Brain-Gut Miscommunication: Biopsychosocial Predictors of Quality of Life in Irritable Bowel Syndrome

Pletikosić Tončić, Sanda; Tkalčić, Mladenka; Hauser, Goran

Download date / Datum preuzimanja: **2025-02-07**

Brain-Gut Miscommunication: Biopsychosocial Predictors of Quality of Life in Irritable Bowel Syndrome

Sanda Pletikosić Tončić and Mladenka Tkalčić

University of Rijeka, Faculty of Humanities and Social Sciences,
Department of Psychology, Croatia

Goran Hauser

University of Rijeka, Division of Gastroenterology, Department of Internal Medicine,
Clinical Hospital Centre Rijeka, Medical Faculty Rijeka,
Faculty of Health Studies Rijeka, Croatia

Abstract

Irritable bowel syndrome (IBS) is a complex disorder that results from interactions of numerous factors. The biopsychosocial model describes a number of predisposing, precipitating, and perpetuating factors, which contribute to the onset and maintenance of symptoms and consequently to quality of life (QoL) impairment. The aim of this study was to examine the impact of several psychological and biological factors on the physical and mental components of QoL in IBS patients. A total of 46 IBS patients completed a set of questionnaires (Big Five Inventory, State-Trait Anxiety Inventory, Beck Depression Inventory-II, Medical Outcome Study Short-Form 36) and kept a diary of their mood, daily stress, and symptoms over a period of two weeks. Patients' heart rate variability, serum cortisol, and fecal calprotectin levels were also measured. The results of regression analyses showed that depression (β = -.30) and negative mood (β = -.28) predicted physical QoL, while depression (β = -.45) and positive mood (β = .33) significantly predicted mental QoL. The model, which included calprotectin, cortisol, anxiety, depression, and positive and negative mood, explained a total of 47% of variance of physical and 57% of variance of mental QoL. Our results confirm the role of negative affect in IBS QoL impairment. They also indicate that biological factors seem important for physical QoL in IBS patients. The role of positive mood as a protective factor for mental QoL might be significant for psychological interventions with IBS patients.

Keywords: Biopsychosocial model, Irritable bowel syndrome, quality of life, depression, positive and negative mood

Introduction

When Engel (Engel, 1977) proposed the biopsychosocial (BPS) model of health and disease, the door for understanding functional disorders opened. Accordingly, this model provides the conceptual basis for defining, understanding, and treating functional gastrointestinal (GI) disorders (Drossman, 1998; Drossman, Camilleri, Mayer, & Whitehead, 2002; Drossman & Hasler, 2016; Surdea-Blaga, Baban, Nedelcu, & Dumitrascu, 2016). It is now clear that irritable bowel syndrome (IBS), one of the most common functional GI disorders, results from complex bi-directional interactions of biological, psychological, and social factors (Muscatello, Bruno, Scimeca, Pandolfo, & Zoccali, 2014; van der Veek, Dusseldorp, van Rood, & Masclee, 2010; van Tilburg, Palsson, & Whitehead, 2013). Models that integrate those factors are necessary to explain the heterogeneity and complexity related to this condition (Spence & Moss-Morris, 2007). IBS is a global disorder whose symptoms are often accompanied by psychological dysfunction such as anxiety and depression, and by a significant impairment of health-related quality of life (Enck et al., 2016; Ford et al., 2014; Lackner et al., 2007; Mykletun et al., 2010; Quigley, 2006; Sibelli et al., 2016; Sood, Gracie, Law, & Ford, 2015; Tang, Lin, & Zhang, 2013). Even though a respectable amount of research on IBS exists, it is still a poorly understood disorder, leaving an urgent need for understanding its pathophysiology and finding effective treatment.

According to the BPS model (Drossman et al., 2002; Van Oudenhove et al., 2016), the integrated effects of altered physiology and the person's psychosocial status will determine the illness experience and the clinical outcome. More specifically, the model postulates that biological and psychosocial predisposing factors-such as genetics, trauma, parental illness behavior, and personality traits (e.g., neuroticism), among others-increase a person's susceptibility to developing IBS. Furthermore, precipitating and perpetuating factors (e.g., gut infection, stressful life events, social support, and affective status) contribute to the onset and the maintenance of symptoms over time (Deary, Chalder, & Sharpe, 2007; Hauser, Pletikosic, & Tkalcic, 2014; Hubbard et al., 2015).

The bi-directional communication system between the brain and the gut with its microbiota and immune system, known as the brain-gut axis, serves as the neurophysiological mechanism that explains the link between psychological, biological and social aspects of IBS (Enck et al., 2016; Jones, Dilley, Drossman, & Crowell, 2006; Katsanos, Giannopoulos, & Tsivgoulis, 2012; Van Oudenhove et al., 2016). According to this conceptualization, IBS symptoms are clinical manifestations of "miscommunication" between the gut and the affective-cognitive and emotional motor systems of the brain (Fichna & Storr, 2012; Lackner et al., 2010; Van Oudenhove et al., 2016).

Psychological distress is an important risk factor for the development and maintenance of IBS symptoms (recurrent abdominal pain or discomfort associated

with altered defecation), but it can also occur because of disease burden (Van Oudenhove et al., 2016). This means that abdominal symptoms can influence anxiety and depression and vice versa; psychosocial factors can influence physiological factors, such as motor function or stress reactivity of the gut (Fond et al., 2014). Epidemiological studies show that anxiety and depression are more common in IBS patients compared with controls (Myers & Greenwood-Van Meerveld, 2009; Sibelli et al., 2016; Zijdenbos, de Wit, van der Heijden, Rubin, & Quartero, 2009). In a recent systematic review, Sibelli (Sibelli et al., 2016) showed that the risk for developing IBS at follow-up was double for persons with higher anxiety and depression at baseline, compared to those with lower levels. Similarly, neuroticism, somatization, and stress (chronic and acute) have all been linked to the onset and course of IBS (Sasaki, 2003; Spence & Moss-Morris, 2007). Research shows that IBS patients have higher levels of neuroticism as a personality trait than healthy persons (Farnam, Somi, Sarami, & Farhang, 2008; Tkalcic, Hauser, & Stimac, 2010) and neuroticism has often been linked to higher pain reports in IBS patients (Tanum & Malt, 2000). Findings on the role of other personality traits (e.g., extraversion, conscientiousness) have been inconsistent. IBS patients report more frequent stressors and more extensive effects of stressful events on everyday life than controls (Myers & Greenwood-Van Meerveld, 2009). Research also shows that daily levels of stress and daily mood have significant effects on both symptom severity and quality of life (Blanchard et al., 2008; Pletikosic & Tkalcic, 2016).

Psychological processes can influence various aspects of GI function through efferent brain-gut pathways − the autonomic nervous system and the hypothalamo-pituitary-adrenal hormonal system (Van Oudenhove et al., 2016). For instance, negative affect plays a key role in the dysregulation of the brain-gut axis, contributing to most pathophysiological and symptomatic correlates of IBS (Mayer, 2000; Muscatello et al., 2014). Mayer (Mayer, 2000) emphasized that stress-induced alterations in autonomic regulation, both sympathetic and parasympathetic, have an important role in the modulation of secretion, motility, inflammation, and sensory response of the gut. Some of these peripheral alterations can influence brain structure and function, setting up circular regulatory loops between the gut and the brain (Enck et al., 2016).

Autonomic dysfunction has been associated with IBS such that persistent alterations of autonomic responsiveness play a role in altered bowel habits and alterations in gastric emptying, as well as in altered visceral perception (Katsanos et al., 2012; Mayer, 2000). Most studies that tried to characterize autonomic dysfunction in patients with IBS by means of heart rate variability (HRV), a non-invasive measure of autonomic function, reported no difference in HRV when the IBS population was compared to healthy controls. However, when comparing subgroups of IBS patients according to their predominant bowel symptoms, the severity of the clinical course, the presence of depressive symptoms, or a history of abuse, results revealed changes in autonomic functioning (Mazurak, Seredyuk,

Sauer, Teufel, & Enck, 2012). Similarly, the results of a meta-analysis (Liu, Wang, Yan, & Chen, 2013) reported that impaired parasympathetic functioning and abnormal sympathovagal balance may be involved in the pathogenesis of IBS, with more obvious vagal dysfunction found in IBS patients with predominant constipation. Several studies have reported a relationship between anxiety and depression with altered ANS function in IBS (Jones et al., 2006; Punyabati, Deepak, Sharma, & Dwivedi, 2000). For example, Punyabati et al. (2000) showed that parasympathetic reactivity was significantly increased in IBS patients compared to controls and their anxiety score was significantly higher. Based on the results of a meta-analysis, Tak et al. (2009) concluded that available evidence is not adequate to firmly reject or accept the role of autonomic dysfunction in IBS due to heterogeneous and inconsistent results.

In addition to autonomic dysfunction, the HPA axis activated by stressors plays an important role in functional visceral syndromes characterized by chronic discomfort and pain (Chang et al., 2009; Mayer, 2000). Correlations among daily stress, anxiety, depression, and GI symptoms indicate that HPA axis dysregulation may be an important component of IBS symptomatology (Myers & Greenwood-Van Meerveld, 2009). Increased expression and release of CRF in IBS patients are consistent with the reported evidence for increased sympathetic responses (Mayer, 2000). In their well-designed experimental study, Kennedy et al. (Kennedy, Cryan, Quigley, Dinan, & Clarke, 2014) used the *Trier Social Stress Test* - a standardized laboratory-based psychosocial stress task - and found that, following acute psychosocial stress, patients with IBS exhibit a more sustained HPA axis response (total salivary cortisol output) when compared to healthy controls, with an increase in self-reported GI symptomatology. It seems that for IBS and depressive patients, HPA-axis dysregulation is an important etiological factor (Karling, Wikgren, Adolfsson, & Norrback, 2016), but inconsistency related to the existence of hypo or hypercortisolism in both conditions is still present.

It is possible that psychosocial factors modulate the immune response of the gut to infectious agents which can cause low level inflammation in the bowel (Fichna & Storr, 2012). Due to this hypothesis, there is a growing interest to identify and validate biological markers that help in diagnosing functional GI disorders, such as IBS (Mujagic et al., 2016). One of those markers which proved to be significantly altered in IBS patients compared to individuals in the healthy control group is fecal calprotectin, pointing to a low-grade pro-inflammatory state in an IBS patient subgroup (Mujagic et al., 2016; Pletikosic, Plavsic, Hauser, & Tkalcic, 2015). Furthermore, our preliminary results (Pletikosic et al., 2015) indicate that fecal calprotectin levels significantly correlate with the physical component of health-related quality of life (HRQoL).

It is doubtless and clear that, regardless of still unsatisfactory and insufficient understanding of IBS pathophysiology, this GI disorder considerably reduces the patients' quality of life (Enck et al., 2016; Kennedy et al., 2014; Muscatello et al.,

2014; Van Oudenhove et al., 2016). HRQoL is an important outcome measure in IBS, and it is related to both the physical and the psychological aspects of symptom severity. Numerous studies show that IBS patients experience a significant impairment in HRQoL compared to patients with other chronic disorders, as well as compared to healthy persons (Frank et al., 2002; Gralnek, Hays, Kilbourne, Naliboff, & Mayer, 2000; Lackner et al., 2007; Spiegel et al., 2004; ten Berg, Goettsch, van den Boom, Smout, & Herings, 2006). A variety of factors may contribute to patients' HRQoL (Wong & Drossman, 2010). For example, Palsson et al. (Palsson, Jones, Turner, Drossman, & Whitehead, 2002) found that the severity and the frequency of symptoms affect HRQoL in IBS, that the presence of multiple non-GI physical symptoms is associated with worse HRQoL, and that depression worsens HRQoL in IBS, even when controlling for the severity of symptoms.

It seems that the search for factors involved in HRQoL impairment in IBS is still ongoing, with important parts of this complex puzzle missing. Therefore, the main goal of this study was to examine the impact of various - *psychological* (personality traits and affect, daily mood, stress intensity, perceived symptom severity) and *biological* (calprotectin, cortisol, and HRV) components of the BPS model on the physical and mental components of general HRQoL in IBS patients. More specifically, the goal was to determine the specific contribution of biological and psychological factors to quality of life impairment in IBS patients.

Materials and Methods

The study was approved by the Ethics Committee of the Clinical Hospital Centre in Rijeka and all participants signed an informed consent form. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Participants

The sample consisted of 46 IBS patients (34 female, 12 male) recruited at the Gastroenterology Department of the Clinical Hospital Centre in Rijeka, Croatia. Patients were diagnosed based on Rome III criteria. The participants' age ranged from 18 to 69 years ($M = 44.42$, $SD = 13.90$); most were married or living with a partner (65.2%), employed (58.7%), and had a high school education (69.6%). Illness duration ranged from 1 to 51 years, with a duration of 1 year in 22.7% of participants, a duration of 2-4 years in 28.3% of participants, 5-10 years in 26% of participants, and over 10 years in 19.8% of participants.

Measures

Psychosocial Measures

The *Big Five Inventory* (BFI) (John & Srivastava, 1999; Kardum, Gračanin, & Hudek-Knežević, 2006) was used to measure five personality factors: neuroticism, extraversion, conscientiousness, agreeableness, and openness. BFI consists of 44 items in the form of short phrases based on adjectives typical of the five personality traits. Participants respond on a five-point scale indicating their degree of agreement with each item (1 - *completely disagree*, 5 - *completely agree*). Previous studies on Croatian samples have replicated the original questionnaire structure, with Cronbach alphas ranging from .72 to .82 (Kardum et al., 2006).

The *State-Trait Anxiety Inventory* (STAI-T) (Spielberger, 2000) measures the dispositional tendency towards anxiety (trait anxiety), and it consists of 20 items. Participants respond on a four-point scale, assessing how often they feel a certain way in general. A higher score indicates a higher proneness to anxiety. This questionnaire has high reliability ($\alpha = .91$) (Spielberger, 2000).

The *Beck Depression Inventory-II* (BDI-II) (Beck, Steer, & Brown, 2011) measures the severity of psychological symptoms of depression using 21 items. Answers are given on a scale from zero to three, assessing the frequency and the intensity of the listed symptoms. Reported reliability coefficients are quite high (Cronbach $\alpha = .90$ for student samples, and .93 for clinical samples) (Beck et al., 2011).

The *Medical Outcome Study Short-Form 36* (SF-36) (Tkalčić, Hauser, Štimac, & Pokrajac-Bulian, 2007; Ware & Sherbourne, 1992) measures both physical and mental health-related QoL. Specifically, it includes four domains of physical health (physical functioning, role limitation [physical], bodily pain, and general health) and four domains of mental health (role limitation [emotional], vitality, mental health, and social functioning). It is possible to obtain eight final scores (one for each domain) and two final summary scores—the physical component summary, which has 21 items, and the mental component summary, which has 14 items. Participants respond to different questions either with yes-no answers, on a 3-point scale (how limited do they feel by their health; 1 - *limited a lot*, 3 - *not limited at all*), on a 5-point scale (indicating the degree to which items hold true for them; 1 - *completely true*, 5 - *completely false*), or on a 6-point scale (indicating the amount of time spent feeling a certain way; 1- *all of the time*, 6 - *none of the time*). Participant responses are transformed and summed to provide scores between 0 and 100 with higher scores reflecting better health-related QoL (Ware & Sherbourne, 1992).

Several scales were used in the longitudinal part of the study and were completed either three times a day, in the morning, afternoon, and evening (daily mood and symptom severity) or once daily (daily stressful events) for two weeks. For all of these measures, 42 (or 14) measurement time points were obtained, but in the following analyses, the mean score of each measure was used for each participant.

Daily mood was measured using an abbreviated version of the *Mood Scale* (Kardum & Bezinović, 1992). The scale measures seven first order factors and two higher order factors: positive mood (PM; consisting of joy, activation, and acceptance) and negative mood (NM; consisting of sadness, anger, rejection, and fear). The abbreviated version used in this study has 15 items, with two items per each lower order factor (except for joy, which has three items) that had the highest factor loadings in previous research (Tončić, 2009). The distribution of NM values proved to be positively skewed (skeweness = 1.02; kurtosis = 0.45) and was recoded as an ordinal variable with three levels, each level containing a third of the sample.

Patients' symptom severity was measured via the *IBS Symptom Severity Scale*, which was constructed based on the Gastrointestinal Symptom Diary (Blanchard, 2001). It contains eight symptoms (constipation, diarrhea, abdominal pain, abdominal tenderness, bloating, nausea, flatulence, belching), and the participants must rate the severity of each symptom on a scale from zero (*absent*) to four (*debilitating*).

Patients' daily stressful events were measured using the *Daily Stressful Events Scale*, which was constructed based on the stressful events classification from the manual for coding interviews of the *Daily Inventory of Stressful Events* (DISE) (Almeida, 1998). Patients marked whether they experienced any of the seven types of stressful events (related to e.g., health, finances, family relationships), how many such events they experienced per type, and for each type they marked how stressful it was from one (*slightly stressful*) to four (*very, intensely stressful*).

Descriptive data for BFI, STAI-T, BDI-II, SF-36, symptom severity and stress intensity are shown in Table 1.

Table 1

Descriptive Data for the Scales Used in the Study

Scale	*M*	*SD*	Obtained range	Cronbach alpha
Neuroticism	24.61	4.94	16 - 35	.73
Extraversion	27.67	5.91	12 - 39	.82
Openness	36.30	6.09	26 - 49	.78
Conscientiousness	34.33	5.94	21 - 43	.85
Agreeableness	34.50	5.67	22 - 44	.81
Anxiety	34.72	11.21	14 - 59	.89
Depression	8.39	6.51	0 - 24	.82
SF-36 physical component	75.90	13.81	41.43 - 97.86	.82
SF-36 mental component	67.20	18.02	32.14 - 95.36	.88
Positive mood	2.37	0.49	1.19 - 3.27	/
Negative mood	0.54	0.42	0 - 1.70	/
Symptom severity	1.52	0.29	1.04 - 2.10	/
Stress intensity	0.89	0.64	0 - 2.74	/

Biological Measures

Several indirect biological measures were used: serum cortisol, fecal calprotectin, and heart rate variability.

To record a marker of HPA activity, serum cortisol levels were obtained from one blood sample, collected during the morning hours. Electrochemiluminescent-immunological method (ECLIA) was used, with possible cortisol values ranging from 0.5 to 1750 nmol/L. Reference values for healthy persons range from 171 to 536 nmol/L in the morning and from 64 to 327 nmol/L in the afternoon (Elecsys Cortisol Assay).

As an indirect measure of gut inflammation, fecal calprotectin levels were obtained from one stool sample. An immunoenzyme assay was used to determine the quantitative levels of calprotectin (Quantum Blue Calprotectin), with possible values ranging from 30 to 300 µg/g. Research shows that a cut-off value of 50 µg/g has high sensitivity (above 95%), and a somewhat lower specificity (74%), which indicates that calprotectin levels under 50 µg/g should be considered normal (Waugh et al., 2013). The distribution of calprotectin values was positively skewed (skeweness = 4.97; kurtosis = 28.02) and was transformed into an ordinal variable, with values of less than 30 µg/g (which the test could not detect) treated as zero calprotectin, values between 30 and 50 µg/g treated as low calprotectin, and values above 50 µg/g as medium to high calprotectin.

As a marker of autonomic function, heart rate variability (HRV) was measured. In order to monitor heart rate, we used Polar RS 800 devices, which consist of a chest strap with a transmitter and electrodes and a wrist watch with a receiver and data storage. The patients recorded their heart rates for 15 minutes, three times a day (morning, afternoon, and evening), for two weeks. The final five minutes of each measurement time point were extracted. A power spectral analysis was performed using a fast Fourier transform with HRV Analysis Software (Niskanen, Tarvainen, Ranta-Aho, & Karjalainen, 2004) in order to calculate power spectral density, or high frequency (HF) and low frequency (LF) HRV measured in absolute power values (ms^2). Sympathovagal balance (LF/HF HRV) was calculated by dividing LF HRV by HF HRV.

Table 2 shows average values and obtained ranges for cortisol, calprotectin and HRV measures.

Table 2

Descriptive Data for Cortisol, Calprotectin, and Heart Rate Variability (HRV) Measures: Low Frequency HRV, High Frequency HRV and Low : High HRV Ratio

Measure	M	SD	Obtained range
Cortisol	367.08	148.94	102.90 - 830.90
Calprotectin	47.95	43.50	30.00 - 300.00
LF HRV	379.69	398.53	5.24 - 1649.42
HF HRV	228.12	289.74	1.54 - 1484.07
LF/HF HRV	3.31	2.63	0.76 - 13.30

Procedure

Data was collected from January 2012 to October 2013. Participants were recruited at the Clinical Hospital Centre in Rijeka, Croatia. They participated in the study in small groups (two to seven people). For each group of participants, the study had three parts (illustrated in Figure 1). In the first part, the participants completed a set of questionnaires (general information, BFI and STAI-T). Each participant individually carried out the second part over the course of two weeks. They completed the Mood Scale, the IBS Symptom Severity Scale, and measured their heart rate for 15 minutes while abstaining from all other activities three times each day (within two hours of waking up, between 16:00 and 18:00 in the afternoon, and within two hours of going to sleep). During the third daily measurement time point, they also completed the Daily Stressful Events Scale. Participants were reminded about each measurement time point via mobile phone text message. During those two weeks, participants also gave one blood sample (for serum cortisol) and one stool sample (for fecal calprotectin). After the two-week period, the participants completed a final set of questionnaires (BDI-II, SF-36).
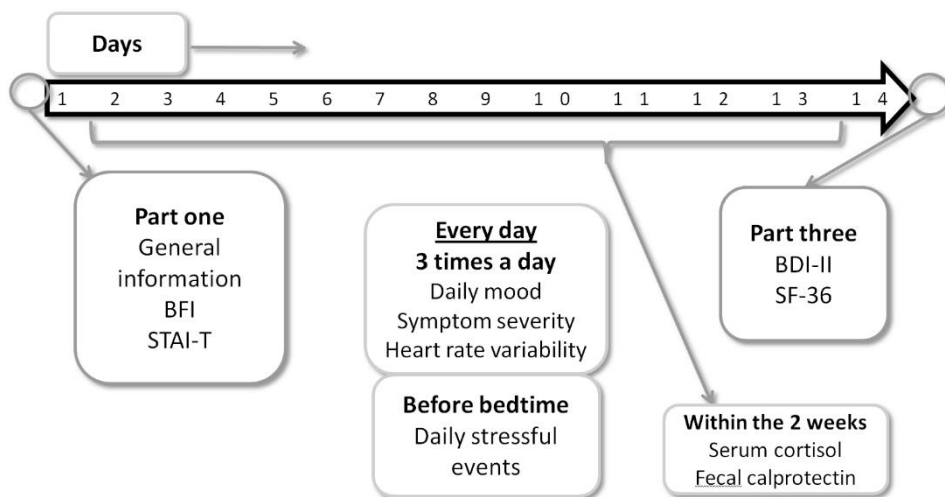
Figure 1. Timetable of the study design. The study was comprised of three parts. Part one and part three consisted of completing a set of questionnaires and were carried out at the Clinical Hospital Centre in Rijeka. The second part lasted 14 days and was carried out at home by each participant individually. They were required to complete a diary consisting of several scales and to record their heart rate. During those 14 days participants were required to give one blood sample and one stool sample for determining their serum cortisol levels and fecal calprotectin levels, respectively.

Results

To estimate the impact of individual components of the BPS model on QoL in IBS patients, we performed two hierarchical regression analyses. Due to the large number of predictors (16) and the relatively small number of participants (43 for the indirect biological measures, 46 for all other measures) we could not use all predictors in the same analyses. We decided to select 2 predictors from each group of predictors, resulting in a total of 6 predictors which were used in the hierarchical regression analyses. Two predictors with the highest correlations with the outcome variables were selected (marked in **bold** in Table 3). The outcome variables used were the two composite scores of the SF-36: the physical and the mental component. Predictors were grouped based on their similarity: indirect biological measures (calprotectin, cortisol, HRV), traits and affect measured once via questionnaires (BFI, STAI-T, BDI-II), and longitudinal data averages calculated from the diary data (mood, symptom severity, stress intensity). Since calprotectin and negative mood (NM) scores were transformed onto an ordinal scale with three levels, dummy coding was used in the analyses: medium and high levels were compared with low levels for both calprotectin and NM. Table 3 shows correlation coefficients of all predictors with both outcome variables.

Table 3

Pearson Correlation Coefficients between Quality of Life Composite Scores and Their Possible Determinants, Grouped by Type of Measurement

Predictors	SF-36 physical component	SF-36 mental component
Biological measures		
High vs. Low Calprotectin	**-.39**[*]	**-.28**
Medium vs. Low Calprotectin	-.04	.10
Cortisol	**.11**	**-.22**
LF HRV	.13	-.01
HF HRV	.12	-.03
LF/HF HRV	.02	.10
Traits and affect		
Neuroticism	-.25	-.25
Extraversion	.41[**]	.32[*]
Openness	.30[*]	.06
Conscientiousness	.16	.23
Agreeableness	-.12	.09
Anxiety	**-.49**[**]	**-.38**[**]
Depression	**-.51**[**]	**-.59**[**]
Longitudinal averages		
Positive mood	**.25**	**.44**[**]
High vs. Low Negative Mood	**-.50**[**]	**-.46**[**]
Medium vs. Low Negative Mood	.16	.01
Stress intensity	-.19	-.30[*]
Symptom severity	-.07	-.06

[*]$p < .05$; [**]$p < .01$.

The physical component of SF-36 had the highest correlation with calprotectin, while the mental component had the highest correlations with calprotectin and cortisol. Participants with calprotectin levels above 50 μg/g had significantly lower physical and mental QoL than participants with lower levels of calprotectin. In addition, higher levels of cortisol were related to lower mental QoL.

Even though several traits had significant correlations with one or both measures of QoL, depression and anxiety showed the highest correlations with both outcome variables. Participants with higher depression and higher anxiety scores had lower QoL.

In the final group of predictors - averages of longitudinally collected data - positive (PM) and negative mood (NM) had the highest correlations with the outcome variables. Participants with the highest average NM had significantly lower physical and mental QoL than participants with lower NM averages. In addition, participants with higher PM averages had higher mental QoL.

All of the predictors described above were used in the two hierarchical regression analyses. The selected predictors were only mildly intercorrelated ($M_{absolute\ r}$ = .28; maximum r = .49). A chronological approach was taken for variable entry into the regression model, with biological measures - calprotectin and cortisol - entered in the first step, traits and long-term mood - depression and anxiety - introduced in the second step, and averages of daily mood - PM and NM - entered in the final step of the regression analyses (Tables 4 and 5).

Due to the small sample size, 95% confidence intervals of each estimated parameter were calculated using bootstrapped samples (N of samples = 1000).

As shown in Tables 4 and 5, the empirically derived confidence intervals closely resemble the results of conventional parameter significance testing.

Table 4

Results of a Hierarchical Regression Analysis for the Physical Component of Quality of Life (With Bootstrap Confidence Intervals)

Predictors	Estimate	Bootstrap 95% CI		β	ΔR^2	R^2
			SF-36 physical component			
Step 1					.15*	.15*
Intercept	80.1952	70.0014;	93.4531			
High vs. Medium and Low Calprotectin	-12.7813	-22.6967;	-2.8180	**-.40***		
Cortisol	-0.0026	-0.0354;	0.0175	-.03		
Step 2					.26**	.41**
Intercept	90.0584	76.0144;	109.5810			
High vs. Medium and Low Calprotectin	-5.7846	-15.9830;	5.1661	-.18		
Cortisol	0.0110	-0.0218;	0.0339	.12		
Anxiety	-0.2578	-0.7656;	0.1068	-.20		
Depression	-0.9278	-1.5808;	-0.1060	**-.42***		

Table 4 - *Continued.*

				SF-36 physical component		
Predictors	Estimate	Bootstrap 95% CI		β	ΔR^2	R^2
Step 3					.06	.47**
Intercept	81.4112	56.7886;	105.9956			
High vs. Medium and Low Calprotectin	-4.5189	-16.0583;	8.3143	-.14		
Cortisol	0.0184	-0.0185;	0.0480	.19		
Anxiety	-0.1959	-0.6913;	0.1536	-.15		
Depression	-0.6668	-1.3837;	0.4054	-.30†		
Positive Mood	1.6751	-6.0991;	10.3227	.06		
High vs. Medium and Low Negative Mood	-8.3491	-20.6410;	3.7270	-.28†		

†$p < .10$; *$p < .05$; **$p < .01$.

Table 5

Results of a Hierarchical Regression Analysis for the Mental Component of Quality of Life (With Bootstrap Confidence Intervals)

				SF-36 mental component		
Predictors	Estimate	Bootstrap 95% CI		β	ΔR^2	R^2
Step 1					.19*	.19*
Intercept	88.1287	76.8686;	101.3753			
High vs. Medium and Low Calprotectin	-15.5857	-28.2827;	-3.5064	**-.40***		
Cortisol	-0.0418	-0.0806;	-0.0123	**-.36***		
Step 2					.25**	.44**
Intercept	92.4656	65.9736;	113.8010			
High vs. Medium and Low Calprotectin	-7.5433	-18.2182;	5.0202	-.19		
Cortisol	-0.0210	-0.0599;	0.0235	-.18		
Anxiety	-0.0650	-0.5661;	0.4929	-.04		
Depression	-1.3982	-2.5820;	-0.6121	**-.52***		
Step 3					.13*	.57**
Intercept	55.8205	19.7878;	84.9981			
High vs. Medium and Low Calprotectin	-3.8942	-16.4151;	8.5626	-.10		
Cortisol	-0.0104	-0.0457;	0.0286	-.09		
Anxiety	0.0445	-0.4433;	0.5742	.03		
Depression	-1.2123	-2.3641;	-0.4952	**-.45***		
Positive Mood	11.9066	2.6444;	21.3216	**.33***		
High vs. Medium and Low Negative Mood	-5.9247	-16.7175;	5.7918	-.16		

*$p < .05$; **$p < .01$.

Biological measures which were entered in the first step of the regression analyses explained a significant proportion of variance of physical and mental QoL (15% and 19% respectively). Calprotectin was a significant predictor for both criteria and cortisol significantly predicted only the mental QoL. After anxiety and depression were added in the second step, the biological measures were no longer significant predictors. Anxiety and depression explained an additional 26% and 25% of QoL variance. In the third step, PM and NM were added, resulting in a total of 47% of variance explained for the physical QoL and 57% for the mental QoL. Depression and NM were marginally significant ($p < .10$) predictors of physical QoL, while depression and PM were significant predictors of mental QoL. Participants with higher depression scores had lower QoL, those with higher PM had higher mental QoL, while those with the highest NM had lower physical QoL.

To test whether biological measures predict QoL beyond psychological measures, we performed two additional hierarchical regression analyses, one for each QoL measure, and we entered the biological measures in the second step, after psychological variables were already included in the model. For physical QoL, biological measures explained an additional 6.5% of variance ($p = .12$; calprotectin $\beta = -.14$ and cortisol $\beta = .19$, both non-significant), but for mental QoL they did not improve the model fit significantly ($\Delta R^2 = .009$).

Discussion

The goal of this study was defined by the constant need to understand the communication between the brain and the bowel through the relationship between biological and psychosocial factors, and building upon the present knowledge derived from the BPS model. The BPS model is very broad, which makes it impossible to consider all relevant factors simultaneously; however, we decided to include several factors from each aspect of the model.

After analyzing correlations of each aspect of the BPS model with QoL separately, the final regression models contained predictors with the highest correlations. In the final step of the hierarchical regression, as shown in the full model, the individual contribution of biological predictors is not significant. However, by reversing the model building strategy, we found that calprotectin and cortisol explain an additional 6.5% of the physical component of QoL (although $p = .12$). Even though all participants had clinically insignificant levels of calprotectin, it seems that levels above 50μg/g can differentiate IBS patients with QoL impairment. Although there are no previous studies linking calprotectin levels to QoL impairment in IBS patients, there are studies showing calprotectin's relation to endoscopic disease activity in IBD patients, with an accuracy of 89% in discriminating between different severities of disease activity (Schoepfer et al., 2009). In addition, it seems that IBD patients in remission, who have IBS-like symptoms, also have higher

calprotectin levels than IBD patients in remission without IBS-like symptoms (Keohane et al., 2010). This relationship might reflect a link between IBS-like symptoms and microscopic inflammation in the absence of structural disease in IBD patients (Long & Drossman, 2010). Similarly, the presence of calprotectin in IBS patients with impaired QoL could suggest that a low-grade inflammation is a relevant component of IBS, at least in a subset of patients. It is important to note that there have been many studies reporting alterations in inflammatory and immune parameters in IBS patients, such as leukocytes, mast cells, and immunoglobulins (Elsenbruch, 2011; Ortiz-Lucas, Saz-Peiro, & Sebastian-Domingo, 2010), which could be indicative of low-grade inflammation. The obtained serum cortisol levels were also mainly within the reference range; however, in this sample, patients with higher levels reported better physical quality of life. This is in line with the findings suggesting a relationship between functional pain symptoms and decreased cortisol levels, and depressed mood and elevated cortisol levels (Ehlert, Gaab, & Heinrichs, 2001; Ehlert, Nater, & Bohmelt, 2005; Karling et al., 2016). If hypocortisolism is indeed related to reports of severe pain and physical symptoms in IBS patients, then we would expect patients with higher cortisol levels to have a better physical quality of life, which is what the results show. On the other hand, if higher cortisol levels are related to depressed mood, we would expect a correlation between cortisol and depression, which was not significant ($r = .22$); however, cortisol had a marginally significant correlation with negative mood ($r = .29$; $p = .058$).

For mental QoL however, even though calprotectin and cortisol were significant predictors of mental QoL when entered as the only predictors, we found that they do not add to the explanation of mental QoL when they are entered after psychological measures. These findings could indicate the involvement of the HPA axis dysregulation in QoL impairment of IBS patients, at least in the case of physical QoL. In our data, HRV measures had no significant correlations with QoL measures. Some previous studies on HRV in IBS have reported increased sympathetic and decreased parasympathetic activity in patients regardless of their subtype (Pellissier, Dantzer, Canini, Mathieu, & Bonaz, 2010), while others reported this pattern in patients with predominating constipation (Mazur et al., 2007), and some observed it only in female patients with severe symptoms (Cain, Jarrett, Burr, Hertig, & Heitkemper, 2007). Since there are no findings linking HRV to QoL in IBS, it is possible no such connection exists, that it might be mediated by symptom severity, or that it is only observable when using postprandial HRV data. We need to point out that biological measures and self-report data are qualitatively different, which inevitably results in lower correlation coefficients compared to those found among self-report measures.

The results of this study show that depression significantly contributes to both physical and mental QoL in IBS patients. Many studies have shown a link between depression and IBS, whether as higher depression levels found in IBS patients compared to healthy persons (Fond et al., 2014; Ladep, Obindo, Audu, Okeke, & Malu, 2006), a high comorbidity of IBS and depression (Cho et al., 2011; Lee et al.,

2017), or as the predictive value of depression for developing IBS (Nicholl et al., 2008). Higher depression levels have been associated with higher symptom severity scores (Cho et al., 2011; Pletikosic & Tkalcic, 2016), as well as quality of life impairment in IBS patients (Cho et al., 2011; Creed et al., 2001; Tkalcic et al., 2010). Although it is not completely clear what the mechanism of this association is, the most plausible one is a circular relationship, possibly including several other psychological states. Patients suffering from chronic conditions, whose QoL is impaired, tend to have higher depression scores, however the opposite is also true— depressed mood can lead to higher disability and lower QoL. It is possible that this relationship is mediated by stressful events, the onset of depression being usually preceded by stressful life events (Mazure, 1998), and depressed persons being prone to interpreting events as negative (Beck et al., 2011), making the relationship a closed circle (Hammen, 2005). It is necessary to mention a possible methodological issue regarding the high correlations (and beta coefficients) between depression and QoL. Since both measures were completed at the same time, the fact that they are both self-report measures could have artificially inflated the magnitude of their relationship. The only personality trait entered in the regression analysis was anxiety, showing the highest correlations with both QoL measures. Entered in the second step of the regression analysis, anxiety and depression explained 26% and 25% of the physical and mental QoL variance, however trait anxiety was not a significant predictor of neither physical nor mental QoL. Research consistently shows that IBS patients have higher anxiety levels than healthy controls (Fond et al., 2014). Higher trait anxiety and anxiety related states, such as visceral anxiety are associated with reduced QoL in iBS patients (Jerndal et al., 2010; Labus et al., 2004; Muscatello, Bruno, Mento, Pandolfo, & Zoccali, 2016). Patients prone to worry, ruminative thoughts and catastrophizing, who tend to focus on their symptoms in a very anxious manner - worrying about their significance and anticipating their exacerbation, also tend to report QoL impairment. Thus, anxiety related states are often considered to be among the key components of symptom perpetuation in IBS patients (Hauser et al., 2014). The results of this study however, seem to indicate that depressed or negative mood is more detrimental to QoL than trait anxiety, but this cannot be generalized to the role of state anxiety. As Table 3 shows, other personality traits, namely extraversion and marginally neuroticism, correlated with mental and physical QoL. Even though they were not included in the regression analyses, we consider them relevant for the BPS model of IBS. However, compared to anxiety and depression, broad personality dimensions seem to have weaker relationships with IBS outcome variables. One possible explanation is that anxiety and depression are more proximally related to QoL especially in relation to content, but in the case of depression also in relation to time of measurement (Figure 1), as explained previously.

The two final predictors - negative and positive mood - were, unlike depression, measured daily and analyzed as two-week averages. This type of measurement provides a more stable and realistic representation of the patients' moods. For the physical component of QoL, the finding on the involvement of negative mood in

QoL impairment is in line with previous studies (Lee et al., 2008; Muscatello et al., 2014, 2016; Pellissier et al., 2010; Rey, Garcia-Alonso, Moreno-Ortega, Alvarez-Sanchez, & Diaz-Rubio, 2008; Spiegel et al., 2004) which reported a significant impact of psychological distress (anxiety, depression, negative mood, somatization, stress) on QoL, as well as on symptom severity. The resulting consensus on the importance of psychological distress has shaped the vast majority of psychological interventions, most of which predominantly focus on QoL improvement and symptom alleviation through the reduction of psychological distress (Surdea-Blaga et al., 2016). Because of this, the most interesting finding of this study is the significance of positive mood for predicting mental QoL. Patients who reported higher positive mood throughout the two-week period, later showed higher mental QoL. Positive mood is related to different positive states such as interest, enthusiasm, happiness, motivation, mental alertness, etc., and is generally associated with improved physical and mental health (Muscatello et al., 2016). There are indications that for long-term illnesses, for which different behavioral factors seem to be significant, eliciting positive mood has beneficial effects on symptom improvement (Pressman & Cohen, 2005). Based on our results, it seems that psychological interventions for IBS should also focus on the patients' positive mood. This could help patients redirect their attention from symptoms and negative aspects of their disorder to more rewarding stimuli in their environment. The two remaining measures obtained from diary data - symptom severity and stress intensity - did not have significant correlations with either QoL measure. Although some previous studies have reported significant relationships between QoL and pain severity (Lee et al., 2008; Rey et al., 2008), there are other findings suggesting that QoL impairment in IBS patients is more affected by psychological states than the severity of symptoms (Michalsen, Vandvik, & Farup, 2015). Finally, even though self-reported stress intensity has previously been linked to symptom exacerbation (Blanchard et al., 2008), our results indicate that it might not be as relevant to QoL, as its resulting psychological states, depression and negative mood, seem to be.

The described results should be cautiously interpreted, due to several limitations of the study. First of all, the small sample size did not permit including all the relevant factors in the tested models, but rather forced us to limit the number of factors per group of predictors (indirect biological measures, traits and affect, longitudinal averages from the diary data). Although this approach seems rather arbitrary, it was a trade-off which allowed us to include the most relevant predictors from all predictor groups. However, such a small sample size limits the generalizability of the obtained results, especially when taking into account the heterogeneous nature of IBS.

In conclusion, this study found indications of a possible role of low-grade inflammation and HPA axis dysregulation in physical QoL impairment in IBS patients. We also found support for a significant role of depression and mood in both physical and mental QoL of IBS patients. Depressed and negative mood have previously been linked to low-grade inflammation and immune activity in IBS

(Muscatello et al., 2016) and are most probably related through the so-called sickness behavior, an effect of proinflammatory cytokines which results in behavior changes directed towards conserving resources and minimizing threat exposure. For IBS patients, such a depressed state might be a chronic one, reflecting a set of psychological traits characterized by negative mood and susceptibility to stress; however, in patients with severe QoL impairment, it might have an inflammatory component as well, accompanied by a dysregulated stress response. Since low cortisol levels are related to both an increased risk of inflammation as well as an increased chance for developing depressed mood (Karling et al., 2016), it is not surprising to find these in IBS patients with severe QoL impairment. The most practically relevant finding of this study is the role of positive mood as a protective factor for emotional and social aspects of QoL, highlighting the need for shifting therapeutic focus from psychological distress to those activities that elicit positive affective states.

References

Almeida, D. (1998). *Daily Inventory of Stressful Events (DISE) expert coding manual.* Tuscon: Division of Family Studies and Human Development, University of Arizona.

Beck, A. T., Steer, R. A., & Brown, G. K. (2011). *Manual for the Beck Depression Inventory-II* (Croatian ed.) Jastrebarsko: Naklada Slap.

Blanchard, E. B. (2001). *Irritable bowel syndrome: Psychosocial assessment and treatment.* Washington, DC: American Psychological Association.

Blanchard, E. B., Lackner, J. M., Jaccard, J., Rowell, D., Carosella, A. M., Powell, C., … Kuhn, E. (2008). The role of stress in symptom exacerbation among IBS patients. *Journal of Psychosomatic Research, 64*(2), 119-128. doi:10.1016/j.jpsychores.2007. 10.010

Cain, K. C., Jarrett, M. E., Burr, R. L., Hertig, V. L., & Heitkemper, M. M. (2007). Heart rate variability is related to pain severity and predominant bowel pattern in women with irritable bowel syndrome. *Neurogastroenterology & Motility, 19*(2), 110-118. doi:10.1111/j.1365-2982.2006.00877.x

Chang, L., Sundaresh, S., Elliott, J., Anton, P. A., Baldi, P., Licudine, A., … Mayer, E. A. (2009). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in irritable bowel syndrome. *Neurogastroenterology & Motility, 21*(2), 149-159. doi:10.1111/j. 1365-2982.2008.01171.x

Cho, H. S., Park, J. M., Lim, C. H., Cho, Y. K., Lee, I. S., Kim, S. W., … Chung, Y. K. (2011). Anxiety, depression and quality of life in patients with irritable bowel syndrome. *Gut and Liver, 5*(1), 29-36. doi:10.5009/gnl.2011.5.1.29

Creed, F., Ratcliffe, J., Fernandez, L., Tomenson, B., Palmer, S., Rigby, C., ... Thompson, D. (2001). Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. *Annals of Internal Medicine, 134*(9, Pt. 2), 860-868.

Deary, V., Chalder, T., & Sharpe, M. (2007). The cognitive behavioural model of medically unexplained symptoms: A theoretical and empirical review. *Clinical Psychology Review, 27*(7), 781-797. doi:10.1016/j.cpr.2007.07.002

Drossman, D. A. (1998). Presidential address: Gastrointestinal illness and the biopsychosocial model. *Psychosomatic Medicine, 60*(3), 258-267.

Drossman, D. A., Camilleri, M., Mayer, E. A., & Whitehead, W. E. (2002). AGA technical review on irritable bowel syndrome. *Gastroenterology, 123*(6), 2108-2131. doi:10.1053/gast.2002.37095

Drossman, D. A., & Hasler, W. L. (2016). Rome IV-functional GI disorders: Disorders of gut-brain interaction. *Gastroenterology, 150*(6), 1257-1261. doi:10.1053/j.gastro.2016.03.035

Ehlert, U., Gaab, J., & Heinrichs, M. (2001). Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: The role of the hypothalamus-pituitary-adrenal axis. *Biological Psycholology, 57*(1-3), 141-152.

Ehlert, U., Nater, U. M., & Bohmelt, A. (2005). High and low unstimulated salivary cortisol levels correspond to different symptoms of functional gastrointestinal disorders. *Journal of Psychosomatic Research, 59*(1), 7-10. doi:10.1016/j.jpsychores.2005.03.005

Elsenbruch, S. (2011). Abdominal pain in irritable bowel syndrome: A review of putative psychological, neural and neuro-immune mechanisms. *Brain, Behavior, and Immunity, 25*(3), 386-394. doi:10.1016/j.bbi.2010.11.010

Enck, P., Aziz, Q., Barbara, G., Farmer, A. D., Fukudo, S., Mayer, E. A., … Spiller, R. C. (2016). Irritable bowel syndrome. *Nature Reviews Disease Primers, 2*, 16014. doi:10.1038/nrdp.2016.14

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science, 196*(4286), 129-136.

Farnam, A., Somi, M. H., Sarami, F., & Farhang, S. (2008). Five personality dimensions in patients with irritable bowel syndrome. *Neuropsychiatric Disease and Treatment, 4*(5), 959-962.

Fichna, J., & Storr, M. A. (2012). Brain-gut interactions in IBS. *Frontiers in Pharmacology, 3*, 127. doi:10.3389/fphar.2012.00127

Fond, G., Loundou, A., Hamdani, N., Boukouaci, W., Dargel, A., Oliveira, J., … Boyer, L. (2014). Anxiety and depression comorbidities in irritable bowel syndrome (IBS): A systematic review and meta-analysis. *European Archives of Psychiatry and Clinical Neuroscience, 264*(8), 651-660. doi:10.1007/s00406-014-0502-z

Ford, A. C., Quigley, E. M., Lacy, B. E., Lembo, A. J., Saito, Y. A., Schiller, L. R., … Moayyedi, P. (2014). Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: Systematic review and meta-analysis. *American Journal of Gastroenterology, 109*(9), 1350-1365. doi:10.1038/ajg.2014.148

Frank, L., Kleinman, L., Rentz, A., Ciesla, G., Kim, J. J., & Zacker, C. (2002). Health-related quality of life associated with irritable bowel syndrome: Comparison with other chronic diseases. *Clinical Therapeutics, 24*(4), 675-689.

Gralnek, I. M., Hays, R. D., Kilbourne, A., Naliboff, B., & Mayer, E. A. (2000). The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology, 119*(3), 654-660.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology, 1*, 293-319. doi:10.1146/annurev.clinpsy.1.102803.143938

Hauser, G., Pletikosic, S., & Tkalcic, M. (2014). Cognitive behavioral approach to understanding irritable bowel syndrome. *World Journal of Gastroenterology, 20*(22), 6744-6758. doi:10.3748/wjg.v20.i22.6744

Hubbard, C. S., Hong, J., Jiang, Z., Ebrat, B., Suyenobu, B., Smith, S., … Labus, J. S. (2015). Increased attentional network functioning related to symptom severity measures in females with irritable bowel syndrome. *Neurogastroenterology & Motility, 27*(9), 1282-1294. doi:10.1111/nmo.12622

Jerndal, P., Ringstrom, G., Agerforz, P., Karpefors, M., Akkermans, L. M., Bayati, A., & Simren, M. (2010). Gastrointestinal-specific anxiety: An important factor for severity of GI symptoms and quality of life in IBS. *Neurogastroenterology & Motility, 22*(6), 646-e179. doi:10.1111/j.1365-2982.2010.01493.x

John, O. P., & Srivastava, S. (1999). The Big Five trait taxonomy: History, measurement, and theoretical perspectives. *Handbook of personality: Theory and research, 2*, 102-138.

Jones, M. P., Dilley, J. B., Drossman, D., & Crowell, M. D. (2006). Brain-gut connections in functional GI disorders: Anatomic and physiologic relationships. *Neurogastroenterology & Motility, 18*(2), 91-103. doi:10.1111/j.1365-2982.2005.00730.x

Kardum, I., & Bezinović, P. (1992). Methodological and theoretical implications of the measurement of emotional experience. *Godišnjak Zavoda za psihologiju, 1*, 53-74.

Kardum, I., Gračanin, A., & Hudek-Knežević, J. (2006). Relations of personality traits and attachment styles with different aspects of sexuality in men and women. *Psihologijske teme, 15*(1), 101-128.

Karling, P., Wikgren, M., Adolfsson, R., & Norrback, K. F. (2016). Hypothalamus-pituitary-adrenal axis hypersuppression is associated with gastrointestinal symptoms in major depression. *Journal of Neurogastroenterology and Motility, 22*(2), 292-303. doi:10.5056/jnm15064

Katsanos, A. H., Giannopoulos, S., & Tsivgoulis, G. (2012). The brain-gut axis in the pathophysiology of irritable bowel syndrome. *Immuno-Gastroenterology, 1*, 23.

Kennedy, P., Cryan, J., Quigley, E., Dinan, T., & Clarke, G. (2014). A sustained hypothalamic-pituitary-adrenal axis response to acute psychosocial stress in irritable bowel syndrome. *Psychological Medicine, 44*(14), 3123-3134.

Keohane, J., O'Mahony, C., O'Mahony, L., O'Mahony, S., Quigley, E. M., & Shanahan, F. (2010). Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: A real association or reflection of occult inflammation? *American Journal of Gastroenterology, 105*(8), 1788, 1789-1794. doi:10.1038/ajg.2010.156

Labus, J. S., Bolus, R., Chang, L., Wiklund, I., Naesdal, J., Mayer, E. A., & Naliboff, B. D. (2004). The Visceral Sensitivity Index: Development and validation of a gastrointestinal symptom-specific anxiety scale. *Alimentary Pharmacology & Therapeutics, 20*(1), 89-97. doi:10.1111/j.1365-2036.2004.02007.x

Lackner, J. M., Gudleski, G. D., Keefer, L., Krasner, S. S., Powell, C., & Katz, L. A. (2010). Rapid response to cognitive behavior therapy predicts treatment outcome in patients with irritable bowel syndrome. *Clinical Gastroenterology and Hepatology, 8*(5), 426-432.

Lackner, J. M., Jaccard, J., Krasner, S. S., Katz, L. A., Gudleski, G. D., & Blanchard, E. B. (2007). How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. *Gastroenterology, 133*(2), 433-444.

Ladep, N. G., Obindo, T. J., Audu, M. D., Okeke, E. N., & Malu, A. O. (2006). Depression in patients with irritable bowel syndrome in Jos, Nigeria. *World Journal of Gastroenterology, 12*(48), 7844-7847.

Lee, S. K., Yoon, D. W., Lee, S., Kim, J., Choi, K.-M., & Shin, C. (2017). The association between irritable bowel syndrome and the coexistence of depression and insomnia. *Journal of Psychosomatic Research, 93*, 1-5.

Lee, V., Guthrie, E., Robinson, A., Kennedy, A., Tomenson, B., Rogers, A., & Thompson, D. (2008). Functional bowel disorders in primary care: Factors associated with health-related quality of life and doctor consultation. *Journal of Psychosomatic Research, 64*(2), 129-138. doi:10.1016/j.jpsychores.2007.09.004

Liu, Q., Wang, E. M., Yan, X. J., & Chen, S. L. (2013). Autonomic functioning in irritable bowel syndrome measured by heart rate variability: A meta-analysis. *Journal of Digestive Diseases, 14*(12), 638-646. doi:10.1111/1751-2980.12092

Long, M. D., & Drossman, D. A. (2010). Inflammatory bowel disease, irritable bowel syndrome, or what? A challenge to the functional-organic dichotomy. *American Journal of Gastroenterology, 105*(8), 1796-1798. doi:10.1038/ajg.2010.162

Mayer, E. A. (2000). The neurobiology of stress and gastrointestinal disease. *Gut, 47*(6), 861-869.

Mazur, M., Furgala, A., Jablonski, K., Madroszkiewicz, D., Ciecko-Michalska, I., Bugajski, A., & Thor, P. J. (2007). Dysfunction of the autonomic nervous system activity is responsible for gastric myoelectric disturbances in the irritable bowel syndrome patients. *Journal of Physiology and Pharmacology, 58*(Suppl 3), 131-139.

Mazurak, N., Seredyuk, N., Sauer, H., Teufel, M., & Enck, P. (2012). Heart rate variability in the irritable bowel syndrome: A review of the literature. *Journal of Neurogastroenterology and Motility, 24*(3), 206-216. doi:10.1111/j.1365-2982.2011.01866.x

Mazure, C. M. (1998). Life stressors as risk factors in depression. *Clinical Psychology: Science and Practice, 5*(3), 291-313. doi:10.1111/j.1468-2850.1998.tb00151.x

Michalsen, V. L., Vandvik, P. O., & Farup, P. G. (2015). Predictors of health-related quality of life in patients with irritable bowel syndrome. A cross-sectional study in Norway. *Health and Quality of Life Outcomes, 13*, 113. doi:10.1186/s12955-015-0311-8

Mujagic, Z., Tigchelaar, E. F., Zhernakova, A., Ludwig, T., Ramiro-Garcia, J., Baranska, A., … Jonkers, D. M. (2016). A novel biomarker panel for irritable bowel syndrome and the application in the general population. *Scientific Reports, 6*, 26420. doi:10.1038/srep26420

Muscatello, M. R., Bruno, A., Mento, C., Pandolfo, G., & Zoccali, R. A. (2016). Personality traits and emotional patterns in irritable bowel syndrome. *World Journal of Gastroenterology, 22*(28), 6402-6415. doi:10.3748/wjg.v22.i28.6402

Muscatello, M. R., Bruno, A., Scimeca, G., Pandolfo, G., & Zoccali, R. A. (2014). Role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome. *World Journal of Gastroenterology, 20*(24), 7570-7586. doi:10.3748/wjg.v20.i24.7570

Myers, B., & Greenwood-Van Meerveld, B. (2009). Role of anxiety in the pathophysiology of irritable bowel syndrome: Importance of the amygdala. *Frontiers in Neuroscience, 3*, 47. doi:10.3389/neuro.21.002.2009

Mykletun, A., Jacka, F., Williams, L., Pasco, J., Henry, M., Nicholson, G. C., … Berk, M. (2010). Prevalence of mood and anxiety disorder in self reported irritable bowel syndrome (IBS). An epidemiological population based study of women. *BMC Gastroenterology, 10*, 88. doi:10.1186/1471-230x-10-88

Nicholl, B. I., Halder, S. L., Macfarlane, G. J., Thompson, D. G., O'Brien, S., Musleh, M., & McBeth, J. (2008). Psychosocial risk markers for new onset irritable bowel syndrome-results of a large prospective population-based study. *Pain, 137*(1), 147-155. doi:10.1016/j.pain.2007.08.029

Niskanen, J.-P., Tarvainen, M. P., Ranta-Aho, P. O., & Karjalainen, P. A. (2004). Software for advanced HRV analysis. *Computer Methods and Programs in Biomedicine, 76*(1), 73-81.

Ortiz-Lucas, M., Saz-Peiro, P., & Sebastian-Domingo, J. J. (2010). Irritable bowel syndrome immune hypothesis. Part one: The role of lymphocytes and mast cells. *Revista Española de Enfermedades Digestivas, 102*(11), 637-647.

Palsson, O., Jones, K., Turner, M., Drossman, D., & Whitehead, W. (2002). Impact of somatization and comorbid medical conditions on health care utilization, disability, and duality of life in irritable bowel syndrome (IBS). *Gastroenterology, 122*(4), A501-A502.

Pellissier, S., Dantzer, C., Canini, F., Mathieu, N., & Bonaz, B. (2010). Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. *Psychoneuroendocrinology, 35*(5), 653-662. doi:10.1016/j.psyneuen.2009.10.004

Pletikosic, S., Plavsic, I., Hauser, G., & Tkalcic, M. (2015). Fecal Calprotectin and serum chromogranin A as potential biomarkers of irritable bowel syndrome symptom severity. *Medical Hypotheses, 85*(3), 339-342. doi:10.1016/j.mehy.2015.06.008

Pletikosic, S., & Tkalcic, M. (2016). The role of stress in IBS symptom severity. *Psychological Topics, 25*(1), 29-43.

Pressman, S. D., & Cohen, S. (2005). Does positive affect influence health? *Psychological Bulletin, 131*(6), 925-971. doi:10.1037/0033-2909.131.6.925

Punyabati, O., Deepak, K. K., Sharma, M. P., & Dwivedi, S. N. (2000). Autonomic nervous system reactivity in irritable bowel syndrome. *Indian Journal of Gastroenterology, 19*(3), 122-125.

Quigley, E. M. (2006). Changing face of irritable bowel syndrome. *World Journal of Gastroenterology,12*(1), 1-5.

Rey, E., Garcia-Alonso, M. O., Moreno-Ortega, M., Alvarez-Sanchez, A., & Diaz-Rubio, M. (2008). Determinants of quality of life in irritable bowel syndrome. *Journal of Clinical Gastroenterology, 42*(9), 1003-1009. doi:10.1097/MCG.0b013e31815af9f1

Sasaki, D. (2003). Irritable bowel syndrome and stress. *Japan Medical Association Journal, 46*(2), 66-69.

Schoepfer, A. M., Beglinger, C., Straumann, A., Trummler, M., Renzulli, P., & Seibold, F. (2009). Ulcerative colitis: Correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflammatory Bowel Diseases, 15*(12), 1851-1858. doi:10.1002/ibd.20986

Sibelli, A., Chalder, T., Everitt, H., Workman, P., Windgassen, S., & Moss-Morris, R. (2016). A systematic review with meta-analysis of the role of anxiety and depression in irritable bowel syndrome onset. *Psychological Medicine, 46*(15), 3065-3080. doi:10.1017/s0033291716001987

Sood, R., Gracie, D. J., Law, G. R., & Ford, A. C. (2015). Systematic review with meta-analysis: The accuracy of diagnosing irritable bowel syndrome with symptoms, biomarkers and/or psychological markers. *Alimentary Pharmacology & Therapeutics, 42*(5), 491-503. doi:10.1111/apt.13283

Spence, M. J., & Moss-Morris, R. (2007). The cognitive behavioural model of irritable bowel syndrome: A prospective investigation of patients with gastroenteritis. *Gut, 56*(8), 1066-1071. doi:10.1136/gut.2006.108811

Spiegel, B. M., Gralnek, I. M., Bolus, R., Chang, L., Dulai, G. S., Mayer, E. A., & Naliboff, B. (2004). Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Archives of Internal Medicine, 164*(16), 1773-1780. doi:10.1001/archinte.164.16.1773

Spielberger, C. D. (2000). *Manual for the State-Trait Anxiety Inventory* (Croatian ed.) Jastrebarsko: Naklada Slap.

Surdea-Blaga, T., Baban, A., Nedelcu, L., & Dumitrascu, D. L. (2016). Psychological interventions for irritable bowel syndrome. *Journal of Gastrointestinal and Liver Diseases, 25*(3), 359-366. doi:10.15403/jgld.2014.1121.253.ibs

Tak, L. M., Riese, H., de Bock, G. H., Manoharan, A., Kok, I. C., & Rosmalen, J. G. (2009). As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. *Biological Psychology, 82*(2), 101-110. doi:10.1016/j.biopsycho.2009.05.002

Tang, Q. L., Lin, G. Y., & Zhang, M. Q. (2013). Cognitive-behavioral therapy for the management of irritable bowel syndrome. *World Journal of Gastroenterology, 19*(46), 8605-8610. doi:10.3748/wjg.v19.i46.8605

Tanum, L., & Malt, U. F. (2000). Personality traits predict treatment outcome with an antidepressant in patients with functional gastrointestinal disorder. *Scandinavian Journal of Gastroenterology, 35*(9), 935-941.

ten Berg, M. J., Goettsch, W. G., van den Boom, G., Smout, A. J., & Herings, R. M. (2006). Quality of life of patients with irritable bowel syndrome is low compared to others with chronic diseases. *European Journal of Gastroenterology and Hepatology, 18*(5), 475-481.

Tkalčić, M., Hauser, G., & Stimac, D. (2010). Differences in the health-related quality of life, affective status, and personality between irritable bowel syndrome and inflammatory bowel disease patients. *European Journal of Gastroenterology and Hepatology, 22*(7), 862-867. doi:10.1097/MEG.0b013e3283307c75

Tkalčić, M., Hauser, G., Štimac, D., & Pokrajac-Bulian, A. (2007). Relation between general and disease-specific health related quality of life of patients with inflammatory bowel disease. In D. L. Dumitrascu (Ed.), *Current topics in neurogastroenterology, Proceedings of the 2nd International Symposium of Neurogastroenterology* (pp. 250-260). Cluj-Napoca, Romania: Editura Medicala Universitara "Iuliu Hatieganu".

Tončić, M. (2009). *Effects of neuroticism on the temporal relationship of mood and heart rate variability.* (Unpublished master's thesis). University of Rijeka, Faculty of Humanities and Social Sciences, Rijeka, Croatia.

van der Veek, P. P., Dusseldorp, E., van Rood, Y. R., & Masclee, A. A. (2010). Testing a biobehavioral model of irritable bowel syndrome. *European Journal of Gastroenterology and Hepatology, 22*(4), 412-419. doi:10.1097/MEG. 0b013e328332f83f

Van Oudenhove, L., Crowell, M. D., Drossman, D. A., Halpert, A. D., Keefer, L., Lackner, J. M., ... Levy, R. L. (2016). Biopsychosocial aspects of functional gastrointestinal disorders. *Gastroenterology*. doi:10.1053/j.gastro.2016.02.027

van Tilburg, M. A., Palsson, O. S., & Whitehead, W. E. (2013). Which psychological factors exacerbate irritable bowel syndrome? Development of a comprehensive model. *Journal of Psychosomatic Research, 74*(6), 486-492. doi:10.1016/j.jpsychores.2013.03.004

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473-483.

Waugh, N., Cummins, E., Royle, P., Kandala, N. B., Shyangdan, D., Arasaradnam, R., … Johnston, R. (2013). Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: Systematic review and economic evaluation. *Health Technology Assessment, 17*(55), xv-xix, 1-211. doi:10.3310/hta17550

Wong, R. K., & Drossman, D. A. (2010). Quality of life measures in irritable bowel syndrome. *Expert Review of Gastroenterology and Hepatology, 4*(3), 277-284. doi:10.1586/egh.10.19

Zijdenbos, I. L., de Wit, N. J., van der Heijden, G. J., Rubin, G., & Quartero, A. O. (2009). Psychological treatments for the management of irritable bowel syndrome. *Cochrane Database of Systematic Reviews, 1*, Cd006442. doi:10.1002/14651858.CD006442.pub2

Obstáculos en la comunicación entre el cerebro y el intestino: Predictores biopsicosociales de la calidad de vida en el síndrome del intestino irritable

Resumen

El síndrome del intestino irritable (SII) es un trastorno complejo, resultado de la interacción de numerosos factores. El modelo biopsicosocial describe algunos factores de predisposición, precipitación y perpetuación que contribuyen a la apariencia y mantenimiento de síntomas, y por consiguiente, al deterioro de la calidad de vida. El objetivo de este trabajo fue examinar el efecto que tienen ciertos factores psicológicos y biológicos sobre los componentes de la calidad de vida en los pacientes que sufren SII. Un total de 46 pacientes con SII completaron un conjunto de cuestionarios (Inventario de Los Cinco Grandes, Inventario de Ansiedad Estado-Rasgo, Inventario de Depresión de Beck II, Cuestionario de Salud SF-36) y durante dos semanas escribían un diario sobre su estado de ánimo, estrés diario y síntomas. Además, se midió su variabilidad del ritmo cardíaco, cortisol sérico y niveles de calprotectina fecal. Los resultados del análisis regresiva mostraron que la depresión (β = -.30) y mal humor (β = -.28) predijeron calidad de vida física, mientras que la depresión (β = -.45) y buen humor (β = -.33) predijeron significativamente calidad de vida mental. El modelo, que incluyó calprotectina, cortisol, ansiedad, depresión y buen y mal humor, explicó el 47% de la varianza de la calidad de vida física y el 57% de la calidad de vida mental. Nuestros resultados confirmaron el papel del afecto negativo en el deterioro de la calidad de vida en el SII. También indicaron que los factores biológicos parecen importantes para la calidad de vida física en los pacientes con SII. El papel del buen humor como un factor protector para la calidad de vida mental podría ser significativo para las intervenciones psicológicas en los pacientes con SII.

Palabras clave: modelo biopsicosocial, síndrome del intestino irritable, calidad de vida, depresión, buen y mal humor