating better QOL.

Abdominal Pain—Abdominal pain intensity was measured with an 11-point pain intensity numerical rating scale, where 0=no pain and 10=worst possible pain (43). Patients circled the number from 0–11 that best described their average abdominal intensity over the past 7 days.

Data Analyses Plan

Data analysis was carried out in 3 steps. The first step was to characterize the nature and pattern of mental and physical comorbidities of IBS patients using means, standard deviations or percentages. At the second step, we conducted partial correlations and linear regressions to estimate the joint relationships between the physical and/or mental comorbidity counts and indicators of illness/symptom burden (quality of life, physical functioning, mental well-being, abdominal pain, IBS symptom severity) after adjusting for potentially confounding variables including age, gender, education, income, marital status, IBS subtype, and duration of symptoms. At this stage, regression (beta) coefficients from linear regression were used to estimate any unit increase in illness/symptom burden indicators that corresponded with every additional number of comorbidities after adjusting

for control variables. The third step involved a series of linear regression analyses to determine whether any specific mental and/or physical diagnostic types were associated with greater illness/symptom burden after holding constant control variables. The first regression examined the association between specific comorbidity types (i.e., top 10 most frequent single comorbidities) and each dependent variable. A second set of regressions examined the association between the top 10 comorbidity pairs (dyads) and burden variables. Given a small anticipated Cohen's effect size (f^2=0.10) and 10 predictors per regression, the study required a sample size of 172 subjects to reach 80% of power under alpha=0.05. All calculations were carried out using SAS 9.3 (Cary, NC).

Results

Sample Characteristics

Table 1 presents the clinical characteristic of the sample which was mostly female, socioeconomically diverse, White, educated and chronically ill (average duration of IBS symptoms = 16.5 years). The mean raw BSI-GSI (distress) score for the sample (14) corresponds to T scores (Mean = 50, SD = 10) of 58 (Female) and 61 (Male). A mean total IBS-SSS score of 284 for the sample falls within high-moderate level of symptom severity (IBS-SSS total score of 300 = severe, 37). Summary scores of SF 12 were 41 and 44 for the PCS and MCS, respectively, and fall within "impaired" (44) ranges of mental and physical functioning for IBS patients. Patients with a mean of 56 on the IBSQOL are regarded as having significant QOL impairment due to IBS (45).

Nature and pattern of comorbidity

Comorbidity was very common in the sample. Nearly all subjects (91%) reported at least one comorbid physical or psychiatric illness. As a group, IBS patients had an average of 1 concurrent psychiatric condition and 4 concurrent physical conditions. With respect to mental conditions, 47% had at least one comorbid mental illness. Twenty one percent had one concurrent mental condition and 26% had 2 or more mental conditions. Of patients who met diagnostic criteria for a mental disorder, the two most common classes were anxiety disorders (69%) followed by affective disorders (38%). Generalized anxiety disorder was the most frequently diagnosed mental comorbidity with 32% of the sample meeting DSM-IV criteria. Within the affective disorders, the most common diagnosis was major depressive disorder (MDD; 22%). With respect to physical comorbidities, 31% reported 0–1 physical comorbidities (0 = 9%); 25% reported 2–3 physical comorbidities; and 44% reported 4 or more physical comorbidities. The most common (50% or more) class of disorders was: ENT (66%), respiratory (59%), musculoskeletal (59%), digestive (58%), kidney (57%). The 10 most common self-reported physical disorders were allergy (32%), gastroesophageal reflux (GERD, 23.4%), low back pain (20%), insomnia (19%), migraine (16%), sinusitis (14%), tension headache (13%), bruxism (10%), low sexual desire (11%), and hyperlipidemia (10%).

Collapsing mental and physical disorders into one comorbidity category, the 10 most common comorbid conditions were allergy, GAD, GERD, major depression, low back pain, insomnia, migraine, sinusitis, tension headache, and agoraphobia. We also conducted a series of analyses to determine specific disease combinations occurring in the IBS patients. This required us to create a new variable for each possible dyad. For example, a patient received a value of 1 if they were diagnosed with the dyad of LBP and GAD and 0 if they did not receive both of these diagnoses. We then computed the frequency for this and every other possible disease pairs. With 144 comorbid conditions, there were 10,296 possible combinations of any two conditions and 487,344 possible combinations of any three

conditions. We developed a scoring algorithm that ran a loop through all possible disease combinations and tabulated their frequency.

The 10 most frequent disease pairs (dyads) all derived from the most common single diagnoses: depression-GAD (14.86%), allergy-GERD (14.29%), insomnia-depression (9.71%), insomnia-GAD (10.86%), low back pain-MDD (9.71%), sinusitis-allergy (9.14%), low back pain-GAD (9.14%), insomnia–allergy (17%), allergy-low back pain (8.57%); allergy-GAD (8%).

Associations between the number of comorbidities and illness/symptom burden

Table 2 displays partial correlations among comorbidity counts (number of physical comorbidities and/or mental comorbidities) after adjusting for control variables. The total numbers of physical and mental comorbidities were modestly intercorrelated ($r = .17$, $p < .05$). Both physical and mental comorbidity counts were associated with IBSQOL (physical, $r = -.28$; mental, $r = -.30$) and overall distress (physical, $r = -.21$; mental, $r = -.64$). That is, individuals diagnosed with more physical and mental disorders had worse quality of life impairment and were more psychologically distressed than IBS patient with fewer physical and mental disorders. Neither physical nor mental comorbidity counts significantly correlated with global IBS symptom severity or average pain intensity. Number of physical comorbidities was associated with physical (PCS, −.41) but not mental (MCS) aspect of QOL. Number of mental comorbidities correlated with both mental (MCS) and physical (PCS) aspect of HRQOL but the magnitude of the association was stronger for MCS (−.45 vs. −.23).

We also conducted a series of linear regression to gauge the incremental change in illness/symptom burden (e.g., QOL) that corresponds with an increase in the number of comorbidities. For every additional physical comorbidity, there was an unit decrease of 0.92 on the IBSQOL ($p < .01$) and a 0.76 on the PCS ($p < .01$) when all confounding variables and number of mental comorbidities were controlled. Every additional mental comorbidity corresponded with unit decreases of 3.01 point on the IBSQOL ($p < .001$) and 1.04 on the PCS, 2.91 ($p < .01$) on the MCS ($p < .01$), and an unit increase of 4.40 points on the GSI ($p < .001$). In other words, quality of life impairment on both the IBSQOL and the SF 12 linearly decreased with every additional mental or physical diagnosis. The pattern of correlations between overall count of physical and mental comorbidities and illness burden indicators was identical to correlations with number of mental comorbidities.

Associations between single comorbidities and illness/symptom burden

To test the hypothesis that illness/symptom burden is a function of specific comorbidities, a series of multiple linear regression analyses were performed for each of the 10 most frequent comorbidities. Potentially confounding variables were entered first followed by diagnoses. Results of regression analyses supported the research hypothesis that type of comorbidity corresponded with illness/symptom burden for 5 (generalized anxiety disorder, major depression, low back pain, tension headaches, and agoraphobia) of 10 diagnoses. Four of the 10 most common comorbid conditions (sinusitis, GERD, migraine, allergy) were unrelated to any of the illness indicators. Table 3 shows the regression coefficients for each independent variable and corresponding p-values for each comorbidity; the order of comorbidities (single, pair) are presented in descending order of the size of the regression coefficients the IBS-SSS. The size of the coefficient reflects the strength of the effect (i.e. effect size) that the independent variable is having on the dependent variable, and the sign on the coefficient (positive or negative) reflects the direction of the effect. The size of the coefficients for each of the variables indicate how much the dependent variable is predicted to increase (if the coefficient is positive) or decrease (if the coefficient is negative) when the

independent variable increases by one unit (i.e., comorbidity type diagnosed vs. undiagnosed) given that all other variables in the model are held constant. To illustrate, patients with GAD had an IBS-SSS score that was, on average, 35 points higher than those without GAD. For QOL, patients diagnosed with GAD had scores that were, on average, 11.55 and 13 points lower on the MCS and IBSQOL, respectively, than patients without a GAD diagnosis after adjusting for control variables. A similar pattern of data held for patients diagnosed with either low back pain or major depression on scores for the IBSQOL. After holding constant control variables, subjects with low back pain had IBS-SSS scores that were 58.81 points higher than patients who were not diagnosed with LBP. Inspection of the regression coefficients indicates that low back pain, MDD, and agoraphobia were associated with the physical aspect of QOL (PCS). For example, patients with MDD had PCS scores that were 6 points lower in the direction of worse QOL than patients without an MDD diagnosis. The highest coefficient values on the PCS were low back pain (−9) and agoraphobia (−8). The lowest significant values were for tension headache and insomnia (−3).

Associations between comorbidity pairs and illness/symptom burden

Similar analyses were run for disease pairs to determine whether their illness/symptom burden was greater than what we observed from single comorbidities. Two dyads (MDD-GAD, LBP-GAD) were significantly associated with all six burden indicators. These patients had more severe IBS symptoms, worse physical (PCS) and mental (MCS) functioning, poorer IBS-specific QOL, more intense abdominal pain, and increased psychological distress (BSI) than patients who were undiagnosed with these comorbid pairs. Two dyads (insomnia-GAD, LBP-MDD) correlated with all burden indicators but abdominal pain intensity. A dyad with consistently large effect sizes was LBP-MDD. For these patients, scores were expected to decrease by 22 points on the IBS QOL, 10.24 on the PCS, 11.76 on the MCS, and increase by 20.61 points on the BSI in comparison to patients who are not diagnosed with MDD and LBP.

For the IBS-SSS, the regression coefficient was 89.67. This means that a patient diagnosed with MDD-LBP had an IBS-SSS score that is, on average, 89.67 units higher than a patient undiagnosed with MDD and LBP. This is a dramatic increase. For a scale whose sample mean is 284 with SD of 76.53, a regression coefficient of 89.67 means that LBP-MDD increases IBS symptom severity by 1.2 times the SD. Inspection of the regression coefficients for the IBS-SSS indicates wide variability in effect sizes for dyads that share a common disease. For example, the coefficients for IBS-SSS for the MDD-LBP dyad were approximately 3 times as large as the coefficient for MDD-insomnia (89 vs. 29). Similarly, the coefficient for IBS-SSS for LBP-GAD was 1.5 times the size of the regression coefficient for GAD-MDD (78 vs. 49.90). In general, comorbidity dyads that included LBP had particularly large effect sizes for IBS symptom severity (IBS-SSS).

Discussion

This study sought to explore the nature and pattern of physical and mental comorbidities and their association with indicators of illness and symptom burden in more severely affected IBS patients. Both mental and physical comorbidity were quite common with IBS patients reporting an average of 5 comorbid conditions (1 mental, 4 physical conditions) at the time of assessment. To put these data in context, approximately 10% of general primary care patients in the United States have three or more co-occurring mental and physical conditions, irrespective of the “index” disease (46). The rate of comorbidity among IBS patients remains high (91%) even when compared to patients diagnosed with a complex disease like Type II diabetes (55%, 47).

The comprehensiveness of our comorbidity assessment battery is a strength of this study and was designed to improve upon previous comorbidity research that has typically focused on either concurrent physical (48) or mental (49) conditions. By systematically assessing concurrent mental and physical comorbidities, we sought to paint a more complete clinical picture that reflects the real world complexity of the IBS patient. We found a "dose response" relationship between the number of comorbidities and quality of life impairment, distress, and reduced physical and mental functioning. Patients reporting more comorbid conditions scored lower on QOL measures and suffered worse physical and mental functioning than those with fewer comorbid conditions. These data obtained in our IBS sample echo the findings of other researchers who have observed dose-response relationship between comorbidity counts and negative health outcomes (e.g., QOL, role impairment) in other chronic diseases including asthma, cancer, and multiple sclerosis (50–53). Consistent with other researchers (51), the number of physical comorbidities was, as we predicted, more strongly associated with the physical aspects of QOL, while the number of mental comorbidities was more strongly correlated with mental aspects of QOL. The number of comorbidities was unrelated to either the intensity of abdominal pain or global severity of IBS symptoms.

One interpretation of these cross sectional data is that comorbidities heightens the impact of symptoms (e.g. quality of life) but not their intensity (e.g., worse abdominal pain). Other aspects of our data caution us against accepting this conclusion. Specific types of comorbid conditions were consistently related to more burden variables than simple disease counts. As noted above, low back pain (LBP) correlated with the same illness burden indicators (worse quality of life) as total number of comorbidities as well as the two symptom burden variables (global IBS symptom severity, abdominal pain intensity). A similar pattern of data applied to MDD and GAD with the exception that their relationships with abdominal pain intensity were nonsignificant (GAD, $p = .051$). Importantly, the frequency of a comorbid disease did not necessarily correspond with its burdensomeness. GAD and allergy were the two most common comorbid diseases each reported by 32% of the sample. Allergy was unrelated to any outcome, while GAD correlated with four of the six indicators of illness/symptom burden. Three other common comorbidities (GERD, sinusitis, migraines) were unrelated to any burden indicators. These findings strongly suggest that the type of reported comorbidities, rather than their number, may be a more useful way of gauging the comorbidity's impact on the affected patient.

Clinical Implications

Our data have other important clinical implications. Managing IBS is challenging given the limited availability of medications for the full range of symptoms, the complexity of patients, and uncertain pathophysiology. Because IBS is a benign disorder whose symptoms lack a reliable biomarker, goals for treatment are to optimize quality of life, well-being, and function. Gastroenterologists strive to achieve these goals by providing symptomatic relief through therapies such as laxatives, antidepressants, antispasmodics, analgesics, bulking agents, and the newer class of secretory agents (lubiprostone, linaclotide). While these agents are useful for some patients, in particular for those with altered bowel habits, they fall short of therapeutic objectives for many patients. Our data suggest that the improved quality of life that eludes IBS patients may not simply be due to the efficacy profile of existing therapies but may be relate to the symptom burden of non-GI comorbidities. These data are in line with the work of Spiegel et al. (54) who found that extraintestinal symptoms such as fatigue, sexual desire and sleep disturbance were consistent predictors of mental and physical aspects of QOL. Building on these findings, our data suggest that the impact of physical-mental comorbidities is not limited to generic QOL but extends to disease-specific domains such as the severity of IBS symptoms and IBS-quality of life impairment

(IBSQOL). One of the most dramatic examples comes from regression data showing that IBS patients with comorbid LBP have a 58 point increase in the IBS-SSS and a 14 point decrease in the IBSQOL compared to patients without LBP. To put these data in perspective, the size of the regression coefficients for these scales (IBS-SSS- 58; IBSQOL – 14.28) is nearly identical to the amount of unit change that represents a clinical significant therapeutic change [(IBS-SSS=50, 37); (IBSQOL=14, 55)]. In effect, an FDA approved IBS drug needs to be twice as effective merely to offset the increased severity of IBS symptoms and quality of life impairment that comes with comorbid low back pain in patients seen in routine clinical settings. This is a tall order and underscores the hardship that comorbidity imposes on physicians in their efforts to provide patients relief of IBS symptoms in routine settings where - unlike clinical trials where novel agents are validated -- co-existing conditions are not systematically excluded. These challenges create opportunities for improving quality of care. These include understanding increasing clinical sensitivity to the nature and patterns of comorbidities, targeting shared processes common across multiple disorders, and developing, when necessary, integrated treatments that harness the clinical efficacy of biological therapies with evidence based behavioral ones (56) that teach patients to make the lifestyle changes necessary to control and reduce symptoms unresponsive to conventional medical or dietary treatments. For these changes to occur, it will be important to recognize that conventional modes of practice based on disease-specific protocols may be better suited for individuals with a well-defined disorder and little comorbidities (57) than those with complex and overlapping symptom profiles characteristic of IBS patients in our sample.

Identifying specific comorbidity clusters that are most burdensome for IBS patients is a novel aspect of this study. This is important because the broader research indicates that the magnitude and nature of illness burden (e.g., impairment) oftentimes depends on the specific combinations of conditions patients experience (18). In other words, certain pairs of conditions have unusually large and specific effects on illness/symptom burden. Identifying clinically relevant disease pairs has been a methodological and logistical challenge. First, pre-determined disease pairs drawn from one sample may not necessarily apply to a different target sample and may exclude some diseases that are frequent and burdensome. Second, an *a priori* selection method of comorbidity clusters relies heavily on subjective judgment about what makes a comorbid condition clinically meaningful a question for which there are at least in the case of IBS few answers. Third, manually identifying all theoretically possible disease pairs is an exhaustive and cumbersomeness process (58) that risks arriving at a chance statistical finding (i.e., Type I error). For these reasons, we developed a novel scoring algorithm for identifying comorbid disease pairs. With over 10,000 theoretically possible disease pairs, six of the 10 most common comorbidities (GAD, MDD, low back pain, insomnia, tension headache, agoraphobia) formed dyads that were consistently related to illness/symptom burden. A particularly pernicious dyad involved back pain and GAD which was associated with poorer mental and physical functioning, distress, worse intense abdominal pain and quality of life, and more severe IBS symptoms. These findings are an important first step in addressing the clinically important question of “How do physical and mental comorbidities jointly impact IBS patients”? Answers to this and other questions are fundamental to improving the quality and efficacy of care of a vulnerable and growing population for whom disorder-specific treatments may not be enough.

Future Directions

With the significant relationships between comorbidities and burden variables involving a set of 6 diseases, we are not inclined to think that the comorbidity clusters are randomly distributed (59). As such, their configuration may shed light on broad biobehavioral mechanisms responsible for the co-occurrence of mental and physical illnesses in IBS.

Clarifying how a common set of factors that cuts across diagnostic boundaries (i.e., transdiagnostic) influence the multiple symptoms of different disorders (e.g., IBS, insomnia) and how symptoms of specific disorders (e.g., LBP, IBS) emerge from a core set of vulnerability factors can help identify what patients are at greatest risk for negative outcome and how best to treat them. One example: of the most common physical comorbidities, comorbid LBP was associated with greater illness/symptom burden than two other pain disorders (GERD, migraine). Because IBS patients who have coexisting conditions are believed to have widespread pain sensitivity (21), we expected more consistency in illness/symptom burden across pain disorders that are highly comorbid with IBS. These observations suggest that certain comorbidities may have similar and synergistic alterations in pain producing mechanisms with IBS and therefore their presence has significant consequences for the clinical presentation and potentially treatment response of affected patients. In the case of LBP and IBS comorbidity, several potential overlapping mechanisms have been suggested including viscerosomatic conversion of afferent inputs at the spinal level, an interplay between somatic muscle tension and visceral organ sensitivity, and common alterations in central pain and affective processing (60). More generally the results of this study are consistent with an emerging model of common brain mechanisms underlying most chronic pain conditions and the high degree of co-occurrence of anatomically diverse pain and other somatic conditions and psychological symptoms(61–64).

Consistent with this emerging model, an examination of the most burdensome illnesses (i.e., MDD, GAD, LBP, insomnia) from the current data suggests that the concept of central sensitization likely plays, as Whitehead et al (6) have suggested, an important role in disorders highly comorbid with IBS. The way patients with all these disorders process information involves a tendency to worry intensely and think repetitively about upsetting problems (e.g., symptoms), their causes and consequences. From an information processing perspective (65, 66), rumination-worry causes thinking errors that overestimates the probability of a negative event occurring (“What if….?”) and the costs and consequences of a negative event that has occurred (“If only …”). This biased pattern of thinking not only can influences brain-gut interactions (67, 68) but has been identified as the core etiological factor that accounts for the extensive co-occurrence of the two most frequent mental comorbidities in IBS patients (anxiety and depression, 69). Worry-rumination is also a pathogenic factor implicated in stress-related physical health problems including upper respiratory infections, chronic pain, cardiovascular disease, immune system impairment (e.g., 70, 71, 72). Because excessive worry-rumination is particularly common in the most burdensome physical comorbidities (e.g., insomnia, LBP) in our patients (73–76), it may be a mechanism underlying their physical comorbidity. Biologically, ruminating about a stressor can sustain a state of physiological arousal long enough to mount an allostatic response (77, 78) well after (and before) a stressful event has ended (or begun). Because ruminative processes stretch the temporal boundaries of an acute stressor, they lengthen the *duration* of stress exposure which is regarded as a more “toxic” ingredient of the stress response than the *magnitude* of the acute response (77, 79, 80). In effect, rumination helps create the necessary conditions (prolonged arousal) under which stress influences physical health problems (81, 82). The extent to which rumination-worry mediates at least part of the effects of chronic stress on IBS symptoms and physical-mental comorbidity is an important avenue for future study.

Limitations

Results should be interpreted in light of study limitations. Because our data are cross sectional, we do not intend to suggest that the findings demonstrate causal relationships among mental-physical comorbidity and illness/symptom burden indicators. At best, our

data can be construed as suggestive of a possible causal relationship that could be confirmed through longitudinal analyses with a larger sample. While our measures satisfy accepted standards for psychometric soundness, data is based on self-report which means they are subject to some bias and measurement error. It is possible that patients may have underreported the presence of certain conditions particularly those that are present but a health care professional has not diagnosed. Comorbidity researchers (83) who have addressed this issue reason that subjects' unreported physical conditions do not typically rise to a level of severity that prompts medical attention and diagnosis in which case their exclusion would strengthen our findings. We recognize that reliance on self-report may mean our findings reflect a degree of measurement error. Even so, previous research indicates that self-report of diagnoses generally show good agreement with physical records data (84–86) and is actually regarded as a more accurate estimate of comorbidity than existing measures that use different methodologies (35). By requiring patients to record precisely defined conditions for which they received a formal medical diagnosis from a physician we attempted to minimize overreporting which typically occurs when respondent misdiagnose medical problems or confuse or not remember names of conditions. We do not believe that psychological distress biased reporting largely because depressive or anxiety symptoms have not been found to result in the "over reporting" of self-reported diagnosed physical conditions (87). In addition, validating self-report against medical records would have been an expensive and logistically onerous process which would have required us to obtain records from several specialists (dentists, physicians, etc.) for every subject to cover the breadth of physical diagnoses covered by the comorbidity checklist. Whether data based on our comorbidity measures stand up to more recently developed omnibus measures of IBS-related comorbidity (88) is an important question. Because of the relative demographic homogeneity of our select sample of patients enlisted in a behavioral trial—mostly white, female, chronically ill, and educated patients seeking non drug treatment—our results may not be generalize to a broader, more diverse population. The meaning of our findings (e.g., whether the effect of comorbidity on GI symptoms is more pronounced in IBS patients) could have been increased with the addition of a control group of non-consulting individuals with IBS symptoms or those with organic GI disease (e.g., IBD). Our two measures of symptom burden are sensitive to pain (89) and invites speculation about whether comorbidity impacts bowel symptoms (e.g., stool consistency, frequency, urgency etc.). Analyses of diagnosed physical comorbidities did no control for co-existing physical condition(s) which would have been an impractical exercise. This means that the distinction between comorbidity types is less clear cut than their labeling implies. Other comorbidity research (86) that has addressed this same issue gives us confidence that the approach we adopted is unlikely to have affected the pattern of results.

Our working definition of comorbidity was the co-occurrence of one or more diagnosed mental or physical conditions (4). In adopting this definition, we focused on MD-assigned diagnoses and not patient reported symptoms which has been a focus of other IBS researchers (1, 61). We reasoned that a diagnostic approach would (1) minimize biases contributing to over reporting and (2) better clarify the relative association between numbers of comorbidities and illness burden because many somatic symptoms (e.g. fatigue, sexual difficulties) that predict illness burden in IBS patients (61) are not specific to a particular psychiatric or physical disorder. Gauging comorbidity on the basis of symptom counts would make it difficult to disentangle the relative illness burden associated with mental vs. physical comorbidities. Another advantage of a diagnostic approach is that it lends uniformity to psychiatric assessments that yield specific DSM diagnoses. Third, while there is no uniformly accepted definition of comorbidity, it has typically been defined in terms of illnesses, conditions, or diseases not discrete symptoms (4). Whether symptomatic or diagnostic comorbidity is more useful way of understanding comorbidity in IBS is an important area of further study. In the meantime, we believe that progress in this important

area requires discarding idiosyncratic definitions of comorbidity and adopting a shared language that reflects a consensus understanding of what comorbidity is.

Conclusion

This study contributes to the literature by detailing the nature and pattern of physical-mental comorbidity among a cohort of severely affected IBS patients and the toll it exacts on their day to day lives, identifying specific co-existing conditions that, both singly and in combination, are most strongly associated with worse GI symptoms, mental and physical functioning, and quality of life, and pointing to further areas of investigation that stand to improve the health, well-being and clinical care for patients with this complex and prevalent GI disorder.

Acknowledgments

We thank Drs Emeran Mayer, Bruce Naliboff, Mel Wilcox, Michael Sitrin, and Larry Bradley for serving as members of an expert panel who recommended items for the comorbidity checklist used in the present study.

Grant support: This study was funded by NIH Grant DK77738.

Abbreviations

SF-12	Short Form-12
PCS	Physical Component Score
MCS	Mental Component Score
BSI	Brief Symptom Inventory
IBSQOL	IBS Quality of Life
IBS-SSS	Irritable Bowel Syndrome Symptom Severity Scale
GAD	Generalized Anxiety Disorder
MDD	major depression disorder
LBP	low back pain
HRQOL	health-related quality of life
IBS	irritable bowel syndrome
DSM	Diagnostic and Statistical Manual of Mental Disorders
MINI	MINI International Neuropsychiatric Interview

References

1. 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; 122:1140–56. [PubMed: 11910364]
2. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. Journal of Chronic Diseases. 1970; 23:455–468.
3. van den Akker M, Buntinx F, Metsemakers JF, et al. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol. 1998; 51:367–75. [PubMed: 9619963]
4. Valderas JM, Starfield B, Sibbald B, et al. Defining Comorbidity: Implications for Understanding Health and Health Services. The Annals of Family Medicine. 2009; 7:357–363.

5. Whorwell PJ, McCallum M, Creed FH, et al. Non-colonic features of irritable bowel syndrome. Gut. 1986; 27:37–40. [PubMed: 3949235]
6. Whitehead WE, Palsson OS, Levy RR, et al. Comorbidity in irritable bowel syndrome. Am J Gastroenterol. 2007; 102:2767–76. [PubMed: 17900326]
7. Lackner JM, Quigley BM, Blanchard EB. Depression and abdominal pain in IBS patients: the mediating role of catastrophizing. Psychosom Med. 2004; 66:435–41. [PubMed: 15184708]
8. Blanchard, EB. Irritable bowel syndrome: Psychosocial assessment and treatment. Washington: APA; 2000.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington. D. C: American Psychiatric Association; 1994.
10. Blanchard EB, Scharff L. Psychosocial aspects of assessment and treatment of irritable bowel syndrome in adults and recurrent abdominal pain in children. Journal of Consulting and Clinical Psychology. 2002; 70:725–38. [PubMed: 12090379]
11. Alegria, M.; Jackson, JS.; Kessler, RS., et al. National Comorbidity Survey Replication (NCS-R)2001–2003. Ann Arbor: Inter-university Consortium for Political and Social Research; 2003.
12. Kessler RC, Berglund P, Chiu WT, et al. The US National Comorbidity Survey Replication (NCS-R): design and field procedures. Int J Methods Psychiatr Res. 2004; 13:69–92. [PubMed: 15297905]
13. Levy RL, Von Korff M, Whitehead WE, et al. Costs of care for irritable bowel syndrome patients in a health maintenance organization. Am J Gastroenterol. 2001; 96:3122–9. [PubMed: 11721759]
14. Johansson PA, Farup PG, Bracco A, et al. How does comorbidity affect cost of health care in patients with irritable bowel syndrome? A cohort study in general practice. BMC Gastroenterol. 2010; 10:31. [PubMed: 20233451]
15. Sandler RS, Drossman DA, Nathan HP, et al. Symptom complaints and health care seeking behavior in subjects with bowel dysfunction. Gastroenterology. 1984; 87:314–318. [PubMed: 6735075]
16. Baumeister H, Kriston L, Bengel J, et al. High agreement of self-report and physician-diagnosed somatic conditions yields limited bias in examining mental-physical comorbidity. J Clin Epidemiol. 2010; 63:558–65. [PubMed: 19959329]
17. Scott KM, Bruffaerts R, Tsang A, et al. Depression-anxiety relationships with chronic physical conditions: Results from the World Mental Health surveys. Journal of Affective Disorders. 2007; 103:113–120. [PubMed: 17292480]
18. Rijken M, van Kerkhof M, Dekker J, et al. Comorbidity of chronic diseases: effects of disease pairs on physical and mental functioning. Qual Life Res. 2005; 14:45–55. [PubMed: 15789940]
19. Riedl A, Schmidtmann M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: A systematic analysis. Journal of Psychosomatic Research. 2008; 64:573–582. [PubMed: 18501257]
20. Blanchard, EB. Irritable bowel syndrome: Psychosocial assessment and treatment. Washington: APA; 2001.
21. Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms? Neurogastroenterology & Motility. 2012; 24:895–913. [PubMed: 22863120]
22. Drossman, DA.; Corazziari, E.; Talley, NJ., et al. Rome III. The functional gastrointestinal disorders: Diagnosis, pathophysiology and treatment: A multinational consensus. 2. McLean, VA: Degnon Associates; 2006.
23. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology. 2003; 125:19–31. [PubMed: 12851867]
24. Lackner JM, Jaccard J, Krasner SS, et al. Self-administered cognitive behavior therapy for moderate to severe irritable bowel syndrome: Clinical efficacy, tolerability, feasibility. Clinical Gastroenterology and Hepatology. 2008; 6:899–906. [PubMed: 18524691]
25. Lackner, JM.; Keefer, L.; Jaccard, J., et al. Contemporary Clinical Trials. The Irritable Bowel Syndrome Outcome Study (IBSOS): Rationale and design of a randomized, placebo-controlled trial with 12 month follow up of self- versus clinician-administered CBT for moderate to severe irritable bowel syndrome.

26. Schoenborn CA, Adams PF, Schiller JS. Summary health statistics for the U.S. population: National Health Interview Survey, 2000. Vital Health Stat. 2003; 10:1–83.
27. Lackner JM, Gudleski GD, Zack MM, et al. Measuring health-related quality of life in patients with irritable bowel syndrome: can less be more? Psychosom Med. 2006; 68:312–20. [PubMed: 16554399]
28. Lackner, JM.; Brenner, DM.; Keefer, L. IBSOS Medical Comorbidity Inventory. Buffalo: 2009.
29. Ormel J, Kempen GI, Penninx BW, et al. Chronic medical conditions and mental health in older people: disability and psychosocial resources mediate specific mental health effects. Psychol Med. 1997; 27:1065–77. [PubMed: 9300512]
30. Lackner JM, Quigley BM. Pain catastrophizing mediates the relationship between worry and pain suffering in patients with irritable bowel syndrome. Behav Res Ther. 2005; 43:943–57. [PubMed: 15896288]
31. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40:373–83. [PubMed: 3558716]
32. Edwards WS, Winn DM, Collins JG. Evaluation of 2-week doctor visit reporting in the national health interview survey. Vital Health Stat. 1996; 2:1–46.
33. Baker, MM.; Stabile, M.; Deri, C. What Do Self-reported, Objective Measures of Health Measure?. Cambridge, MA: National Bureau of Economic Research; 2001.
34. Revicki DA, Rentz AM, Dubois D, et al. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. Qual Life Res. 2004; 13:833–44. [PubMed: 15129893]
35. Bayliss EA, Ellis JL, Steiner JF. Subjective assessments of comorbidity correlate with quality of life health outcomes: initial validation of a comorbidity assessment instrument. Health Qual Life Outcomes. 2005; 3:51. [PubMed: 16137329]
36. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998; 59 (Suppl 20):22–33. [PubMed: 9881538]
37. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997; 11:395–402. [PubMed: 9146781]
38. Derogatis, LR. Brief Symptom Inventory (BSI) 18. Minneapolis: National Computer System; 2000.
39. Dorn SD, Palsson OS, Thiwan SI, et al. Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity. Gut. 2007; 56:1202–9. [PubMed: 17483191]
40. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol. 2000; 95:999–1007. [PubMed: 10763950]
41. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996; 34:220–33. [PubMed: 8628042]
42. Ware, JE.; Snow, KK.; Kosinski, M. SF-36 Health Survey and Interpretation Guide. Lincoln, RI: QualityMetric Incoporated; 2000.
43. Turk DC, Dworkin RH, Burke LB, et al. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain. 2006; 125:208–15. [PubMed: 17069973]
44. Koloski NA, Boyce PM, Jones MP, et al. What level of IBS symptoms drives impairment in health-related quality of life in community subjects with irritable bowel syndrome? Are current IBS symptom thresholds clinically meaningful? Qual Life Res. 2012; 21:829–36. [PubMed: 21833813]
45. Patrick, DL.; Drossman, DA.; Frederick, IO. A Quality of Life Measure for Persons with Irritable Bowel Syndrome (IBS-QOL): User's Manual and Scoring Diskette for United States Version. Seattle, Washington: University of Washington; 1997.

46. Perruccio AV, Katz JN, Losina E. Health burden in chronic disease: multimorbidity is associated with self-rated health more than medical comorbidity alone. J Clin Epidemiol. 2012; 65:100–6. [PubMed: 21835591]
47. Lewis R, Dixon J. Rethinking management of chronic diseases. BMJ. 2004; 328:220–2. [PubMed: 14739194]
48. Vandvik PO, Wilhelmsen I, Ihlebaek C, et al. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. Aliment Pharmacol Ther. 2004; 20:1195–203. [PubMed: 15569123]
49. Sykes MA, Blanchard EB, Lackner J, et al. Psychopathology in irritable bowel syndrome: support for a psychophysiological model. J Behav Med. 2003; 26:361–72. [PubMed: 12921009]
50. Marrie, RA.; Horwitz, R.; Cutter, G., et al. Cumulative impact of comorbidity on quality of life in MS.
51. Baumeister H, Balke K, Harter M. Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients. J Clin Epidemiol. 2005; 58:1090–100. [PubMed: 16223651]
52. Kurtz ME, Kurtz JC, Stommel M, et al. Loss of physical functioning among geriatric cancer patients: relationships to cancer site, treatment, comorbidity and age. Eur J Cancer. 1997; 33:2352–8. [PubMed: 9616281]
53. Erickson SR, Christian RD Jr, Kirking DM, et al. Relationship between patient and disease characteristics, and health-related quality of life in adults with asthma. Respir Med. 2002; 96:450–60. [PubMed: 12117046]
54. Spiegel B, Strickland A, Naliboff BD, et al. Predictors of patient-assessed illness severity in irritable bowel syndrome. Am J Gastroenterol. 2008; 103:2536–43. [PubMed: 18637089]
55. Drossman DA, Morris CB, Yu H, et al. Minimally Important Differnces (MID) for Health Related Quality of Life (HRQOL) Measures in Functional Bowel Disorders (FBD). Gastroenterology. 2006; 130:A-xx.
56. Mayer EA. Clinical practice. Irritable bowel syndrome. N Engl J Med. 2008; 358:1692–9. [PubMed: 18420501]
57. Smith SM, O' Dowd T. Chronic diseases: what happens when they come in multiples? British Journal of General Practice. 2007; 57:268–270. [PubMed: 17394728]
58. Fortin M, Dubois MF, Hudon C, et al. Multimorbidity and quality of life: a closer look. Health Qual Life Outcomes. 2007; 5:52. [PubMed: 17683600]
59. Sturt E. Hierarchical patterns in the distribution of psychiatric symptoms. Psychol Med. 1981; 11:783–92. [PubMed: 7323234]
60. Smith MD, Russell A, Hodges PW. How common is back pain in women with gastrointestinal problems? Clin J Pain. 2008; 24:199–203. [PubMed: 18287824]
61. Chen H, Slade G, Lim PF, et al. Relationship between temporomandibular disorders, widespread palpation tenderness, and multiple pain conditions: a case-control study. J Pain. 2012; 13:1016–27. [PubMed: 23031401]
62. Diatchenko L, Nackley AG, Slade GD, et al. Idiopathic pain disorders--pathways of vulnerability. Pain. 2006; 123:226–30. [PubMed: 16777329]
63. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: Overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. NeuroImmunoModulation. 1997; 4:134–153. [PubMed: 9500148]
64. Phillips K, Clauw DJ. Central pain mechanisms in rheumatic diseases: Future directions. Arthritis Rheum. 2012
65. Matthew, G.; Funke, GJ. Worry and information processing. In: Davey, GCL.; Wells, A., editors. Worry and Its Psychological Disorders: Theory, Assessment and Treatment. West Sussex, England: John Wiley & Sons; 2006.
66. Beck, AT.; Emery, G. Anxiety disorders and phobias. New York: Basic Books; 1985.
67. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. Annu Rev Med. 2011; 62:381–96. [PubMed: 21090962]

68. Almy TP, Abbot FK, Hinkle LE Jr. Alterations in colonic function in man under stress; hypomotility of the sigmoid colon, and its relationship to the mechanism of functional diarrhea. Gastroenterology. 1950; 15:95–103. [PubMed: 15421433]
69. Nolen-Hoeksema S. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. J Abnorm Psychol. 2000; 109:504–11. [PubMed: 11016119]
70. Pieper S, Brosschot JF, van der Leeden R, et al. Cardiac effects of momentary assessed worry episodes and stressful events. Psychosom Med. 2007; 69:901–9. [PubMed: 17991822]
71. Thayer JF, Brosschot JF. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology. 2005; 30:1050–8. [PubMed: 16005156]
72. Segerstrom SC, Glover DA, Craske MG, et al. Worry affects the immune response to phobic fear. Brain Behavior and Immunity. 1999; 13:80–92.
73. Carney CE, Harris AL, Moss TG, et al. Distinguishing rumination from worry in clinical insomnia. Behav Res Ther. 2010; 48:540–6. [PubMed: 20362977]
74. Chibnall JT, Tait RC. Confirmatory factor analysis of the Pain Catastrophizing Scale in African American and Caucasian Workers' Compensation claimants with low back injuries. Pain. 2005; 113:369–75. [PubMed: 15661446]
75. Harvey AG, Greenall E. Catastrophic worry in primary insomnia. J Behav Ther Exp Psychiatry. 2003; 34:11–23. [PubMed: 12763390]
76. Sullivan M, Stanish W, Waite H, et al. Catastrophizing, pain, and disability in patients with soft-tissue injuries. Pain. 1998; 77:253–60. [PubMed: 9808350]
77. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998; 338:171–9. [PubMed: 9428819]
78. Thayer JF, Lane RD. Perseverative thinking and health: Neurovisceral concomitants. Psychology and health. 2002; 17:685–695.
79. Pieper S, Brosschot JF. Prolonged stress-related cardiovascular activation: Is there any? Ann Behav Med. 2005; 30:91–103. [PubMed: 16173905]
80. McRae S, Younger K, Thompson DG, et al. Sustained mental stress alters human jejunal motor activity. Gut. 1982; 23:404–9. [PubMed: 7076017]
81. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. Prog Brain Res. 2000; 122:25–34. [PubMed: 10737048]
82. Brosschot JF, Pieper S, Thayer JF. Expanding stress theory: prolonged activation and perseverative cognition. Psychoneuroendocrinology. 2005; 30:1043–9. [PubMed: 15939546]
83. Kessler RC, Ormel J, Demler O, et al. Comorbid mental disorders account for the role impairment of commonly occurring chronic physical disorders: results from the National Comorbidity Survey. J Occup Environ Med. 2003; 45:1257–66. [PubMed: 14665811]
84. Kehoe R, Wu SY, Leske MC, et al. Comparing self-reported and physician-reported medical history. Am J Epidemiol. 1994; 139:813–8. [PubMed: 8178794]
85. Kriegsman DM, Penninx BW, van Eijk JT, et al. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. J Clin Epidemiol. 1996; 49:1407–17. [PubMed: 8970491]
86. Scott KM, Von Korff M, Alonso J, et al. Mental-physical co-morbidity and its relationship with disability: results from the World Mental Health Surveys. Psychol Med. 2009; 39:33–43. [PubMed: 18366819]
87. Kolk AM, Hanewald GJ, Schagen S, et al. Predicting medically unexplained physical symptoms and health care utilization. A symptom-perception approach. J Psychosom Res. 2002; 52:35–44. [PubMed: 11801263]
88. MacLean EW, Palsson O, Turner MJ, et al. Development and validation of new disease-specific measures of somatization and comorbidity in IBS. Journal of Psychosomatic Research. in press.
89. Lackner JM, Jaccard J, Baum C, et al. Patient-Reported Outcomes for Irritable Bowel Syndrome Are Associated With Patients' Severity Ratings of Gastrointestinal Symptoms and Psychological Factors. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2011; 9:957–964. e1. [PubMed: 21699821]

Table 1

Irritable Bowel Syndrome Sample Characteristics (N=175)

	N (%)	M (SD)
Sex		
Male	38 (21.7)	
Female	137 (78.3)	
Education		
High School or less	36 (20.6)	
College degree	75 (42.9)	
Post-college degree	51 (29.1)	
Other	13 (7.4)	
Race		
Non White	15 (8.6)	
White	159 (91.4)	
MD-rated IBS subtype		
IBS-C	45 (25.7)	
IBS-D	76 (43.4)	
IBS-M	46 (26.3)	
IBS-U	8 (4.6)	
Yearly Income		
< 15,000	14 (6.6)	
15,001 – 30,000	21 (10.1)	
30,001 – 50,000	35 (16.9)	
50,001 – 75,000	30 (14.5)	
75,001 – 100,000	11 (5.3)	
100,001 – 150,000	15 (7.2)	
>150,000	20 (9.7)	
Don’t know/Not sure	9 (4.3)	
Prefer not to answer	20 (9.7)	
Relationship Status		
Married/Life Partner	72 (41.4)	
Divorced	17 (9.8)	
Widowed	2 (1.2)	
Separated	3 (1.7)	
Single, never married	64 (36.8)	
Cohabitating	16 (9.2)	
Age		41.00 (15.00)
Durations of symptoms (years)		16.50 (14.30)
IBSSSS		284.50 (76.53)
IBS-QOL		56.07 (19.15)
BSI-GSI		14.43 (12.79)
SF12-PCS		44.04 (9.50)

	N (%)	M (SD)
SF12-MCS		41.02 (10.77)
Ave. pain past 7 days		5.00 (2.00)

Note: IBS-C=IBS Constipation; IBS-D=IBS Diarrhea; IBS-M=IBS-Mixed; IBS-U=IBS Undifferenstiated

Table 2

Partial Correlations between Comorbidity and Illness/Symptom Burden Variables (Controlling for Confounding Variables)

	1	2	3	4	5	6	7	8	9
1. Medical Comorbidities	-								
2. Mental Comorbidities	0.17*	-							
3. Total Comorbidities	0.94**	0.51**	-						
4. IBS-SSS	0.14	0.10	0.16	-					
5. Abdominal Pain	0.09	0.13	0.12	0.47**	-				
6. IBSQOL	−0.28**	−0.30**	0.35**	−0.41**	−0.21*	-			
7. BSI-GSI	0.21*	0.64**	0.42**	0.29**	0.15	−0.42**	-		
8. MCS	−0.08	−0.46**	−0.24**	−0.35**	−0.14	0.47**	−0.52**	-	
9. PCS	−0.41**	−0.23**	−0.45**	−0.35**	−0.18*	0.36**	−0.35**	−0.04	-

Note:

* p<.05;

** p<.01. Total comorbidities = overall number of mental and physical comorbidities; SF-12 = Short Form-12; PCS = Physical Component Summary Scale; MCS = Mental Component Summary Scale; BSI-GSI = Brief Symptom Inventory-Global Severity Index; IBSQOL = IBS Quality of Life; IBS-SSS = Irritable Bowel Syndrome Symptom Severity Scale

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2014 September 01.

Table 3

Regression coefficients and corresponding p-values for each mental-physical comorbidities across illness burden indicators after adjusting for confounding variables

	N (%)	IBS-SSS		SF12-MCS		Abdominal pain		BSI-GSI		SF12-PCS		IBSQOL	
		Coeff	p	Coeff	p	Coeff	p	Coeff	p	Coeff	p	Coeff	p
Single Comorbidities													
Low back pain	35 (20.0)	58.81	**0.000**	−5.41	**0.022**	0.37	0.372	10.28	**0.000**	−9.38	**0.000**	−13.81	**0.001**
Major Depression	38 (21.7)	42.40	**0.006**	−13.00	**0.000**	0.48	0.229	21.32	**0.000**	−6.04	**0.001**	−14.38	**0.000**
Generalized Anxiety	56 (32.0)	35.23	**0.008**	−11.55	**0.000**	0.66	0.051	12.15	**0.000**	−2.28	0.166	−13.07	**0.000**
Insomnia	34 (19.4)	16.10	0.306	−7.24	**0.002**	−0.43	0.274	11.55	**0.000**	−3.45	0.074	−11.03	**0.005**
Tension headache	24 (13.7)	13.53	0.455	−5.12	**0.050**	−0.09	0.834	8.50	**0.004**	−3.13	0.151	−8.97	**0.044**
Allergy	56 (32.0)	12.21	0.367	1.64	0.407	0.22	0.523	−1.66	0.464	0.80	0.626	−1.86	0.586
GERD	41 (23.4)	10.54	0.499	1.01	0.660	−0.16	0.679	2.06	0.430	−2.81	0.138	−6.88	0.076
Agoraphobia	20 (11.4)	−6.14	0.755	−7.51	**0.009**	0.48	0.328	13.81	**0.000**	−8.02	**0.001**	−11.02	**0.024**
Sinusitis	25 (14.3)	−18.02	0.311	−1.95	0.457	0.18	0.683	−0.77	0.797	−0.23	0.916	−5.47	0.219
Migraine Headache	28 (16.0)	−20.17	0.233	−1.84	0.443	−0.29	0.503	−1.38	0.614	−0.90	0.653	−3.59	0.379
Comorbidity Dyads													
LBP - MDD	17 (9.7)	89.67	**0.000**	−11.76	**0.000**	0.85	0.115	20.61	**0.000**	−10.24	**0.000**	−21.93	**0.000**
Low back pain-GAD	16 (9.1)	78.38	**0.000**	−9.86	**0.002**	1.16	**0.033**	17.41	**0.000**	−10.95	**0.000**	−20.75	**0.000**
MDD - GAD	26 (14.9)	49.90	**0.004**	−13.41	**0.000**	0.88	**0.045**	22.46	**0.000**	−9.02	**0.000**	−18.34	**0.000**
Allergy - LBP	15 (8.6)	45.66	**0.048**	−1.83	0.575	0.10	0.868	3.42	0.363	−8.28	**0.002**	−10.33	0.063
Allergy - GAD	14 (8.0)	35.22	0.116	−10.11	**0.002**	0.55	0.336	8.66	**0.022**	−3.35	0.224	−14.71	**0.008**
Insomnia - Allergies	15 (8.6)	28.71	0.206	−5.13	0.126	−0.11	0.853	11.03	**0.004**	−3.84	0.170	−18.17	**0.001**
Insomnia - MDD	17 (9.7)	26.86	0.208	−12.32	**0.000**	−0.57	0.293	20.23	**0.000**	−6.61	**0.010**	−16.48	**0.002**
Allergy - GERD	25 (14.3)	24.54	0.181	3.62	0.181	−0.12	0.804	0.48	0.877	−1.97	0.383	−3.10	0.502
Insomnia - GAD	19 (10.9)	4.75	0.806	−10.61	**0.000**	−0.28	0.571	16.18	**0.000**	−5.79	**0.020**	−13.07	**0.010**
Sinusitis - Allergies	16 (9.1)	−16.31	0.453	−3.94	0.232	0.22	0.695	−2.85	0.454	−0.31	0.910	−9.36	0.096

Note: Bolded p values = significant at $p < .05$. GAD=Generalized Anxiety Disorder; GERD=Gastroesophageal Reflux Disease; MDD=Major Depressive Disorder; IBS-SSS=IBS Symptom Severity Scale; LBP=Low Back Pain; SF12-MCS=SF12 Mental Component Summary Score; Abdominal pain=Average abdominal pain past 7 days; BSI-GSI=Brief Symptom Inventory-Global Severity Index; SF12-PCS=SF12 Physical Component Summary Score; IBSQOL=IBS Quality of Life