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Factors associated with co-morbid irritable bowel syndrome and chronic fatigue-like symptoms in functional dyspepsia

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Abstract

Background *It is unclear which factors explain the high co-morbidity between functional dyspepsia (FD) and other functional somatic syndromes. The aim of this study is to investigate the association between gastric sensorimotor function, psychosocial factors and 'somatization' on the one hand, and co-morbid irritable bowel syndrome (IBS) and chronic fatigue (CF)-like symptoms on the other, in FD.* ***Methods*** *In 259 tertiary care FD patients, we studied gastric sensorimotor function with barostat (sensitivity, accommodation). We measured psychosocial factors (abuse history, alexithymia, trait anxiety, depression, panic disorder) and 'somatization' using self-report questionnaires, and presence of IBS and CF-like symptoms. Hierarchical multiple logistic regression was used to determine which of these factors were independently associated with co-morbid IBS and CF-like symptoms, including testing of potential mediator effects.* ***Key Results*** *Co-morbid IBS or CF-like symptoms respectively were found in 142 (56.8%) and 102 (39.4%) patients; both co-morbidities were not significantly associated ($P = 0.27$). Gastric accommodation ($\beta = 0.003$, $P = 0.04$) and 'somatization' ($\beta = 0.17$, $P = 0.0003$) were independent risk factors for IBS ($c = 0.74$, $P < 0.0001$); the effect of adult abuse ($\beta = 0.72$, $P = 0.20$) was mediated by 'somatization'. Depression ($\beta = 0.16$, $P = 0.008$) and 'somatization' ($\beta = 0.18$, $P = 0.004$) were overlapping risk factors for CF-like symptoms ($c = 0.83$, $P < 0.0001$); the effects of alexithymia and lifetime abuse were mediated by depression and 'somatization', respectively.* ***Conclusions & Inferences*** *'Somatization' is a common risk factor for co-morbid IBS and CF-like symptoms in FD and mediates the effect of abuse. Gastric sensorimotor function and depression are specific risk factors for co-morbid IBS and CF-like symptoms, respectively.*

Keywords *functional somatic syndromes, gastric sensorimotor function, psychiatric disorders, somatization.*

Abbreviations: CF(S), chronic fatigue (syndrome); DIF, difficulty identifying feelings & distinguishing between feelings and bodily sensations; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSS, dyspepsia symptom score; FD, functional dyspepsia; FGID, functional gastrointestinal disorders; FM, fibromyalgia; FSS, functional somatic syndromes; GI, gastrointestinal; IBS, irritable bowel syndrome; MDP, minimal distending pressure; PHQ, Patient Health Questionnaire; STAI, State-Trait Anxiety Inventory; TAS, Toronto Alexithymia Scale.

INTRODUCTION

Functional dyspepsia (FD) is one of the most prevalent functional gastrointestinal disorders (FGID).[1] Its etiopathogenesis remains incompletely understood and is likely to be heterogeneous and multifactorial.[1] According to the 'biopsychosocial model', FGID and other 'functional somatic syndromes' (FSS) result from a complex and reciprocal interaction between biological, psychological and social factors.[2,3]

Co-morbidity between FSS is high, with rates up to 50% and higher.[3–10] Moreover, co-morbidity is associated with increased severity, greater impairment in

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quality of life, excess healthcare use including referrals to secondary and tertiary care, and high direct and indirect healthcare costs.[11–15] Furthermore, co-morbidity is not only high *within* the FGID group [e.g. between FD and irritable bowel syndrome (IBS)][4,5,8,13,16,17] but also *between* FGID and other FSS [e.g. fibromyalgia (FM) and chronic fatigue syndrome (CFS)] (although specific data on FD are rather sparse).[3,6,10,12,13,18] Finally, there is high co-morbidity with psychiatric disorders (especially mood and anxiety disorders) and a significant association with psychosocial factors (including history of sexual or physical abuse, 'trait'/personality factors, etc.) in all FSS.[2,19–21]

It remains highly unclear how this co-morbidity should be explained. First, co-morbidity may simply be an artifact caused by overlapping symptom criteria and/or medical subspecialization.[6,12,22,23] Second, it may result from some common etiopathogenetic factor(s) that may be primarily peripheral and/or central in origin.[24] Potential *peripheral* mechanisms include a 'panintestinal' sensorimotor disorder of the gastrointestinal (GI) tract (for the overlap within the FGID group) and/or primary immunological abnormalities, whether or not triggered by an acute (GI) infection.[5,12] Important examples of putative *central* mechanisms are mainly psychobiological in nature. Psychiatric disorders (e.g. depression) and a history of abuse interfere with pain-processing systems in the brain.[25,26] 'Somatization', descriptively defined as a tendency to experience and report multiple somatic symptoms that cannot be adequately explained by organic findings, seems to play an important role in FSS co-morbidity.[3,12,13,27–29] It remains a matter of debate whether 'somatization' needs to be conceptualized as a primary phenomenon ('functional somatization') or rather as the result of a complex psychobiological process in which psychological factors/processes such as abuse history, hypervigilance, symptom-specific anxiety or negative affect lead to amplification of bodily signals through central sensitization of interoceptive/pain-processing neural systems (secondary phenomenon, 'presenting somatization').[19,24,28,30,31] Although the presently used measures conceptualize 'somatization' in a purely descriptive way (i.e. by simply counting 'unexplained' somatic symptoms, corresponding at best with 'functional somatization'), evidence for the 'presenting somatization' hypothesis is growing generally[30,31] and also more specifically applied to FGID.[13,32]

The potential explanations for FSS co-morbidity described in the paragraph above are not mutually exclusive and indeed likely to interact in a complex way. Moreover, their relative contribution may vary in these heterogeneous symptom-based disorders. More specifically, several of the putative central and peripheral mechanisms are likely to reciprocally influence each other through the 'brain-gut axis'.[24] So far, none of these explanations has been found to explain co-morbidity to the full extent.[12,13,18,21,23]

Given the paucity of co-morbidity research in FD, the general aim of this study was to investigate the role of gastric sensorimotor function, psychosocial factors/psychiatric co-morbidity and 'somatization' as risk factors for co-morbid IBS and chronic fatigue (CF)-like symptoms in FD. More specifically, we aimed to test the following hypotheses, based on the literature in other FSS. The model underlying these hypotheses is that FSS co-morbidity may result from a temporal and potentially causal chain from childhood events to symptom reporting in adulthood (from sexual/physical abuse over stable psychological traits and vulnerability for psychiatric co-morbidity to 'somatization'). First, 'somatization' is a common risk factor for both co-morbid IBS and CF-like symptoms in FD.[12,18,33] Second, 'somatization' is a 'mediator' of the effect of psychosocial factors (especially abuse history) on co-morbidity.[12,19,32,34] Third, depression is a more important risk factor for CF-like symptoms than IBS co-morbidity.[18,21,35] Fourth, gastric sensorimotor dysfunction is a risk factor for IBS, but not for CF-like symptom co-morbidity.[5]

METHODS

Patient sample

Consecutive Dutch-speaking patients recently diagnosed with FD (either at their visit to our clinic or at a recent secondary care gastroenterologist visit that led to referral to our center) were recruited between January 2002 and February 2009. The patient sample of the present study does partially overlap with two recent studies from our group.[36,37] However, the hypotheses tested in the present study are novel and have not been reported elsewhere. Further details about patient selection have been published before.[36]

Gastric sensorimotor function testing

Details about gastric sensorimotor function testing have been published before.[36] Briefly, we used our standard barostat protocol. During isobaric stepwise distension, patients scored their perception of upper abdominal sensation at the end of every distending step using a graphic rating scale (0–6) with verbal descriptors. Discomfort threshold was defined as the lowest pressure above minimal distending pressure evoking a perception score of 5 or more. Meal-induced gastric relaxation (accommodation) was quantified as the difference between the average volumes during 30 min before and 60 min after meal administration.

Abuse history

A sexual and physical abuse questionnaire, developed and validated in a GI population, was filled out on the day of the study together with the questionnaires described below. This questionnaire yields dichotomous answers for sexual and physical abuse during childhood and adulthood.[38]

'Trait' psychological factors

Alexithymia Alexithymia is a stable psychological trait consisting of three dimensions: difficulty identifying feelings & distinguishing between feelings and bodily sensations (DIF), difficulty describing feelings and externally oriented thinking.[39,40] As particularly the DIF dimension may play an important role in FSS, including FGID,[29,39,41] the DIF subscale of the well-validated 20-item Toronto Alexithymia Scale (TAS-20) was used throughout the present study, yielding continuous scores.[40]

Trait anxiety The 20-item trait scale of the State-Trait Anxiety Inventory (STAI) measures stable individual differences in 'anxiety proneness', that is, 'differences between people in the tendency to perceive situations as threatening and to respond to them with elevations in state anxiety'[42] and yields a continuous total score.

'State' psychiatric disorders

Depression The depression module of the Patient Health Questionnaire (PHQ-9) was used to screen for depressive co-morbidity according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[43] The nine DSM-IV depressive symptoms (past 2 weeks) are rated on Likert scales (0–3). Depression score (sum of the nine items) was used as a continuous variable.

Panic disorder The panic disorder module of the PHQ was completed, allowing a diagnosis of current DSM-IV panic disorder in a dichotomous (yes/no) way.[44]

Somatic symptom reporting

'Somatization' The PHQ somatoform disorder module (PHQ-15) is a well-validated self-report questionnaire composed of 15 somatic symptoms, including 14 of the 15 most prevalent DSM-IV somatization disorder criteria.[45] All items are rated on Likert scales (0–2). Current 'somatization' (past month) was measured.

To avoid overlap with the depression measure (PHQ-9), which may be problematic in the multiple regression models, and with the fatigue outcome measure, we did not take into account the two PHQ-15 items that are also included in the PHQ-9 depression module (sleep, fatigue). Thus, the 'somatization' score we used throughout the study is the sum of the remaining 13 items ('PHQ-13'). It should be noted that this abbreviated version is not a validated instrument, which should be considered a limitation; however, using the full PHQ-15 score yields similar results.

Moreover, a limitation of the PHQ-15 as a self-report measure (without interview) is that it cannot distinguish between 'medically explained' and 'unexplained' symptoms,[45] which is an important feature of the somatization concept.[27,28] In this study, adequate clinical and technical investigations were performed to rule out a medical explanation of GI symptoms and other potentially relevant symptoms, and major non-GI medical co-morbidity that may account for these somatic symptoms was ruled out on an 'as needed' basis. On the other hand, no systematic investigation of all somatic symptoms included in the PHQ-15 was conducted, as this is hardly practically feasible. Thus, the PHQ symptom count in this study can only be characterized as indicative of '(functional) somatization'. However, total self-reported PHQ somatic symptom counts are highly associated with physician-rated somatoform disorder symptom counts.[45,46] Furthermore, the distinction between medically explained and unexplained symptoms may be problematic and less relevant than previously thought.[14,47–49]

Dyspepsia symptom severity (DSS) On the day of the study, the intensity of nine dyspeptic symptoms was scored on Likert scales [0–3 (absent, mild, moderate, severe)], as previously reported. Dyspepsia symptom severity is defined as the sum of all nine items.[50]

Weight loss Weight loss since the onset of dyspepsia symptoms was determined by self-report at the inclusion outpatient clinic visit (i.e. patients were weighed and were asked about the amount of weight loss since the onset of their dyspepsia symptoms).

Co-morbid IBS and CF measurements

IBS Irritable bowel syndrome was assessed with a previously used 10-item yes/no self-report questionnaire, yielding a categorical outcome (IBS diagnosis according to Rome II criteria).[51]

CF-like symptoms Chronic fatigue-like symptoms were considered present when the answers on two previously used yes/no screening questions regarding duration (>6 months) of and disability due to fatigue were both positive.[51]

Statistical analysis

SAS 9.2 (SAS Institute, Cary, NC, USA) was used. If one or more variables were missing for a patient, this patient was excluded from all analyses in which the missing variable(s) was (were) used. Data were presented as mean ± SD. Significance level was set at $P = 0.05$ (two-tailed). One-way ANOVA and chi-square test for contingency tables were used to compare groups according to co-morbidity (none, IBS alone, CF-like symptoms alone, or both co-morbidities).

Bivariate associations between gastric sensorimotor variables, abuse history, 'trait' and 'state' psychological variables and 'somatic symptom reporting' variables on the one hand and presence of co-morbid IBS or CF-like symptoms on the other were calculated using simple logistic regression models.

Two *multiple logistic regression* models were built with the presence of co-morbid IBS and CF-like symptoms as the dependent variables. Gastric sensorimotor variables, abuse history, 'trait' and 'state' psychosocial variables and 'somatic symptom reporting' variables that were bivariately associated with the dependent variable ($P < 0.05$) were entered into the regression model as independent variables in a hierarchical way. Gastric sensorimotor variables were entered in the first step, abuse history variables in the second step, 'trait' psychological variables in the third step, 'state' psychiatric co-morbidity in the fourth step and 'somatic symptom reporting' variables in the final step. Although it remains to a certain extent speculative given the cross-sectional nature of the present data, this order was chosen because it reflects the putative temporal order of events leading to co-morbidity best. For example, sexual/physical abuse has been shown to be a risk factor for 'trait' psychological factors, 'state'

psychiatric co-morbidity and 'somatization' in longitudinal studies,[19,32,52–54] 'trait' psychological factors are a risk factor for 'state' psychiatric co-morbidity,[55] which has been demonstrated to be a risk factor rather than a consequence of functional somatic symptoms.[56,57] Moreover, entering variables in this order (especially 'somatization' in the last step) can give an indication about the putative mediational effects formulated in the hypothesis. Although it should be noted that in principle, it is not theoretically possible to study mediation in a cross-sectional sample because it assumes temporal precedence (see definition below in this paragraph). Therefore, the term mediation as used throughout this article should be interpreted in a more limited sense, i.e. devoid of its temporal precedence aspect. However, we decided to use the term mediation as the order in which variables were entered may well reflect the putative temporal order of events based on the literature (see above).

When potential mediation was detected in the hierarchical regression model, the mediation hypothesis was further tested as described by Baron and Kenny, including the Sobel test for significance of the indirect effect.[58] We will use the classification of risk factors formulated by Kraemer *et al.* throughout this article.[59]

RESULTS

Patient characteristics

Three hundred thirty FD patients were asked to participate. There were four refusals to participate (1.2% of the total sample). Forty-six patients (13.9%) canceled their study visit or didnot show up, allowing 280 barostat investigations to be performed. In 21 patients (6.4%), the procedure had to be stopped prematurely as patients didnot tolerate tube insertion or had severe discomfort once the tube was inserted. Two hundred fifty-nine patients (78.5%) completed the study. One hundred ninety-five patients (75.3% of the completers) were women; the mean age was 39.5 ± 12.9 years.

Prevalence of co-morbidity and comparison between co-morbidity groups

One hundred forty-two (56.8%) and 102 (39.4%) patients had co-morbid IBS or CF-like symptoms, respectively. Sixty-one patients (23.5%) had both co-morbidities. Despite this overlap, IBS and CF-like symptom co-morbidity were not significantly associated [$\chi^2_{(1)} = 1.19$, $P = 0.27$].

Table 1 shows the differences between four groups based on co-morbidity: no co-morbidity ($n = 70$), co-morbid IBS only ($n = 80$), co-morbid CF-like symptoms only ($n = 40$) and both co-morbidities ($n = 61$). Patients with co-morbid CF-like symptoms only and, to a lesser extent, with co-morbid IBS-symptoms only and both co-morbidities, differed significantly from the patients with no co-morbidity. Most differences between the co-morbidity groups were not significant.

Table 1 Comparison between FD patients with and without co-morbid IBS and/or chronic fatigue-like symptoms

	Functional somatic symptom co-morbidity				
	None ($n = 70$)	IBS only ($n = 80$)	CF-like symptoms only ($n = 40$)	IBS and CF-like symptoms ($n = 61$)	*P*-value
Gastric sensorimotor function					
Discomfort threshold	*11.3 ± 4.0*	*9.4 ± 3.3⋆*	*9.4 ± 3.5⋆*	*9.4 ± 3.5⋆*	*0.005*†
Accommodation	*97.4 ± 136.2*	*122.7 ± 133.2*	*79.4 ± 117.5*	*157.9 ± 143.8°*	*0.02*†
Abuse history (%)					
Childhood abuse	*10*	*20.7*	*33.3*	*25*	*0.04*‡
Adulthood abuse	*3.7*	*17.2*	*16.7*	*22.7*	*0.01*‡
Lifetime abuse	*11.8*	*29.8*	*38.7*	*37.2*	*0.004*‡§
'Trait' psychological					
Trait anxiety	*38.0 ± 10.8*	*40.5 ± 11.4*	*44.3 ± 11.6⋆*	*43.1 ± 12.4*	*0.03*†
Alexithymia – DIF	15.5 ± 6.0	16.4 ± 6.1	17.7 ± 6.6	17.4 ± 6.5	0.25†
'State' psychological/psychiatric					
Depression	*6.2 ± 4.1*	*7.9 ± 5.7*	*11.5 ± 5.5⋆^*	*9.6 ± 4.4⋆*	*<0.0001*†§
Panic disorder (%)	*7.25*	*15*	*25*	*18*	*0.05*‡
Somatic symptom reporting					
'*Somatization*'	*7.7 ± 3.2*	*10.8 ± 3.7⋆*	*10.3 ± 4.8⋆*	*13.2 ± 4.3⋆°^*	*<0.0001*†§
Dyspepsia symptoms	*12.0 ± 5.2*	*13.8 ± 4.1*	*14.5 ± 4.4⋆*	*14.0 ± 4.9*	*0.03*†
Weight loss	*5.9 ± 6.2*	*8.6 ± 7.6*	*12.0 ± 10.4⋆*	*10.9 ± 8.5⋆*	*0.001*†§

Significances in italic.
IBS, irritable bowel syndrome; CF, chronic fatigue; DIF, difficulty identifying and describing feelings.
†*P*-value from one-way ANOVA with *post hoc* tests and Tukey adjustment for multiple comparisons (⋆significantly different from 'none'; °significantly different from 'CF-like symptoms only'; ^significantly different from 'IBS only').
‡*P*-value from chi-square test for 2 × 4 contingency tables.
§Remains significant after Bonferroni correction for multiple testing.

Bivariate associations

Co-morbid IBS was associated with gastric sensorimotor function (discomfort threshold, accommodation), abuse history (adulthood sexual/physical abuse) and 'somatization', but not with 'trait' psychological factors or 'state' psychiatric co-morbidity (Table 2). The association with 'somatization' remains significant after Bonferroni correction for multiple testing. No association with gender was found [$\chi^2_{(1)} = 0.05$, $P = 0.82$].

Co-morbid CF-like symptoms were not associated with gastric sensorimotor function, but with abuse history (lifetime sexual/physical abuse), 'trait' psychological factors (trait anxiety and alexithymia), 'state' psychiatric co-morbidity (depression, panic disorder) and 'somatization', DSS and weight loss. The associations with depression, 'somatization' and weight loss remain significant after Bonferroni correction for multiple testing. No association with gender was found [$\chi^2_{(1)} = 1.95$, $P = 0.16$].

Multiple logistic regression

Gastric accommodation ($P = 0.04$) and 'somatization' ($P = 0.0003$) were significant risk factors for co-morbid IBS in the final model (Table 3). This model was highly significant ($P < 0.0001$), with concordance index (c) = 0.74. The concordance index is a measure of the predictive ability/discriminative power of a model and represents the percent of all possible pairs of cases in which the model assigns a higher probability to a correct case than to an incorrect case; it gives an estimate of the area under the receiver operating characteristic (ROC) curve. As gastric accommodation and 'somatization' are not correlated ($r = 0.06$,

Table 2 Bivariate associations of IBS and chronic fatigue-like symptom co-morbidity with GI sensorimotor, psychosocial and somatic symptom variables (from simple logistic regression)

Variable	$\beta \pm$ SE	OR (95% CI)	P
Irritable bowel syndrome (positive cases $n = 142$)			
Gastric sensorimotor function			
Discomfort threshold	*−0.09 ± 0.04*	*0.92 (0.86–0.99)*	*0.02*
Accommodation	*0.003 ± 0.001*	*1.003 (1.001–1.004)*	*0.01*
Abuse history			
Childhood abuse*	−0.23 ± 0.38	0.80 (0.38–1.66)	0.55
*Adulthood abuse**	*−0.99 ± 0.47*	*0.37 (0.15–0.93)*	*0.03*
Lifetime abuse*	−0.56 ± 0.34	0.57 (0.29–1.12)	0.10
'Trait' psychological			
Trait anxiety	0.01 ± 0.01	1.01 (0.99–1.03)	0.35
Alexithymia – DIF	0.01 ± 0.02	1.01 (0.97–1.06)	0.57
'State' psychological/psychiatric			
Depression	0.02 ± 0.02	1.02 (0.97–1.07)	0.53
Panic disorder°	0.17 ± 0.36	1.19 (0.59–2.40)	0.64
Somatic symptom reporting			
'Somatization'	*0.20 ± 0.04*	*1.22 (1.13–1.31)*	*<0.0001*†
Dyspepsia symptoms	0.04 ± 0.03	1.04 (0.99–1.10)	0.12
Weight loss	0.02 ± 0.02	1.02 (0.99–1.06)	0.23
Chronic fatigue-like symptoms (positive cases $n = 102$)			
Gastric sensorimotor function			
Discomfort threshold	−0.06 ± 0.04	0.94 (0.88–1.01)	0.10
Accommodation	0.001 ± 0.001	1.001 (0.999–1.003)	0.45
Abuse history			
Childhood abuse*	−0.67 ± 0.37	0.51 (0.25–1.05)	0.07
Adulthood abuse*	−0.74 ± 0.42	0.48 (0.21–1.08)	0.08
*Lifetime abuse**	*−0.73 ± 0.33*	*0.48 (0.25–0.92)*	*0.03*
'Trait' psychological			
Trait anxiety	*0.03 ± 0.01*	*1.03 (1.01–1.06)*	*0.008*
Alexithymia – DIF	*0.04 ± 0.02*	*1.04 (1–1.09)*	*0.05*
'State' psychological/psychiatric			
Depression	*0.13 ± 0.03*	*1.14 (1.08–1.20)*	*<0.0001*†
Panic disorder°	*0.78 ± 0.35*	*2.17 (1.09–4.33)*	*0.03*
Somatic symptom reporting			
'Somatization'	*0.16 ± 0.03*	*1.17 (1.10–1.25)*	*<0.0001*†
Dyspepsia symptoms	*0.06 ± 0.03*	*1.06 (1.00–1.12)*	*0.04*
Weight loss	*0.08 ± 0.02*	*1.08 (1.04–1.13)*	*0.0002*†

Significances in italic.
OR, odds ratio; DIF, difficulty identifying and describing feelings.
*Reference category = abuse; °reference category = no panic disorder.
†Remains significant after Bonferroni correction for multiple testing.

Table 3 Hierarchical multiple logistic regression model with IBS co-morbidity as the dependent variable (positive cases n = 142)

Variable	$\beta \pm SE_{variable}$	OR (95% CI)	$p_{variable}$	c_{model}
Step 1: Gastric sensorimotor function				
Discomfort threshold	*−0.08 ± 0.04*	*0.93 (0.86–0.99)*	*0.04*	0.63
Accommodation	*0.002 ± 0.001*	*1.002 (1.00–1.004)*	*0.03*	
Step 2: Abuse history				
Discomfort threshold	−0.08 ± 0.05	0.92 (0.84–1.01)	0.09	0.66
Accommodation	0.002 ± 0.001	1.002 (1.00–1.004)	0.07	
*Adult abuse**	*−1.04 ± 0.51*	*0.35 (0.13–0.97)*	*0.04*	
Step 3: Somatic symptom reporting				
Discomfort threshold	−0.04 ± 0.05	0.96 (0.88–1.06)	0.46	0.74
Accommodation	*0.003 ± 0.001*	*1.003 (1.00–1.005)*	*0.04*	
Adult abuse*	−0.72 ± 0.55	0.49 (0.17–1.45)	0.20	
'Somatization'	*0.17 ± 0.05*	*1.18 (1.08–1.29)*	*0.0003*	

Significances in italic.
Probability modeled = presence of co-morbid IBS; all models $P < 0.01$.
*Reference category = abuse.

P = 0.32), they can be considered *independent* risk factors for IBS co-morbidity.[59] Adult sexual/physical abuse history was a significant risk factor for IBS co-morbidity before 'somatization' was entered into the model, which may be indicative of mediation of the effect of abuse by 'somatization'. Further formal testing confirmed this mediational hypothesis (Fig. 1). Significance of the indirect effect was confirmed using the Sobel test (Z = −2.63, P = 0.008).

Significant risk factors for co-morbid CF-like symptoms in the final model were depression (P = 0.008), 'somatization' (P = 0.004) and weight loss (P = 0.05) (Table 4). Given the fact that all these variables are mutually correlated ($0.21 < r < 0.36$, all $P < 0.002$), they should be considered *overlapping* risk factors for co-morbid CF-like symptoms.[59] The model was highly significant ($P < 0.0001$, c = 0.83). Furthermore, the effect of alexithymia – DIF was 'mediated' by depression (Fig. 2A). Significance of the indirect effect was confirmed using the Sobel test (Z = 3.95, $P < 0.0001$). The effect of lifetime overall abuse history was 'mediated' by 'somatization' (Fig. 2B); significance of this indirect effect was borderline (Sobel test Z = −1.90, P = 0.057).

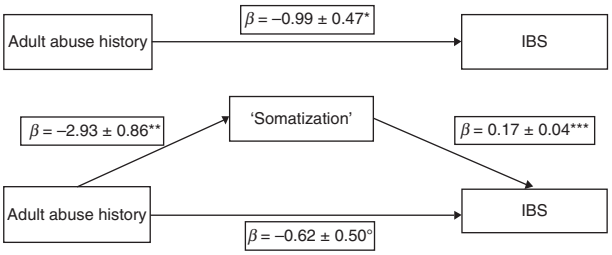

Figure 1 The effect of adult abuse history on co-morbid IBS is mediated by 'somatization'. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; °P = 0.22; Sobel test Z = −2.63, P = 0.008.

DISCUSSION

To the best of our knowledge, this is the first study in FD to investigate an extensive set of potential risk factors for co-morbid IBS and CF-like symptoms, including gastric sensorimotor function, psychosocial factors/psychiatric co-morbidity and 'somatization'.

Prevalence of co-morbidity

Fifty-seven percent of our FD patients had co-morbid IBS. This is in line with previous research, although most studies have reported somewhat lower figures (in the 20–50% range), even in tertiary care.[4,5,7,8,16] The higher prevalence of co-morbid IBS in tertiary care is in line with the finding that IBS is a predictor of referral in primary care FD.[11] Reported prevalences of the reverse co-morbidity pattern (i.e. co-morbid FD in patients presenting primarily with IBS) are generally even higher, with figures up to 80% and more in tertiary care,[7–9] although considerably lower rates are reported as well.[13]

Co-morbid CF-like symptoms were present in 40% of the present FD sample. This is a novel finding, as data on fatigue *symptoms* and co-morbidity with chronic fatigue *syndrome* in FD are lacking. Data in IBS are sparse as well, but generally lower than in the present study (around 20% of co-morbid CF in IBS samples); this may be due to the lack of data in tertiary care.[9,13] However, about 50% of CFS patients are reported to have co-morbid IBS.[9]

Of our FD patients, 23.5% had both co-morbid IBS and CF-like symptoms. This figure is in line with previous studies on multiple co-morbidities in IBS.[12,13] Both co-morbidities were not significantly associated and most patient characteristics in the overlap group were not different from both groups with only one

Table 4 Hierarchical multiple logistic regression model with chronic fatigue-like symptoms as the dependent variable (positive cases n = 102)

Variable	$\beta \pm SE_{variable}$	OR (95% CI)	$p_{variable}$	c_{model}
Step 1: Abuse history				
Lifetime abuse⋆	*−0.73 ± 0.33*	*0.48 (0.25–0.92)*	*0.03*	0.58
Step 2: 'Trait' psychological				
Lifetime abuse⋆	*−0.90 ± 0.36*	*0.41 (0.20–0.82)*	*0.01*	0.69
Trait anxiety	0.013 ± 0.017	1.01 (0.98–1.05)	0.45	
Alexithymia – DIF	*0.06 ± 0.03*	*1.07 (1.00–1.13)*	*0.04*	
Step 3: 'State' psychological/psychiatric				
Lifetime abuse⋆	*−1.02 ± 0.38*	*0.36 (0.17–0.76)*	*0.007*	0.75
Trait anxiety	−0.01 ± 0.02	0.99 (0.95–1.03)	0.60	
Alexithymia – DIF	0.03 ± 0.03	1.03 (0.97–1.10)	0.36	
Depression	*0.14 ± 0.04*	*1.16 (1.06–1.26)*	*0.001*	
Panic disorder°	0.21 ± 0.51	1.24 (0.46–3.35)	0.67	
Step 4: Somatic symptom reporting				
Lifetime abuse⋆	−0.71 ± 0.45	0.49 (0.20–1.19)	0.11	0.83
Trait anxiety	0.001 ± 0.02	1.00 (0.96–1.04)	0.95	
Alexithymia – DIF	0.005 ± 0.04	1.01 (0.93–1.08)	0.90	
Depression	*0.16 ± 0.06*	*1.17 (1.04–1.31)*	*0.008*	
Panic disorder°	0.84 ± 0.65	2.32 (0.64–8.35)	0.20	
'Somatization'	*0.18 ± 0.06*	*1.20 (1.06–1.35)*	*0.004*	
Dyspepsia symptoms	−0.08 ± 0.05	0.92 (0.83–1.02)	0.11	
Weight loss	*0.06 ± 0.03*	*1.06 (1.00–1.12)*	*0.05*	

Significances in italic.
Probability modeled = presence of co-morbid CF; all models $P < 0.05$.
⋆Reference category = abuse; °Reference category = no panic disorder.

co-morbidity. Therefore, we limited the risk factor analyses to co-morbid IBS (yes/no) and co-morbid CF-like symptoms (yes/no), ignoring overlap.

Hypothesis 1 & 2: 'Somatization' as a risk factor for co-morbid IBS and CF-like symptoms

'Somatization' was an *independent* risk factor for IBS co-morbidity, whereas it acted as an *overlapping* risk factor (with depression and weight loss) for CF-like symptom co-morbidity. This is in line with both epidemiological and psychophysiological work in IBS, indicating that a 'psychological' tendency to perceive and report somatic symptoms in general may be an important mechanism underlying FSS symptom formation and co-morbidity without, however, completely explaining co-morbidity.[12,13,60,61] Furthermore, 'somatization' *mediated* (in its limited sense defined in the methods section) the effect of abuse history on both co-morbidities. It is conceivable that some intermediate psycho(bio)logical processes underlie the link between abuse and 'somatization', including attachment, hypervigilance toward somatic symptoms, pain coping mechanisms and others. These psychological processes may drive maladaptive mechanisms at the neurobiological level such as deficient endogenous pain modulation.[19,30,31,34] The fact that such mechanisms, and potential important precipitating factors, including infections,[18,21] were not included in this study may account for the fact that the models reported here do not classify all cases correctly.

Hypothesis 3: Depression is a risk factor for co-morbid CF-like symptoms, but not IBS

This hypothesis was confirmed; a more important role for depression in CF(S) compared to IBS is in line with previous findings.[18,21,35] It has indeed been shown that psychiatric co-morbidity may explain FSS co-morbidity partially but not fully.[12,13,20,62] In the present study, we found that depression and 'somatization' were both significant, though *overlapping* risk factors for CF-like symptom co-morbidity. It is indeed known that depression and 'somatization' frequently occur together, without, however, being identical entities. This may be due to various reasons, including the fact that current symptom criteria for depression contain somatic items and/or the fact that depression interferes with autonomic nervous system activity or interoceptive/pain processing at the brain level.[26–28] Furthermore, the finding that depression 'mediates' the effect of alexithymia (DIF dimension) on co-morbid CF-like symptoms is also in line with previous research.[29,55]

Hypothesis 4: Gastric sensorimotor function is a risk factor for co-morbid IBS, but not CF-like symptoms

Gastric sensorimotor function was not associated with CF-like symptoms, even in bivariate analysis. Gastric accommodation was a significant *independent* risk factor for co-morbid IBS, providing some support for the 'panintestinal (sensori)motor disorder hypothesis'

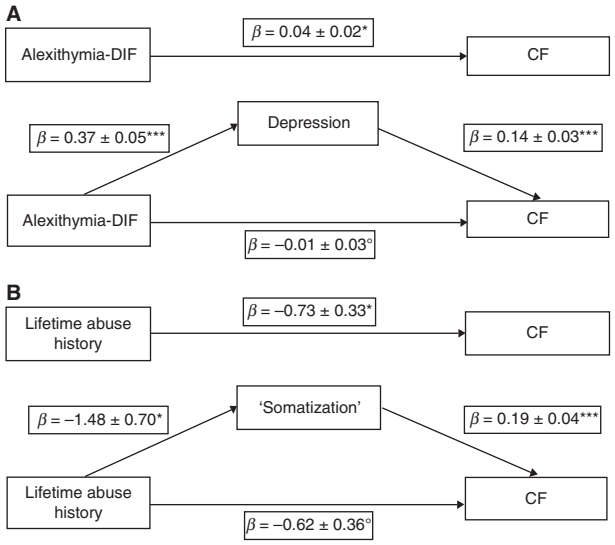

Figure 2 (A) The effect of alexithymia – DIF on co-morbid CF is mediated by depression. $^{*}P < 0.05$; $^{***}P < 0.001$; $^{\circ}P = 0.57$; Sobel test $Z = 3.95$, $P < 0.0001$. (B) The effect of lifetime abuse history on co-morbid CF is mediated by 'somatization'. $^{*}P < 0.05$; $^{***}P < 0.001$; $^{\circ}P = 0.09$; Sobel test $Z = -1.90$, $P = 0.057$.

to explain co-morbidity within the FGID group. Gastric sensitivity was a (borderline) significant risk factor for co-morbid IBS before 'somatization' was entered into the model. Gastric hypersensitivity as measured here may be the manifestation of a more generalized hypersensitivity for somatic stimuli. Such a generalized hypersensitivity may be a key physiological mechanism in FSS in general and in one of the psychobiological mechanisms underlying 'somatization'.[10,30,31] We therefore may speculate that gastric sensitivity and 'somatization' may act as *proxy* risk factors for IBS co-morbidity, which is supported by their significant correlation ($r = -0.22$, $P = 0.0006$); this term does, contrary to 'mediator', not contain an assumption on temporal precedence.[59] In other words, gastric hypersensitivity would be one aspect or manifestation of the multidimensional process of 'somatization'. This is supported by evidence showing that psychosocial factors may influence (gastric) sensory thresholds.[63]

Limitations

First, we used self-report measures, which may be prone to certain forms of bias. For example, abuse history questionnaires may be prone to recall bias and their results may be confounded by present depressive symptoms.[64] However, the abuse measures we used are validated specifically in (functional) GI populations[38] and have been widely used. Although a structured clinical interview remains the 'gold standard' for diagnosing psychiatric co-morbidity, we chose self-report measures that have been validated with a structured interview as a comparison. Furthermore, some potentially relevant variables, including coping strategies, were not evaluated in this study but should be included in future research.

Second, this is a cross-sectional observational study, permitting conclusions about associations but not about causality, temporal order or directionality of the relationships between the variables studied. For example, the order in which (groups of) variables were entered in the regression models was chosen to reflect the putative temporal order of things in the best way possible (based on conceptual and empirical grounds), but this remains an assumption. Strictly speaking, mediation requires temporal precedence of the mediator by the mediated variable.[59] However, we used the term mediation in a more limited sense (i.e. devoid of its temporal precedence aspect) throughout this paper. Therefore, the results should be interpreted with sufficient caution and require replication in longitudinal studies before any definite conclusions can be drawn.

Third, the patient population consists of tertiary care FD patients, limiting generalizability of the results toward other populations of FD patients.

Fourth, the CF measurement was based on two non-validated screening questions; it should therefore be regarded as indicative of co-morbid *CF-like symptoms*, not as a full assessment of chronic fatigue *syndrome* according to its diagnostic criteria.

CONCLUSION

First, 'somatization' is a common risk factor for co-morbid IBS and CF-like symptoms in FD. Second, 'somatization' is a 'mediator' of the effect of abuse history on co-morbid IBS and CF-like symptoms. Third, co-morbid depression is a risk factor for CF-like symptoms, but not IBS co-morbidity; it 'mediates' the effect of alexithymia (DIF dimension). Fourth, gastric sensorimotor dysfunction is a risk factor for IBS, but not CF-like symptom co-morbidity. These findings add to the existing evidence on co-morbidity with other FSS in FD, which is likely to be the result of a complex interplay between biological, psychological and social factors. More specifically, different FSS seem to share certain etiopathogenetic mechanisms [especially (abuse-induced) 'somatization'] without, however, being completely overlapping and/or identical, which is in line with previous research in FSS.[9,12,13,23]

In other words, the truth may lie somewhere in between completely 'lumping' or 'splitting' these disorders but it remains to be elucidated which of these two extreme positions comes closest to reality. Further research is especially needed to elucidate the psychobiological mechanisms that may underlie what we now descriptively call 'somatization'.

The clinical message emerging from this study may lie in the importance of screening for co-morbid 'intestinal' and 'extra-intestinal' FSS in patients presenting primarily with FD symptoms. This approach may identify a subgroup of patients that may benefit most from interventions, whether pharmacological or psychotherapeutical, that target psychiatric co-morbidity and/or 'somatization' and its putative underlying psychobiological mechanisms, rather than the organ that corresponds to the primary symptoms with which the patient is primarily presenting.[65]

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AUTHOR CONTRIBUTION

LVO contributed to study design, data analysis and writing of the paper; JVDB contributed to study design and data collection; RV and LH contributed to patient recruitment and data collection; JT contributed to study design, patient recruitment and writing of the paper.

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