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Original Article

Risk Factors for Self-reported Irritable Bowel Syndrome With Prior Psychiatric Disorder: The Lifelines Cohort Study

Francis Creed

Neuroscience and Mental Health, University of Manchester, UK

Background/Aims
The role of psychiatric disorder in irritable bowel syndrome (IBS) is not clear. This study aims to assess whether individuals who have psychiatric disorder prior to IBS onset differ in their risk factors from the remainder.

Methods
The prospective, population-based Lifelines cohort study includes 132 922 adults without prior IBS or taking IBS medication at baseline. Baseline data included socio-demographic status, physical and psychiatric disorders, psycho-social and behavioral variables. At follow-up (mean 2.4 years later) new onsets of IBS were recorded by self-report. The predictors of new onsets of IBS were assessed using logistic regression; participants with and without prior psychiatric disorders were analyzed separately.

Results
At follow-up 1507 (1.1%) participants reported new onset IBS. Of these, 27% reported prior psychiatric disorder. Predictors of IBS in this group were: 2 or more psychiatric disorders (OR, 2.74; 95% CI, 1.3-5.6), female sex, proton pump inhibitors, numerous bodily symptoms, impaired sleep, low BMI and negative health perception. These variables, except psychiatric disorders and BMI, also predicted IBS in those without prior psychiatric disorder but, in this group, gallstones, asthma, fibromyalgia, reported allergies, impairment through bodily pain, and frequent healthcare were also predictors.

Conclusions
Despite its limitations this study suggests that prior psychiatric disorder is an important risk factor in a quarter of IBS onsets. Negative health perception and multiple bodily symptoms are associated with all IBS onsets in line with the cognitive-behavior model of IBS. Prior psychiatric disorder may predict an optimal response to psychiatric treatment. Further studies could usefully study mechanisms linking IBS to prior psychiatric disorder.
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Key Words
Anxiety; Depression; Epidemiology; Irritable bowel syndrome; Risk factors

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*Correspondence: Francis Creed, MD
Neuroscience and Mental Health, University of Manchester, The Rawnsley Building, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, UK
Tel: +44-0161-276-5331 (or +44-0786-798-2710), Fax: +44-0161-273-2135, E-mail: francis.creed@manchester.ac.uk

Introduction

Although anxiety and depression are recognized as frequent concomitants of irritable bowel syndrome (IBS) their precise role in the disorder is not understood.[1-6] Some authors regard such psychiatric disorders simply as one of a number of comorbid conditions but others regard anxiety and depression as an integral part of the brain-gut axis and therefore a component of all IBS.[1,2,7-9] Clarifying the role of psychiatric disorders (ie, anxiety and depressive disorders) in the development of IBS is crucial to understanding its etiology and improving the efficacy of psychological treatments.

Anxiety and depression may have preceded the onset of IBS (the "brain-gut" axis) or they may develop subsequently (the "gut-brain axis").[8,10] In prospective studies anxiety and depression have been shown to double the risk of subsequent IBS but this risk factor is only found in a quarter of people who develop IBS.[11-19] Thus three-quarters of IBS onsets are not preceded by psychiatric disorders and other risk factors must be important in these people. It is possible that individuals who have psychiatric disorders prior to IBS onset should be regarded as a subgroup of IBS sufferers with a different pattern of etiological factors from the remainder but no previous study has addressed this issue.[9,11]

Clarifying the mechanisms of effective psychological treatments for IBS could further our understanding of the role of psychiatric disorder in IBS, but the evidence here is conflicting.[20,21] It has been shown that cognitive behavioral therapy leads to improved IBS symptoms by directly modifying gastrointestinal-related cognitions and behaviors; improved anxiety or depression is regarded as secondary and there is no modification of autonomic nervous system activity in response to pain.[22-25] On the other hand, other treatment studies have shown that improvement of IBS symptoms correlates closely with reduction of depression or anxiety and, in 1 study, improved tolerance to rectal distension was associated strongly with improved depression.[4,26-29] IBS is clearly an heterogeneous disorder and psychological treatments can only be optimized once we understand better the relationship between psychological factors and IBS symptoms.

The present study aims to identify the role of prior psychiatric disorder (anxiety and depressive disorders) in a large population-based prospective study. The data came from the same Lifelines database as a previous study in which 26 predictors of new onset IBS were identified (prior psychiatric disorder was one of these).[30] Specifically, this study aims to test the hypothesis that participants with a prior psychiatric history show a different pattern of risk factors for IBS onset from participants without prior psychiatric disorder. This hypothesis was tested using both univariate and multivariate analyses.

Materials and Methods

Study Design and Participants

The data used in this study came from the LifeLines study, a multi-disciplinary prospective population-based cohort study examining in a unique 3-generation design the health and health-related behaviors of 167 729 individuals living in the north of the Netherlands.[31] The study assessed a broad range of biomedical, socio-demographic, behavioral, physical, and psychological factors which may contribute to future health outcomes.[31] The sample is broadly representative of the total Dutch population.[32] Exclusion criteria were: severe psychiatric disorders (eg, schizophrenia) or severe physical illness, inability to visit the general practitioner, limited life expectancy ($<$ 5 years) or insufficient fluency in the Dutch language to complete questionnaires. The participants were recruited between 2006 and 2013 and followed up twice during the subsequent 3 years, on average 17 months and 29 months after the baseline. At follow-up abbreviated versions of the baseline questionnaire were administered. Written informed consent was obtained from all participants. The study followed the guidelines of the Declaration of Helsinki and the Lifelines protocol was approved by the University Medical Center Groningen, Medical ethical committee (No. 2007/152).

The present study included respondents who were 18 years and older at baseline and had completed the questionnaire items relevant to IBS at baseline and follow-up. In order to identify incident cases, participants were excluded if they reported at baseline that they had ever had a diagnosis of IBS or were currently taking antispasmodics (ATC code A03A) or drugs for constipation (ATC code A06). A new onset of IBS was recorded when, at either follow-up questionnaire, the respondent answered yes to the question "have you had the following health problem since the last questionnaire: spastic colon (IBS)?".

Predictors

The baseline predictor variables were chosen if they had been reported as predictors in the recent detailed review or our previous analysis.[11,30] They included: socio-demographic variables, prior general medical diseases and psychiatric disorders, body mass index (BMI), health behaviors, healthcare use, and medication use. The

questionnaire asked respondents to indicate which of the following disorders they have had depression, anxiety, burnout, panic disorder, social phobia, agoraphobia, obsessive compulsive disorder, other anxiety disorders, and eating disorder (see Appendix 1). This variable was entered into the logistic regression as 1, 2, or 0 psychiatric disorders. Somatic symptoms were measured using the somatization scale of the Symptom Check List-90 questionnaire.[33] Current health status was assessed using the RAND 36-Item Health Survey General Health scale.[34] The dimension referred to below as "negative health perception" was comprised of agreement with 3 statements: "My health is not good," "I seem to get sick easier than other people," and "I am definitely not as healthy as others." Healthcare use was recorded on the database in 2 ways; no contact with a doctor in the past 5 years is referred to as "zero contact with doctors"; contact with general practitioner (GP) more than 4 times per year is also referred to as "frequent GP contact."

Recent stress was assessed using the List of Threatening Experiences and Long-term Difficulties Inventory.[35,36] For the purpose of analysis, we derived one score for recent illness affecting the participant and a second score for all remaining items (ie, severe illness or death in close others, marked difficulties or changes in work, close relationships, and financial or housing) with a high score representing greater stress. The complete list of predictors is provided in the Appendix 2.

The previous study had used Least Absolute Shrinkage and Selection Operator logistic regression to identify predictors of IBS.[30] This statistical technique avoided overfitting of study data by applying a penalization/shrinkage process.[37] It produced a parsimonious model including only the most important predictors for an outcome and the present study included the variables that had been shown to predict IBS onset in the previous study.[30] The previous study included "diseases of the gastrointestinal system" as a predictor; in the present study this was replaced by the constituent disorders: chronic inflammation of the throat, stomach ulcer, gallstones, and inflammatory bowel disease. The previous study had not included interaction between variables; the present analyses examined also interactions between relevant variables (see Appendix 2).

For the present analyses the participants were divided into those with and without a prior psychiatric disorder. Depression was the most common prior psychiatric disorder (8.9% of the population); the frequency of other psychiatric disorders is presented in Appendix 1.

Outcome

The analysis used the self-reported onset of IBS at 1 or both of the 2 follow-up assessments (at 17 months or 29 months) as the outcome variable. This occurred when a respondent answered yes to the question "have you had the following health problem since the last questionnaire: spastic colon (IBS)?".

Statistical Methods

All analyses were performed on SPSS statistics version 25 (IBM Corp, Armonk, NY, USA). The first analysis compared the respondents who developed IBS during the follow-up period with the remainder using chi-square or *t* test to assess differences between the groups.

The second analysis divided the sample into those respondents who reported prior psychiatric disorder and those who did not. A comparison was made of those who did and did not develop IBS

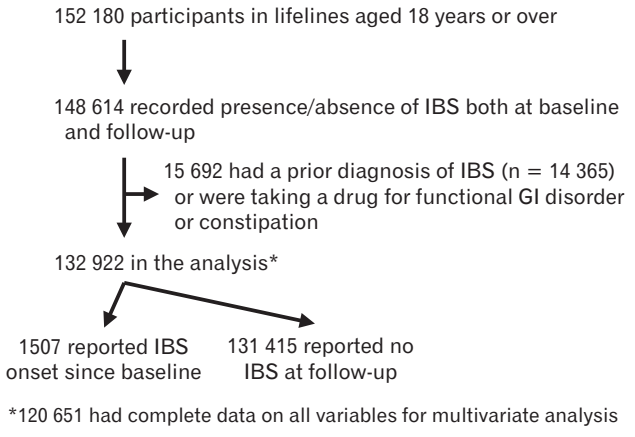

Figure 1. Flowchart of participants. IBS, irritable bowel syndrome; GI, gastrointestinal.

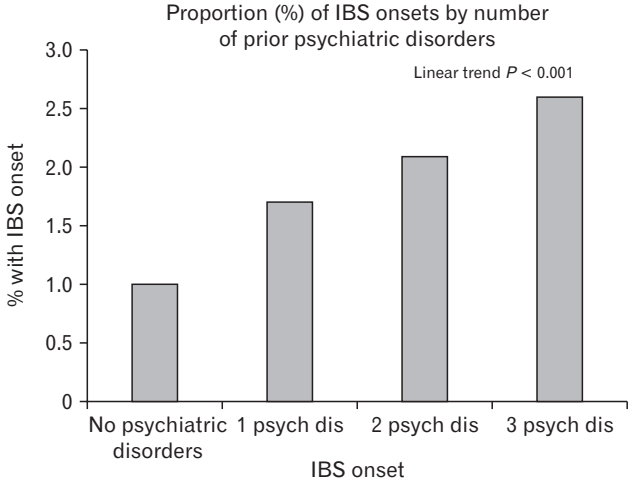

Figure 2. Proportion (%) of self-reported irritable bowel syndrome (IBS) onsets by number of psychiatric disorders (psych dis).

within each of these 2 groups. This analysis only included the key predictors of IBS onset and it used chi-square and *t* tests to assess the statistical significance of differences between IBS onset and no onset.

Thirdly, logistic regression analysis with backward elimination of variables was used to identify the baseline variables which were independently associated with onset of IBS during the follow-up period. This analysis was performed twice. The first included those

Table 1. Baseline Data of Sample and Comparison of Irritable Bowel Syndrome Onset and No Onset Groups

Categorical variables	Total sample (N = 132 922)	No IBS onset (n = 131 415)	IBS onset (n = 1507)	*P*-value: IBS vs no IBS
Female sex	55.9%	55.7%	76.9%	< 0.001
Age (yr)	44.2 (12.8)	44.2 (12.7)	43.9 (13.8)	NS
Married/cohabiting	80.7%	80.8%	75.3%	< 0.001
Education				
2ndary only	28.7%	28.6%	31.6%	
Intermediate	39.2%	39.3%	38.0%	0.041
Higher (18 yr or older)	32.1%	32.1%	30.4%	
Paid work > 32 hr per wk	41.6%	41.8%	26.8%	< 0.001
Low income	15.1%	15.0%	20.3%	< 0.001
Unable to work through illness	2.8%	2.8%	5.4%	< 0.001
3 or more allergies	8.2%	8.1%	13.0%	< 0.001
Alcohol consumed 2 or more times per week	44.6%	44.7%	37.1%	< 0.001
Smoking	20.5%	20.5%	19.2%	0.156
Asthma/inhaler	10.2%	10.1%	15.8%	< 0.001
Chronic inflammation of throat/nasal cavity	4.9%	4.8%	9.0%	< 0.001
Gallstones	3.2%	3.1%	6.0%	< 0.001
Osteoarthritis	6.8%	6.8%	10.7%	< 0.001
Diabetes mellitus	2.3%	2.3%	3.3%	0.012
Fibromyalgia	2.3%	2.2%	7.4%	< 0.001
Chronic fatigue syndrome	1.0%	1.0%	2.2%	< 0.001
Migraine	17.1%	17.1%	23.2%	< 0.001
Proton Pump Inhibitor at baseline	6.5%	6.4%	13.5%	< 0.001
Diclofenac	1.6%	1.6%	3.5%	< 0.001
No. of prior psychiatric disorders				
0	82.7%	82.8%	72.4%	
1	12.5%	12.4%	17.9%	< 0.001
2 or more	4.8%	4.8%	9.8%	
General health perception items: I seem to get sick a little easier than others	3.7%	3.7%	9.6%	< 0.001
My health is not good	9.4%	9.3%	17.8%	< 0.001
4 or more GP visits in last year	1.3%	1.3%	2.3%	0.003
Not seen any health professional in last year	8.4%	8.5%	3.2%	< 0.001
BMI (kg/m^2)	26.02 (4.29)	26.03 (4.29)	25.72 (4.42)	0.006
Life events and difficulties score	2.6 (1.7)	2.6 (1.7)	3.0 (1.7)	< 0.001
SCL somatization score	15.9 (4.2)	16.0 (4.2)	17.9 (4.9)	< 0.001
PSQI score	4.09 (2.2)	4.0 (2.2)	4.7 (2.6)	< 0.001
General health perception[a]	−0.09 (0.6)	−0.09 (0.6)	−0.28 (0.6)	< 0.001
Physical function[a]	0.36 (0.60)	0.36 (0.60)	0.18 (0.75)	< 0.001
Bodily pain[a]	0.45 (0.79)	0.46 (0.79)	0.11 (0.90)	< 0.001

[a]Low score indicates greater impairment.
IBS, irritable bowel syndrome; NS, not significant; GP, general practitioner; BMI, body mass index; SCL, Symptom Checklist; PSQI, Pittsburgh Sleep Quality Index.
Data are presented as % or mean (SD).

participants who had reported 1 or more prior psychiatric disorders in the baseline questionnaire; the second analysis included the remainder. Both analyses included all the predictor variables listed in Appendix 2.

Some variables in the regression analyses are difficult to interpret either because of reverse scoring (eg, a low score represents more severe bodily pain), or because it relates to a scale score (eg, Pittsburgh Sleep Quality Inventory score). Where this occurred an odds ratio (OR) is provided in the text, which has been transformed so that the all variables can be interpreted in the same way (higher score or top quartile represents a greater chance of IBS onset).

Results

Sample

The Lifelines database includes 148 614 participants aged 18 or over who had completed the question regarding IBS both at baseline and follow-up (Fig. 1). Of these, 15 692 had a prior diagnosis of IBS or were taking a drug for functional GI disorder or constipation. Of the 132 922 participants free of IBS at baseline, 1507 (1.1%) reported a new onset of IBS during the subsequent 2.4 years (Fig. 1). The characteristics of the sample are shown in Table 1. Of the 1507 participants with a new onset of IBS, 77.0% were female and mean age was 43.9 (SD 13.8) years. Of the participants with IBS 416 (27.6%) reported 1 or more prior psychiatric disorders

Table 2. Predictor Variables by Irritable Bowel Syndrome Onset. Sample Divided by Prior Psychiatric Disorder

Categorical variables	No prior psychiatric disorder (n = 109 914)			Prior psychiatric disorder (n = 23 008)		*P*-value
	No IBS (n = 108 823)	IBS (n = 1091)	*P*-value	No IBS (n = 22 592)	IBS (n = 416)	
Female sex	53.8%	76.0%	< 0.001	64.8%	79.3%	< 0.001
2 or more prior psychiatric disorders	NA	-NA		27.7%	35.3%	0.001
Gallstones	2.9%	5.7%	< 0.001	4.1%	7.0%	0.004
3 or more allergies	7.7%	13.4%	< 0.001	10.5%	11.8%	0.400
Asthma/inhaler	9.7%	15.9%	< 0.001	12.0%	15.4%	0.035
Fibromyalgia	1.8%	7.1%	< 0.001	4.2%	7.9%	< 0.001
PPI	5.8%	12.6%	< 0.001	9.5%	16.1%	< 0.001
General health:						
I seem to get sick a little easier than other people	2.9%	7.8%	< 0.001	7.4%	14.4%	< 0.001
My health is not good	7.6%	14.8%	< 0.001	17.5%	25.7%	< 0.001
4 or more GP visits in last year	1.3%	2.4%	0.003	1.2%	1.9%	0.173
Zero doctor visits in the past 5 yr	9.3%	3.4%	< 0.001	4.3%	2.6%	0.092
Continuous variables						
BMI	26.0 (4.2)	25.89 (4.4)	0.830	26.3 (4.6)	25.5 (4.5)	0.001
Life events and difficulties score	2.4 (1.7)	2.8 (1.7)	< 0.001	3.3 (1.7)	3.51 (1.6)	0.022
SCL somatization score	15.5 (3.7)	17.4 (4.7)	< 0.001	17.9 (5.3)	19.1 (5.0)	< 0.001
PSQI score	3.7 (2.1)	4.4 (2.4)	< 0.001	4.6 (2.5)	5.6 (3.0)	< 0.001
General health perception	−0.06 (0.6)	−0.2 (0.6)	< 0.001	−0.27 (0.6)	−0.42 (0.7)	< 0.001
Bodily pain	0.5 (0.7)	0.1 (0.9)	< 0.001	0.20 (0.9)	0.016 (0.9)	< 0.003
High scorers on continuous variables						
SCLsom top quartile	19.9%	37.9%	< 0.001	40.7%	53.6%	< 0.001
PSQI top quartile	34.6%	53.2%	< 0.001	47.1%	67.5%	< 0.001
Body pain top quartile	22.4%	37.1%	< 0.001	38.5%	43.6%	0.003
General health top quartile	14.4%	23.5%	< 0.001	26.7%	38.0%	< 0.001

IBS, irritable bowel syndrome; NA, not applicable; PPI, proton pump inhibitor; GP, general practitioner; BMI, body mass index; SCL, Symptom Checklist; PSQI, Pittsburgh Sleep Quality Index.
Data are presented as % or mean (SD).

and the incidence of IBS was associated with number of psychiatric disorders (Fig. 2). Of those with psychiatric disorder 79.0% were female and the mean age was 44.8 (12.1) years. A few participants (n = 12 251) had data missing for 1 or more predictor variables and these participants were omitted from the logistic regression leaving 120 671 of whom 1371 developed IBS (Fig. 1).

Predictors of Irritable Bowel Syndrome Onset

Univariable analyses

Table 1 shows the large number of variables which were associated with IBS onset. Table 2 shows that, among the group without a prior psychiatric disorder, those developing IBS showed a strong significant association with all predictors in the table except BMI. Within the group who had a prior psychiatric disorder there were some predictors that did not show a strong ($P < 0.001$) association with IBS onset (eg, reported allergies, asthma, gallstones, bodily pain, and number of doctor visits over 5 years).

Multivariable analysis

Irritable bowel syndrome onset in those with a prior psychiatric history. The regression analysis for those with 1 or more prior psychiatric disorders included 20 581 participants, 376 of whom reported a new onset of IBS (Table 3A). Two or more prior psychiatric disorders was the strongest predictor of subsequent IBS (OR, 2.74; 95% CI, 1.3-5.6). The other predictors were: fe-

Table 3. Logistic Regression Analysis Including Those Participants With Prior Psychiatric Disorder and Without Prior Psychiatric Disorder

A. Participants With Prior Psychiatric Disorder (n = 20 581, Out of Whom New Onset IBS = 376)

Baseline variables	B	SE	Sig.	Exp(B) (95% CI)
No. of prior psychiatric disorders	1.007	0.366	0.006	2.74 (1.33-5.61)
Female sex	0.626	0128	< 0.001	1.87 (1.45-2.40)
BMI (kg/m^2)	−0.053	0.012	< 0.001	0.95 (0.92-0.97)
PPIs at baseline	0.550	0.152	< 0.001	1.73 (1.29-2.34)
SCL somatization score	0.089	0.036	0.013	1.09 (1.02-1.17)
PSQI score	0.086	0.017	< 0.001	1.09 (1.05-1.13)
General health perception	−0.188	0.090	0.036	0.83 (0.70-0.98)
Somatization score × no.of prior psychiatric disorders	−0.019	0.009	0.036	0.98 (0.96-0.99)
Constant	−5.921	0.653	< 0.001	0.003

B. Participants Without Psychiatric Disorder (n = 100 090, Out of Whom New Onset IBS = 995)

Baseline variables	B	SE	Sig.	Exp(B) (95% CI)
Female sex	1.445	0.265	< 0.001	4.24 (2.52-7.13)
Age at baseline (yr)	0.026	0.010	0.010	1.03 (1.0006-1.046)
Married/cohabiting	−0.307	0.078	< 0.001	0.73 (0.63-0.86)
Paid work, 32 hr or more per wk	−0.274	0.079	0.001	0.76 (0.65-0.89)
Fibromyalgia	0.631	0.137	< 0.001	1.88 (1.44-2.46)
Prior gallstones	0.378	0.141	0.007	1.46 (1.11-1.92)
Asthma	0.237	0.096	0.013	1.27 (1.05-1.53)
No. of allergies	0.125	0.029	< 0.001	1.13 (1.07-1.20)
PPIs at baseline	0.551	0.108	< 0.001	1.73 (1.40-2.14)
SCL somatization score	0.030	0.008	< 0.001	1.03 (1.01-1.05)
PSQI score	0.049	0.014	< 0.001	1.05 (1.02-1.08)
General health perception	−0.207	0.057	< 0.001	0.81 (0.73-0.91)
Zero health care in the past 5 yr	−0.675	0.179	< 0.001	0.51 (0.36-0.72)
Bodily pain	−0.251	0.048	< 0.001	0.78 (0.71-0.90)
Life events and difficulties score	0.039	0.020	0.050	1.04 (1.00-1.08)
Physical function	0.261	0.065	< 0.001	1.30 (1.14-1.47)
Age × sex interaction	−0.018	0.006	0.001	0.98 (0.97-0.99)
Constant	−7.487	0.519	< 0.001	0.001

B, beta; SE, standard error; Sig, significance; BMI, body mass index; PPIs, proton pump inhibitor; SCL, Symptom Checklist; PSQI, Pittsburgh Sleep Quality Index.

male sex, taking proton pump inhibitors (PPIs), impaired sleep (for top quartile OR, 2.05; 95% CI, 1.6-2.5), low BMI (for top quartile OR, 1.56; 95% CI, 1.2-2.0), somatization (for top quartile OR, 1.4; 95% CI, 1.1-1.8), and general health perception (OR, 1.2; 95% CI, 1. −1.4).

Irritable bowel syndrome onset in those without a prior psychiatric history. This regression analysis included 100 090 individuals, of whom 995 reported a new onset of IBS (Table 3B). The predictors with the strongest association with IBS onset were: female sex (OR, 4.24; 95% CI, 2.5-7.1), fibromyalgia, taking PPIs, gallstones, asthma, number of allergies (up to 3 or more), impaired sleep (OR for top quartile versus the rest, 1.7; 95% CI, 1.4-1.9), somatization (OR for top quartile, 1.4; 95% CI, 1.2-1.7), impairment through bodily pain (OR, 1.3; 95% CI, 1.1-1.4), and general health perception (OR, 1.2; 95% CI, 1.0-1.4) (Table 2). No contact with a doctor in the past 5 years was associated with a 50% reduction of chances of developing IBS (OR, 0.5; 95% CI, 0.4-0.7). The individual items of the general health perception scale were: "My health is not good" (OR, 1.4; 95% CI, 1.1-1.9), "I seem to get sick a little easier than other people" (OR, 1.3; 95% CI, 1.2-1.4) and "I am definitely not as healthy as others" (OR, 1.2; 95% CI, 1.0-1.3).

Discussion

The study hypothesis was confirmed. This comprehensive population-based study has shown, for the first time, that participants with a prior psychiatric disorder did not have the same risk factors for IBS as those without such disorders. Whereas female sex, taking PPIs, impaired sleep, somatization, and negative health perception were risk factors in both groups the following were risk factors only in the non-psychiatric group: fibromyalgia, gallstones, asthma, reported allergies, impairment through bodily pain, and pattern of healthcare use. Of particular note was the finding that, within the prior psychiatric disorder subgroup, the strongest predictor of IBS onset was the number of psychiatric disorders.

This study is the first to include most of the recognized risk factors for IBS in a single large cohort; the findings concur well with the established literature.[11] As with many previous studies, female sex was a strong risk factor in both psychiatric and non-psychiatric groups. This is striking: the inclusion of so many predictors in a single analysis may have led to the female predominance becoming less marked but this was so only in the analysis which included respondents who reported a prior psychiatric disorder. This suggests that some of the female predominance is explained by psychiatric disorders. The strength of the female predominance in the remainder presumably means that the sex difference in IBS is explained by biological factors, which were not measured in this study.[38] Several other risk factors, namely psychiatric disorder, gastroesophageal reflux disease, asthma, fibromyalgia, and sleep disorder, are well established and have been shown to have a bidirectional relationship with IBS, ie, IBS is also a risk factor for each of these diseases, suggesting possible commonality of etiology.[11,30,39-43] All of these are represented in the present study; PPIs may be a marker for gastroesophageal reflux disease although they may also have a direct effect on the gut as they can lead to small intestinal bacterial overgrowth, which is associated with IBS.[44,45] Reported allergies have only been associated with IBS onset previously in cross-sectional studies.[46,47] Migraine was not a risk factor in the regression analyses reported here, though it was associated with IBS onset in the univariable analysis. It has been reported twice previously but, interestingly, it was only a risk factor for IBS in participants who did not have prior psychiatric disorder in the 1 prospective study which examined participants with and without anxiety/depression separately.[12] That study is also the only previous report of a greater chance of IBS onset in the presence of 2, as opposed to a single, psychiatric disorder.[12]

The psychiatric and non-psychiatric disorders groups of this study correspond respectively to the "brain-gut" and "gut-brain" groups described by Koloski et al[48]; the size of the groups roughly match those in the Australian study despite the current study being very much larger. The results may apply to post-infectious IBS (PI-IBS) as anxiety, depression, and somatization have been shown to be risk factors for PI-IBS.[49] One detailed study showed that anxiety, depression and somatization increase the susceptibility to develop PI-IBS but there was an even stronger direct effect of these psychological parameters on IBS onset.[50]

It is striking that, within the psychiatric group, 2 or more psychiatric disorders was the strongest predictor of subsequent IBS onset; this risk factor showed an exposure–response relationship with IBS onset which is one of the criteria demonstrating that psychological factors are causal in IBS.[9] Although it has been shown previously that anxiety and depression can double the risk of subsequent IBS, few studies have recognized that only 25% of IBS onsets are preceded by such disorders.[11-19] This proportion seems low compared to the high prevalence of psychiatric disorders in clinic cases (< 50%).[51,52] It can be explained by the fact that the prevalence of psychiatric disorders increases after the onset of IBS and, in addition, is higher in those seeking treatment for IBS.[7,15]

The corollary to this relatively low proportion with prior anxiety and depression is that three-quarters of IBS onsets are not preceded by these psychiatric disorders. This study has shown that gallstones,

asthma and allergies are risk factors independent of psychiatric disorder; interestingly, the same is true of fibromyalgia and susceptibility to pain. The risk factors for IBS in both psychiatric and non-psychiatric groups included some which have an important psychological component: somatization and negative health perception. They are important components of the brain-gut axis.[7,9,53,54] They concern the perception of bodily symptoms, beliefs about their significance, and the experience of pain, and resemble some of the variables addressed in cognitive behavior therapy, which is probably why such therapy may help a broad range of patients with IBS.[22,23] Their determinants include previous general medical disorders, personality, educational level, as well as anxiety and depression.[7,9,55,56]

It is beyond the scope of this study to examine in detail possible mechanisms for the link between psychiatric disorders and some IBS onsets; several are possible. One explanation may involve a genetic link as twin studies have shown that the genetic variance for IBS may be mediated by anxiety and depression.[57-59] A further twin study concluded that IBS and depression were on the same biological pathway but was unable to say which came first.[60] Other explanations may involve changes in the hypothalamic-pituitary-adrenal axis which, if dysregulated by anxiety or depression may increase susceptibility to IBS.[9] Anxiety and depression have also been associated with changes to the intestinal microbiome and/or immune responses but no studies have examined these associations separately in IBS patients with and without prior psychiatric disorders. It has been suggested that the subgroup with prior psychiatric disorders represents an important subgroup of IBS cases.[4,9]

The study findings are relevant also to psychological treatment studies. IBS which has anxiety and depression as its primary risk factor is likely to be particularly responsive to psychological treatment aimed at reduction of psychiatric symptoms; it is in these patients that a reduction of bowel symptoms would be clearly correlated with reduction of psychiatric symptoms.[26,29] On the other hand, IBS in the absence of prior psychiatric disorders would be expected to respond to cognitive behavior therapy which addresses the dimensions of experience and beliefs concerning bodily symptoms reflected in the measures of somatization and health perception in this study.

This study has strengths and limitations that must be recognized. The strengths include its prospective design, the wide range of predictors and the exclusion of participants who reported current or previous IBS or who were taking IBS medications at baseline. The sample size was large enough to analyze participants with and without prior psychiatric disorders separately. The findings concur with what is already known about risk factors for IBS.[11,30]

The main limitation was the reliance on self-report for the main outcome, which means that inaccurate diagnosis cannot be ruled out. Self-reported IBS is used in large population-based studies where it is impossible to collect detailed diagnostic data. For example, in the United Kingdom Biobank study (n = 500 000 participants) studies have shown that self-report IBS is associated with (1) altered gut microbiota composition, (2) 2 genetic links (single nucleotide polymorphisms) in genome-wide association studies, and (3) to high comorbidity with depression only when the depression precedes the onset of IBS and has marked somatic symptoms.[61-63] Other population-based studies have shown that the age of onset of self-reported IBS appears to be decreasing over time and that prior psychopathology is an important risk factor.[19,64]

Other population-based studies have shown that self-reported IBS is more prevalent in the general population than IBS diagnosed by the Rome I and Rome IV criteria.[65-67] Most importantly, the symptom pattern, bowel symptom severity, impact on daily life, inability to work, and health care utilization were similar in self-report IBS and IBS diagnosed by the Rome IV criteria; the latter is associated with more severe pain.[66,67] Furthermore, medication use is similar in self-report IBS to that of Rome IV IBS and, relevant to the present study, the 2 groups were nearly identical in terms of the proportion with anxiety and depression.[65] A recent study showed that nearly 80% of self-reported IBS in the general population fulfill Rome III criteria for IBS.[68]

It is a limitation that the study did not include gastroenteritis or sexual abuse as possible risk factors, nor did it categorize IBS into diarrhea or constipation subtypes. The relatively short duration of the study yielded relatively few new onset cases compared to the large population under study. In spite of these limitations, the incidence of IBS (47.2 per 10 000 person years) was within the range of physician-diagnosed IBS (19.6-51.3 per 10 000 person-years).[11] The proportion of females and mean age of onset match very closely the published data in comparable studies from United States of America and Europe.[11] The proportion reporting prior psychiatric disorders was remarkably similar to previous studies, 27.6% compared to the median (24.0%) of 8 previous studies.[11-19]

The findings of this study are relevant to a northern European population and the results may be different in other cultures, as has been shown in a cross-sectional studies of IBS and dyspepsia in India and Pakistan.[69,70] The findings of such cross-sectional studies need to be repeated in prospective studies such as the present one as has been demonstrated in prospective studies of depression in United Kingdom and Pakistan.[71,72]

This study should be regarded as hypothesis-generating be-

cause of its main limitation; this work needs to be repeated using standardized diagnostic criteria for IBS diagnosis. This could lead to further research to examine whether IBS with prior psychiatric disorder has the same changes in gut microbiota, intestinal permeability, immune cell reactivity, and sensitivity of the enteric nervous system as those without prior psychiatric disorder. At present, pathophysiological research is hampered by the lack of large, well-characterized patient subgroups; prior psychiatric disorder has been suggested as a useful subgrouping for future studies.[9]

Clinically, these findings are a prompt to ask IBS patients if they have had any psychiatric disorder(s) in the past. Further research is needed to examine whether the mechanisms of psychological treatments differ in the subset of patients whose IBS is closely associated with prior anxiety or depression.

Conclusions

Overall, this study has shown that negative health perception and multiple bodily symptoms are associated with all self-reported IBS onsets; this finding is in line with the cognitive-behavioral model of IBS. On the other hand, in about a quarter of IBS onsets prior psychiatric disorder is a strong predictor and this subgroup of self-reported IBS only shares some of the risk factors found in the remainder. Prior psychiatric disorder, if there are current psychiatric symptoms, should predict optimal response to specific psychiatric treatment. Recognition of the self-reported IBS groups with and without prior psychiatric disorders could lead to theoretically driven studies of treatment response as well as the pathophysiological mechanisms of IBS.

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Appendices

Appendix 1. Rate of prior psychiatric disorders in the whole sample

Depression 8.9%, burnout 7.9%, panic disorder 2.6%, other anxiety disorders 2.7%, social phobia 0.8%, agoraphobia 0.5%, obsessive compulsive disorder 0.3%, and eating disorder 1.3%

Appendix 2. List of variables used in the analysis

Socio-demographic

Sex, age, married/cohabiting, low income, years of education as 3 groups, paid work (32 or more hours per week), and not working because of illness

Medical and psychiatric disorders

Prior diagnosis of chronic fatigue syndrome, fibromyalgia, stomach ulcer, chronic inflammation of throat, inflammatory bowel disease, gallstones, eczema, diabetes, asthma, chronic obstructive pulmonary disease, osteoarthritis, osteoporosis, anaemia, migraine, repetitive strain injury, and incontinence

Prior diagnosis of depression, anxiety disorders, bipolar, agoraphobia, panic disorder, eating disorder, obsessive/compulsive, schizophrenia, burnout, and social phobia

Health problems and lifestyle

Body mass index, smoking, alcohol consumption, sleep (Pittsburgh Sleep Quality Index), allergies to dust, animals, pollen, foods, medication, and contact allergy and insects (total score)

Healthcare use

No contact with general practitioner nor specialists in the past 5 years and contact with general practitioner more than 4 times per year

Psychosocial parameters

Long-term Difficulties Inventory and the List of Threatening Experiences combined to form 2 scores; 1 for illness affecting the participant and another for all remaining items (eg, severe illness in close others, marked difficulties or changes in work, close relationships, and financial or housing) with a high score representing greater stress

Somatization scale of Somatic Symptom Checklist (SCL-90) with high score representing numerous somatic symptoms

Health status

Bodily pain, general perception of health, vitality, physical role function, social function scale scores of Short Form-36 (RAND)

Medication use

Proton pump inhibitor, thyroid preparations, paracetamol, diclofenac, inhalants for obstructive airways diseases, contraceptive pill, oxazepam, and selective serotonin receptor inhibitor antidepressants

Interaction terms included in the final regression analysis as they were significant

Age x sex, SCL somatization score x prior psychiatric disorders, and bodily pain x prior psychiatric disorders