

Testing a biobehavioral model of irritable bowel syndrome

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Objective The pathogenesis of irritable bowel syndrome (IBS) is probably multifactorial with dysfunction at different levels of the brain-gut axis. The aim of this study was to evaluate an existing biobehavioral model of IBS symptom generation in a large group of patients.

Material and methods In 104 IBS patients, we assessed symptom severity by a symptom diary, visceral hypersensitivity using a barostat, autonomic function by measuring arterial baroreflex sensitivity and psychological functioning using questionnaires. Structural equation modeling was used to calculate the reciprocal and chronological relationships between the model variables.

Results Analysis of the adjusted original model indicated poor fit [Satorra-Bentler $\chi^2=28.47$; degrees of freedom (df)=11, $P<0.01$; comparative fit index (CFI)=0.78], which was caused by omission of two paths (illness behavior-IBS symptoms and trauma-IBS symptoms). The revised model yielded a reasonable fit ($\chi^2=13.88$, df=9, $P=0.13$; CFI=0.94). The model explained 18.7% of the variance in IBS symptoms. Illness behavior completely mediated the effect of cognitions on IBS symptoms and partly mediated the effect of trauma on IBS symptoms. The fit of this

alternative model was good ($\chi^2=9.85$, df=8, $P=0.28$; CFI=0.98). The alternative model explained 20.0% of the variance in IBS symptoms.

Conclusion The proposed biobehavioral model could not be validated. Although visceral hypersensitivity and IBS symptom severity significantly correlate, autonomic function and IBS symptoms do not. Cognitive-behavioral aspects are important in the clinical expression of IBS, with illness behavior playing an intermediate and central role. *Eur J Gastroenterol Hepatol* 22:412–419 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized by recurrent abdominal pain and altered bowel habits such as diarrhea and/or constipation [1]. IBS is the most frequent functional gastrointestinal disorder with an estimated prevalence of 6 to 22% [2,3] and substantial economic impact [4,5]. Despite the growing body of literature, the pathophysiology of IBS remains poorly understood and a variety of mechanisms have been proposed in symptom generation. These include enhanced visceral sensitivity [6,7], disturbed intestinal motility [8,9], autonomic dysfunction [10,11], inflammatory processes [12,13], altered immune activity [14,15], altered processing of afferent sensory information [16,17], and psychological disturbances [18,19]. These alterations probably reflect the dysfunction at different levels of the brain-gut axis, a conceptual framework which has recently emerged in an attempt to improve our understanding of the etiology, pathogenesis, and clinical expression of IBS [20]. Although a biobehavioral model of IBS based on of the brain-gut axis would be of great assistance to gain further insight in the relationship between these disturbances, few attempts have been made to construct such a model.

In 1998, Naliboff *et al.* [21] proposed an initial but comprehensive working model of IBS, incorporating the central nervous system, visceral sensory and motor functioning, and cognitive-behavioral systems [21]. This biobehavioral model implies that internal or external stimuli, for example, dysenteric illness or sexual or physical abuse, affect visceral sensory and motor function either directly or by an arousal-induced autonomic response autonomic nerve system ('ANS stress response'), that is, hypervigilance. Furthermore, the model suggests that visceral motor and sensory disturbances subsequently give rise to IBS symptoms, and that prolonged symptom duration will lead to the alterations in illness behavior, environmental responses, and health beliefs. These biobehavioral changes in turn increase hypervigilance and, ultimately, deteriorate IBS symptoms. Thus, the proposed model represents the clinical manifestation of IBS as interplay between the biological and psychological factors, which is in agreement with the current concept of IBS as a multifactorial condition [22,23]. It also provides a verifiable theoretical framework that may improve our understanding of the pathophysiological mechanisms involved in IBS.

The aim of this study was to evaluate this biobehavioral model of IBS [21] in a relatively large group of patients. We tested the validity of the model using structural equation modeling, as it allows calculation of reciprocal and chronological relationships between the model variables. Lackner *et al.* [24] recently showed that structural equation modeling is a valid method to test a sequential model of pain processing in IBS. The ratio between the number of patients and the number of parameters restricted testing possibilities using a model with latent variables and therefore constrained us to perform a path analysis (as was done by Lackner *et al.*). We followed Kline's recommendation of at least a 10:1 ratio to obtain results that are reasonably stable [25]. To apply a path analysis to the working model proposed by Naliboff *et al.* [21], we modified the model slightly, that is, we eliminated the feedback loop from IBS symptoms, illness behavior, environmental responses, health beliefs, and vigilance back to IBS symptoms (see Fig. 1). On the basis of the proposed model, the existing literature, and the above-mentioned statistical restrictions, we built the following hypotheses (Fig. 1):

- (1) Trauma involving the abdomen, for example, acute gastroenteritis, abdominal surgery, or sexual or physical abuse, will influence IBS symptom severity by modification of autonomic functioning and/or visceral sensitivity [26–28].
- (2) Autonomic dysfunction [reflected by low baroreflex sensitivity (BRS)-values] is associated with increased visceral sensitivity and hypervigilance [29–31].
- (3) Hypervigilance will lead to increased IBS symptom severity, either directly or by influencing visceral sensitivity.
- (4) Dysfunctional cognitions regarding functional bowel disorders will lead to increased IBS symptom severity, either directly or by increasing vigilance [32].

- (5) Illness behavior aggravates dysfunctional cognitions [33].
- (6) Visceral hypersensitivity will lead to increased IBS symptom severity [6,34].

Methods

Participants

Between March 2001 and July 2002, IBS patients between 18 and 65 years of age were invited to participate in a clinical trial assessing the effect of a brief psychological intervention on IBS symptom severity. This trial included baseline psychological assessment, combined autonomic nerve function and rectal sensitivity testing (day 0), and IBS symptom severity measurement (day 1–14). All these data were used for this study.

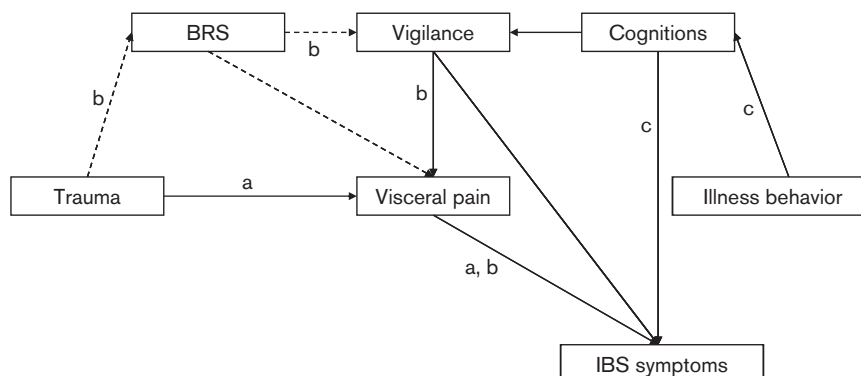
Patients were recruited through a tertiary referral centre (the outpatient department of Gastroenterology of the Leiden University Medical Centre) and through a local advertisement. All eligible participants were screened by one of the investigators (PvdV). All patients met Rome II criteria for IBS [1]. Exclusion criteria were organic disease, earlier abdominal surgery (except cholecystectomy and appendectomy), and pregnancy. Use of antispasmodics, laxatives, bulking agents, and occasional use of analgesics was permitted. We used the Mini International Neuropsychiatric Interview (Dutch version 5.0.0) [35] to exclude patients with psychotic disorder, or risk of suicide. Informed consent was obtained from each participant. The Leiden University Medical Centre ethics committee had approved the study protocol.

Measures

Irritable bowel syndrome symptom severity

Patients rated the severity of five symptoms, that is, discomfort, abdominal pain, constipation, diarrhea, and

Fig. 1



The biobehavioral test model of irritable bowel syndrome (IBS) adapted with permission [21]. Dashed arrows indicate a negative coefficient. Note the sequential links between (a) trauma, visceral pain, and IBS symptoms (visceral component); (b) trauma, baroreflex sensitivity (BRS), vigilance, visceral pain, and IBS symptoms (central nervous system component); (c) illness behavior, cognitions, and IBS symptoms (cognitive-behavioral component). The model contains two exogenous variables (trauma and illness behavior).

bloating, daily for 14 days, on a 5-point Likert scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe symptoms) using a symptom diary card. A composite score was computed by summing up the 14-day mean scores for each symptom (range 0–20). This diary was based on an earlier validated IBS severity scale, which scores the severity and duration of pain, abdominal bloating, bowel satisfaction, and interference with daily activities and then calculates an overall IBS severity score, ranging from 0 (least severe) to 500 (most severe) [36].

Visceral sensitivity

An electronic barostat (Synectics Visceral Stimulator, Synectics Medical, Stockholm, Sweden) was used to assess rectal visceral perception. This device maintains constant pressure within an infinitely compliant balloon by injecting air when the rectal wall relaxes and aspirating air during rectal contraction [37]. Participants were permitted a small standardized breakfast at 8:00 h before arriving at our department at 10:00 h. They received a tap water enema to evacuate the rectum and were placed in a bed, which was in a 6° head-down position to abolish gravitational effects of abdominal contents on the rectal balloon. The bag was inserted into the rectum and the catheter was connected to the barostat. A slow rectal ramp distension procedure was performed (1 mmHg increase/min, maximum 30 mmHg), during which rectal pain perception was quantified on a 100 mm Visual Analogue Scale [38] at every even pressure. End points ranged from 'none' to 'intolerable'.

Autonomic function

Autonomic function was assessed by measuring the arterial BRS. BRS is defined as the prolongation of the interval between heartbeats (milliseconds) induced by aorta and carotid baroreceptor activation when, because of any cause (e.g. stress or pain), arterial blood pressure rises by 1 mmHg. BRS measurements are complex procedures involving simultaneous recording of arterial blood pressure (finger cuff) and heart rate (surface ECG), while patients perform metronome respiration, as was described earlier [39]. We chose to use BRS rather than more conventional autonomic measures, such as heart rate variability, because the arterial baroreflex not only modulates sympathetic and parasympathetic autonomic outflow, which governs gastrointestinal motor function, but also affects cortical arousal [30,31] and somatic [31,40] and visceral [29] pain perception. Thus, BRS may well be involved in conditions associated with altered visceral sensory and motor function, such as IBS.

Trauma

A history of trauma involving the abdomen was assessed by asking patients whether they ever experienced (i) sexual abuse, (ii) physical violence or abuse involving the abdomen, and/or (iii) abdominal illness, for example,

acute gastroenteritis, appendicitis etc. Scores ranged from 0 (no trauma, answer is 'no' to all questions) to 3 (answer is 'yes' to all questions).

Vigilance

We used the validated Somatosensory Amplification Scale [41,42] to determine the extent to which an individual is likely to report enhanced perception of physical symptoms (i.e. lower cognitive perception thresholds). This scale comprises 10 items, with each item being scored on a 0 ('this statement does not apply to me') to 4 ('this statement is fully applicable to me') scale, yielding a total score range from 0 (best score) to 40 (worst score).

Dysfunctional cognitions

The recently developed 31-item Cognitive Scale for Functional Bowel Disorders was used to measure patients' levels of dysfunctional cognitions concerning their IBS [43]. Scores for individual items range from 1 (I completely agree) to 7 (I completely disagree), which yields a total score ranging from 31 (best) to 217 (worst).

Illness behavior

Illness behavior was assessed using the 6-item illness behavior subscale of the earlier validated Illness Attitude Scale [41,44]. Patients were asked to estimate their frequency of doctor visits, number of doctors visited, and treatment frequency (e.g. medication change, surgery), and to specify the extent to which their symptoms prevented them from having a normal career or concentrate on a particular task. Scores for individual items range from 0 ('not at all') to 4 ('very much'). The total score was divided by the number of items, yielding an illness behavior score ranging from 0 (best score) to 4 (worst score).

Statistical analysis

The univariate distributions of the variables were checked for normality, using standard errors of $\sqrt{6/N}$ and $\sqrt{24/N}$ to evaluate the skewness and kurtosis values, respectively. We examined model-based outliers using linear regression analyses for each of the regression equations derived from the path model (see Fig. 1). For each participant in each regression equation, we inspected Cook's distance, a measure of the change in regression coefficients produced by leaving out that participant. Little's test of missing completely at random was performed to evaluate the missing data mechanism. These analyses were performed with SPSS, version 14.0 (SPSS for Windows, Chicago, Illinois, USA).

Before performing the path analyses, missing values were imputed using expectation maximization estimation [45]. The missing data imputation and the path model analyses were performed with EQS, version 6.1 (Multivariate Software Inc., Encino, California, USA). For each path analysis, we used the option METHOD = ML, ROBUST. Because of the existence of nonnormally

distributed variables, the corrections of Satorra and Bentler [46] to the test statistics of the path model (i.e. the robust estimates of the goodness-of-fit indices and standard errors) were used to evaluate the model. We examined the following goodness-of-fit indices: the Satorra–Bentler scaled χ^2 , the root mean square error of approximation (RMSEA), the nonnormed fit index (NNFI), and the comparative fit index (CFI). The χ^2 is the likelihood ratio test statistic for testing the model against the alternative that the covariance matrix is unconstrained. A nonsignificant χ^2 indicates a good fit. A RMSEA value of less than 0.05 reflects a good fit, and a value of less than 0.08 reflects a reasonable fit [47]. Values of NNFI and CFI greater than 0.95 indicate an acceptable fit, and values of at least 0.97 indicate a good fit [48]. Because we hypothesized a priori the sign of the path coefficients of a model, we computed for each path coefficient a one-sided *P*-value, using the robust estimates of the standard errors.

Results

Patients

We screened 130 patients of whom 26 did not meet Rome II criteria [1], so that 104 patients were included in the analysis. Mean age was 42.0 ± 13.8 years. Seventy-four patients (71%) were women. Thirty-three patients (32%) were recruited through the outpatient department and 71 patients (68%) were recruited through advertisement in a local newspaper. Psychological variables were similar between these groups (data not shown). However, patients from the outpatient department received tertiary care whereas patients recruited through an advertisement did not. Furthermore, baseline IBS composite scores were higher in patients recruited through the outpatient clinic compared with patients recruited through an advertisement (5.50 ± 0.4 vs. 3.85 ± 0.3 , $P = 0.002$). Additional analyses showed that these subgroup differences did not affect main outcome (data not shown).

Preliminary analyses

Means, standard deviations, skewness, and kurtosis values for each quantitative variable are displayed in Table 1.

Table 1 Descriptive statistics of the quantitative model variables in 104 IBS patients

Variable	<i>N</i>	Mean	SD	Skewness	Kurtosis
Trauma (0–3)	103	0.64	0.67	0.76	0.30
BRS	84	7.93	5.42	1.64	4.35
Visceral pain (0–10)	101	2.50	2.67	0.97	–0.31
Vigilance (0–40)	103	9.68	5.75	1.48	3.87
Cognitions (31–217)	101	110.57	35.56	0.36	–0.28
Illness behavior (0–4)	103	1.88	0.63	0.25	–0.22
IBS symptoms (0–20)	98	4.43	2.52	0.69	0.73
Age (years)	104	41.67	13.83	0.01	–1.05

Score range for each variable is denoted between parentheses when applicable. BRS, baroreflex sensitivity; IBS, irritable bowel syndrome.

Two variables showed both a significant positive skewness and kurtosis value: BRS, and vigilance ($z > |3.29|$; $P < 0.001$). Visceral pain showed a significant positive skewness value ($z = 3.97$; $P < 0.001$). No outliers (i.e. a Cook's distance > 1) were detected.

Table 1 also shows the number of patients (*N*) per variable. Only BRS had a high number of missing values (20, being 19.2%), which can be explained by the technical difficulties that occurred during the complex BRS measurements (see above) in a relatively large number of patients. Little's test of missing completely at random revealed that this assumption was not rejected [$\chi^2 = 770.395$, degrees of freedom (df) = 72, $P = 0.311$]

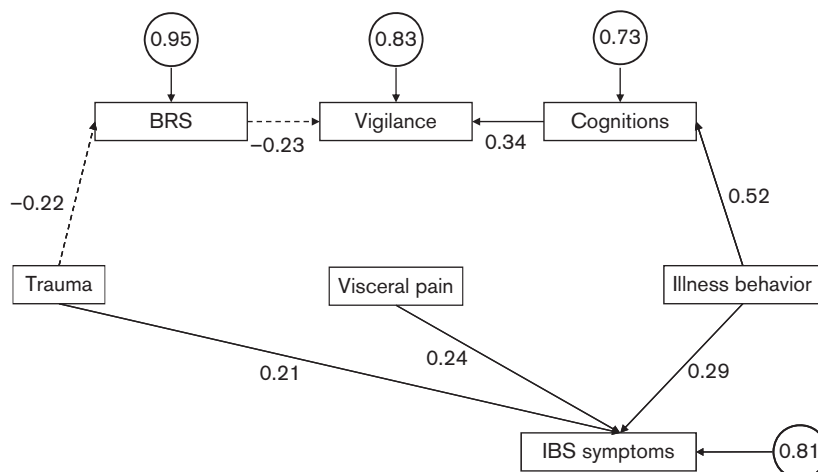
Model tests

Figure 1 shows the biobehavioral model of IBS that was tested. A dashed arrow is displayed if a negative coefficient was expected for that path. Important features of the model are the sequential links between (a) trauma, visceral pain, and IBS symptoms (comparable to the 'visceral' component in Naliboff's model); (b) trauma, BRS, vigilance, visceral pain, and IBS symptoms (the 'central nervous system' component in Naliboff's model); (c) illness behavior, cognitions, and IBS symptoms (the 'cognitive-behavioral' component in Naliboff's model). The model contains two exogenous variables (trauma and illness behavior), which were assumed to be uncorrelated. All goodness-of-fit measures indicated a poor fit ($\chi^2 = 28.47$; df = 11, $P < 0.01$; RMSEA = 0.12; NNFI = 0.57; CFI = 0.78). The standardized residual matrix revealed that the ill fit was caused by the omission of two paths, one between illness behavior and IBS symptoms, and one between trauma and IBS symptoms (the corresponding residuals were 0.276 and 0.260). The model was revised by adding these two paths to the model. The revised model yielded a reasonable fit, with the exception of a low value of the NNFI ($\chi^2 = 13.88$, df = 9, $P = 0.13$; RMSEA = 0.07; NNFI = 0.85; CFI = 0.94). The model explained 18.7% of the variance in IBS symptoms. The significant standardized path coefficients of this model are shown in Fig. 2. The values of the standardized error variances are displayed in the circles.

Illness behavior as a mediator

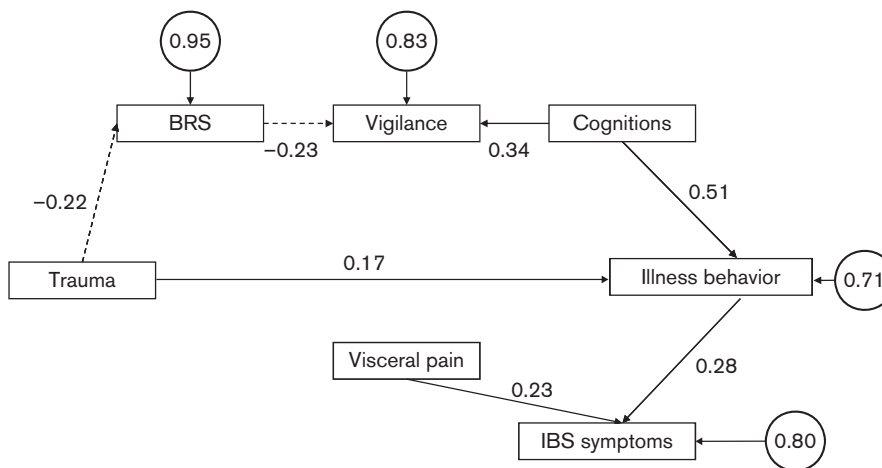
The cognitive-behavioral component of the model proposed by Naliboff *et al.* [21] suggests that the effect of illness behavior on IBS symptoms is possibly mediated by environmental response and health beliefs (operationalized as 'cognitions' in this study). However, Naliboff *et al.* [21] also remarked that the unidirectional relationships in their figure were greatly simplified and that a more complete model would need to include reciprocal influences and feedback mechanisms. Our model tests of Fig. 1 revealed that a direct path was needed from illness behavior to IBS symptoms. By adding this path to the model, the coefficient of the path from cognitions

Fig. 2



Trimmed model showing the standardized path coefficients after deleting nonsignificant paths and addition of a path between illness behavior and irritable bowel syndrome (IBS) symptoms and a path between trauma and IBS symptoms. This was necessary because of ill model fit in the initial analysis, in which these paths were omitted. The values of the standardized error variances are displayed in the circles. The trimmed model explains 18.7% of the variance of IBS symptoms.

Fig. 3



Alternative model to Fig. 1 after paths were added between trauma and illness behavior, trauma and irritable bowel syndrome (IBS) symptoms and illness behavior and IBS symptoms and nonsignificant paths were deleted. Reversal of the path direction from cognition to illness behavior yielded a significantly better fit than the fit of the model of Fig. 2 (20% of variance of IBS symptoms explained by the model).

to IBS symptoms was no longer significant (see Fig. 2). These results, together with the qualifications of Naliboff *et al.* [21], lead us to formulate the following alternative hypothesis: the effect of cognitions on IBS symptoms is mediated by illness behavior.

We tested if illness behavior met the conditions to be considered as a mediator by means of four linear regression analyses. The variable cognitions were significantly associated with both illness behavior and IBS symptoms (two-tailed $P < 0.05$). Illness behavior was significantly associated with IBS symptoms. The effect of cognitions

on IBS symptoms was no longer significant (two-tailed $P = 0.82$) when the effect of illness behavior on IBS symptoms was controlled. The corresponding standardized regression coefficient decreased from 0.21 to 0.03 when illness behavior was added to the regression analysis. These findings support the hypothesis that illness behavior mediates the effect of cognitions on IBS symptoms completely.

Investigation of the standardized residuals of the model displayed in Fig. 2 revealed a relatively large residual (0.21) between trauma and illness behavior. This result

indicated that the model could be improved by adding an additional path from trauma to illness behavior. The addition of this path gave us the possibility to investigate whether the effect of trauma on IBS symptoms was also mediated by illness behavior. We tested this hypothesis by a series of linear regression analyses as mentioned above. Trauma was significantly associated with both illness behavior and IBS symptoms (two-tailed $P < 0.05$). The effect of trauma on IBS symptoms was no longer significant (two-tailed $P = 0.06$) when the effect of illness behavior on IBS symptoms was controlled. The corresponding standardized regression coefficient decreased from 0.24 to 0.18 when illness behavior was added to the regression analysis. These findings support the hypothesis that illness behavior partly mediates the effect of trauma on IBS symptoms.

Taking into account the mediating role of illness behavior, an alternative model to Fig. 2 was formulated. We added a path from trauma to illness behavior and we reversed the direction of the path from cognitions to illness behavior. The fit of this model was much better than the fit of the earlier models ($\chi^2 = 9.85$, $df = 8$, $P = 0.28$; $RMSEA = 0.05$; $NNFI = 0.94$; and $CFI = 0.98$). The model explained 20.0% of the variance in IBS symptoms. Figure 3 displays the significant path coefficients of this model.

Discussion

The biobehavioral model proposed by Naliboff *et al.* [21] was one of the first attempts to improve our understanding of the pathophysiology and clinical expression of IBS. In this study, this model was operationalized to be able to determine the effect of (i) ANS function, (ii) local (visceral) factors, and (iii) cognitive-behavioral aspects on IBS symptom severity, and also the interaction between these domains. Our data do not support the operationalized version of the biobehavioral model presented in Fig. 1. In particular, we found no association between ANS functioning (represented by baroreceptor reflex sensitivity) and IBS symptom severity. Although the working model indicates that autonomic dysfunction modulates IBS symptoms by increasing visceral sensitivity and/or inducing hypervigilance, these path coefficients were not significant. This leads to rejection of hypotheses 1 and 2 (see Introduction), and raises the question whether ANS-stress responses are involved in symptom generation. However, a growing body of literature highlights ANS alterations in IBS patients [10,11,16,17,49], with most studies suggesting sympathetic predominance and/or reduced parasympathetic activity. It is likely that altered autonomic functioning is involved in the pathophysiology of IBS, but this probably takes place through different mechanisms than those proposed in this model, for example, by modifying intestinal motility [50]. Our finding that ANS functioning was significantly correlated to (hyper) vigilance without

affecting IBS symptom severity is consistent with a recent study showing that repeated exposure to aversive visceral stimuli in IBS patients leads to habituation of visceral perception, whereas central processing of anticipation of visceral pain (i.e. vigilance) remains activated [51].

The relationship between visceral pain during rectal balloon distension and IBS symptoms has been established in the last decades and was confirmed by our model. Hypothesis 6 can thus be accepted. The model also predicts that visceral pain or hypersensitivity would be defined by a history of 'abdominal trauma' (sexual or physical abuse and inflammatory processes), autonomic dysfunction, and vigilance. Yet, none of these path coefficients were significant, thereby rejecting hypotheses 1, 2, and 3. One explanation may be that the level of visceral sensitivity is determined by other factors that are currently unknown, or factors that were not the subject of investigation. A possible candidate is the presence of psychiatric comorbidity, for example, depression [52]. Alternatively, it is possible that (i) other measures for assessment of abdominal trauma, ANS function, and vigilance are required, or (ii) these domains interact in a different way than proposed in the model.

The working model suggests that illness behavior influences cognitions, which in turn modulate symptom severity. This association was indeed present, but not in the form we anticipated. A better model fit was achieved when the proposed correlation between illness behavior and cognitions was inversed and an additional path from illness behavior to IBS symptoms was added. The alternative model proposes illness behavior as a mediator between cognitions and IBS symptoms and omits the direct relationship between cognitions and symptoms that was initially assumed. This suggests that dysfunctional cognitions on IBS do not affect symptom severity by themselves but are modulated by a patient's approach to their symptoms (illness behavior). These findings lead to rejection of hypotheses 4 and 5. Moreover, these results present cognitions as an autonomic or exogenous variable in the model, rather than illness behavior. The final model suggests that more dysfunctional cognitions lead to altered illness behavior and, subsequently, to increased symptom severity. The hypothesized effect of illness behavior on IBS symptoms is thereby confirmed, although the model by Naliboff *et al.* [21] postulates an indirect association involving environmental response, health beliefs, and vigilance.

An interesting finding of this study is that a history of 'abdominal trauma' leads to increased IBS symptoms, but in a different way than we expected. Although the working model predicts that a history of abdominal trauma aggravates IBS symptoms by increasing visceral pain perception, the alternative model shows that the effect of trauma on IBS symptoms is mediated by illness behavior. The traumatic effect of sexual and/or physical

abuse on illness behavior has long been established [53], but the effect of abdominal illness such as acute gastroenteritis (another form of ‘trauma’) on illness behavior is not clear. Although the direct relationship between trauma and visceral pain was omitted while testing the model, this does not exclude a role for ‘traumatic’ abdominal events in IBS symptom generation. For instance, long-lasting gut dysmotility and visceral hyperalgesia develop in mice after transient colonic inflammation [54], suggesting a relationship between abdominal illness (i.e. colonic inflammation) and visceral hypersensitivity. Unfortunately, our sample-size was too small to perform subgroup analyses in patients with postinflammatory IBS and in those with a history of abuse. Nonetheless, the relationship between any kind of abdominal trauma and symptom severity in IBS is interesting and deserves further investigation.

A possible limitation of our study is the adjustment we made to the cognitive-behavioral section in the biobehavioral model proposed by Naliboff *et al.* [21]. The original model suggests that IBS symptoms successively modify illness behavior, environmental responses, health beliefs, vigilance, and visceral motor and sensory function, eventually leading back to IBS symptoms. The model also predicts a direct effect of IBS symptoms on health beliefs and vice versa. As explained earlier, we were coerced to perform a path analysis rather than a structural equation model analysis (including latent variables) because of the ratio between the number of observed variables and the number of patients. In addition, our data were from a cross-sectional design, not a longitudinal design. By eliminating the above mentioned feedback loop, we simplified the model to be able to test its validity, but at the same time denied some of the interactions that may be important in the pathophysiology of IBS. Larger patient samples and a longitudinal design are required to overcome this limitation. Another possible limitation is that ‘arousal’ and ‘environmental responses’ were not incorporated in the working model. These were omitted because no accurate measures were available to quantify these domains. Finally, visceromotor activity and viscerosensory activity were operationalized as ‘visceral pain’ because verification of the proposed interaction would require a much larger sample size and more complex statistical calculations that would exceed the aim of this study.

The results of this study are also relevant from a clinical point of view. The strong association between visceral hypersensitivity and IBS symptoms implies a potential therapeutic role for pharmacological compounds affecting visceral sensitivity. Furthermore, the importance of illness behavior in modulating IBS symptoms suggests that psychological behavioral interventions may have additional benefit when combined with pharmacotherapy. In general, the independent association of IBS symptoms

with both visceral hypersensitivity and illness behavior confirms the dual, biobehavioral nature of IBS. This should encourage clinicians to attend to both physical and mental well-being of their IBS patients.

In conclusion, the original biobehavioral model that was proposed by Naliboff *et al.* [21] to improve our understanding of the pathophysiology of IBS could not be validated in this study. Although the association between visceral hypersensitivity and IBS symptom severity was clearly present, a relationship between ANS function and IBS symptoms could not be confirmed. Cognitive-behavioral aspects are important in the clinical expression of IBS, with illness behavior playing an intermediate and modulating but not an autonomic role. Internal and/or external stimuli seem to affect IBS symptoms by modulating illness behavior rather than ANS function or visceral sensitivity. These findings suggest a central role of illness behavior in the pathophysiology of IBS and thereby provide an interesting candidate therapeutic target in IBS treatment. Future longitudinal studies in larger patient samples are required to further investigate the mechanisms involved in the pathophysiology of IBS.

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Conflict of interest: none declared.

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