ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld.2014.1121.273.bab

Predictors of Outcome in Cognitive and Behavioural Interventions for Irritable Bowel Syndrome. A Meta-Analysis

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Received: 16.05.2018
Accepted: 30.07.2018

ABSTRACT

Background & Aims: Cognitive behavioural therapy (CBT) has small to medium effects in alleviating emotional distress and psychosomatic symptoms in irritable bowel syndrome (IBS). However, the mechanism through which CBT exerts its effects is less studied. Mediation analysis examines the extent to which intermediate variables explain the effect of the intervention on outcomes. The meta-analysis aims to identify and assess the impact of CBT mediators identified in previous research on IBS.

Methods: An extensive search of studies investigating the effects of CBT for IBS published before January 2018 was conducted. A total of 699 studies were identified through database search and 6 studies including data from 638 patients were analysed. The selected studies had to clearly define the CBT intervention, include IBS patients, report sufficient data to allow calculation of effect sizes and provide a clear mediation analysis of one or several variables on the outcome.

Results: The total effect of CBT was significant for both categories of outcomes (i.e. IBS symptom severity and psychosocial distress), with a low-to-moderate effect on psychosocial distress (r=0.222) and a medium-to-large effect on IBS symptom severity (r=0.413). In fact, the total effect of CBT on IBS symptom severity is significantly higher than the total effect on psychosocial distress Q(1)= 5.06, p= 0.024. Both behaviours and emotions (r=0.158) as well as cognitions (r=0.141) generated significant mediated effects on psychosocial distress, with no significant differences between them (Q(1)= 0.05, p=0.825). Behaviours and emotions mediated 71.1% of the total effect of CBT on psychosocial distress and cognitions mediated 63.5% of the total effect.

Conclusion: Although significant for both outcomes, the statistical analysis revealed CBT interventions have a greater effect on alleviating IBS symptoms severity rather than on reducing psychological distress. Of the mediators investigated, behaviours, emotions and cognitions seem to have a small to moderating effect in reducing IBS symptom and psychological distress.

Key words: cognitive-behavioural therapy – irritable bowel syndrome – meta-analysis, mediators.

Abbreviations: CBT: cognitive behavioural therapy; GI: gastrointestinal; IBS: irritable bowel syndrome.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, functional gastrointestinal (GI) condition, characterized by recurrent episodes of abdominal pain and altered bowel habits [1-4]. The symptoms may restrict daily activities and increase psychological distress [5-7]. Irritable bowel syndrome is a complex and multifactorial condition, influenced by a number of biological (e.g. alteration of the gut-brain axis), psychological (e.g. neuroticism, somatisation) and social (e.g. life stressors) factors [1, 4]. Management interventions include pharmacological treatments (e.g. antispasmodics, antidiarrheal, low-dose antidepressants, probiotics etc.), modifications in lifestyle and dietary changes [8]. Although the specific role of psychological interventions in the management of IBS is to some extent still unclear [9, 10], overall IBS symptoms (i.e. psychosomatic symptoms, daily functioning, emotional distress) seem to be improved by psychological interventions such as cognitive behavioural therapy (CBT), hypnotherapy and psychodynamic interpersonal therapy [2, 11].

In CBT beliefs are seen to mediate the impact of activating events on various emotional and behavioural consequences. Emotional distress is regarded as emerging from problematic,

maladaptive, and/or unrealistic interpretations of events [12]. CBT interventions have been shown to reduce IBS symptoms, improve quality of life and help patients adapt to their symptoms by targeting maladaptive thoughts and behaviours that exacerbate or maintain these symptoms [10, 13]. Previous systematic-reviews and meta-analyses [9, 14] concluded that CBT has a medium effect in improving global symptoms, abdominal pain and quality of life, with an increased efficacy when used together with standard medical treatment [14].

Clearly, we do not fully understand the mechanisms through which CBT exerts its effect. It is not yet clear why, how or when CBT works [15]. Although there are several theoretical models describing how thoughts, behaviours and emotions can influence gastrointestinal symptoms [6], few studies have tried to clarify these mechanisms. The following mediators have been studied: doctor-patient relationship [16], illness perception [3], catastrophizing [4, 17], somatization [4], irrational beliefs and coping strategies [18], beliefs about emotions and emotional suppression [19], changes in neural activity of cortical-limbic regions (e.g. amygdala, anterior cingulate cortex, medial frontal cortex) [20] and abuse and mood disorders [21].

The few studies available suggest conflicting conclusions. CBT is hypothesized to exert its effect by first improving IBS symptoms and then independently reducing somatization, catastrophizing and improving mood [15]. Another hypothesis is that changes in IBS severity are directly associated with mood improvement [22] or with changes in behaviour and cognition [23], which in turn improve GI symptoms. A more recent hypothesis suggests that changes mainly occur by targeting illness specific factors (e.g. GI specific anxiety, cognitions and behaviours) rather than general anxiety [24].

The lack of consistency of results is due to several factors: (i) various psychological treatments use labels such as CBT but in fact they are not comparable (e.g. problem solving, behavioural strategies, coping skills, cognitive interventions, face-to-face, group or online); (ii) variation of IBS diagnosis criteria used; (iii) methodological diversity of the studies and insufficient reported data.

The main objective of this meta-analysis is to identify and assess the impact of mediators found in previous research (e.g. illness perception, catastrophizing, fear avoidance, symptom attribution, visceral sensitivity, anxiety, depression) on IBS. Mediation analysis examines the extent to which intermediate variables explain the effect of the intervention on outcomes and therefore can clarify the mechanisms of change through which CBT exerts its effects for IBS.

METHODS

Literature review

An extensive electronic search was conducted investigating the literature published until January 2018. The studies included were identified through a search of PubMed, PsycInfo and Cochrane Reviews databases. The following key words were used to conduct the literature search: irritable bowel syndrome (IBS), cognitive behavioural therapy (CBT), cognitive therapy, mediation, mediators, and mechanisms of change.

Inclusion / Exclusion criteria for study selection

Inclusion criteria were studies published in English that investigated patients diagnosed with IBS, where clearly defined CBT interventions were used and where mediators or mechanisms of change were investigated. We only included studies that reported sufficient data to allow calculation of the mediation effects and effect sizes. We excluded studies discussing mediation analyses for other psychological interventions than CBT, cross-sectional studies, qualitative data, reviews or studies where CBT was investigated but the mechanisms of change or mediators were not addressed.

Study coding procedures

Studies were coded to identify: (1) data about participants: number, age, gender, source of recruitment, diagnosis (e.g. IBS or functional somatic syndromes), IBS type (diarrhoea, constipation, mixed), diagnostic criteria used (e.g. Rome I, II, III or other), mean duration of disorder, comorbidities (e.g. psycho-affective disorders or gastrointestinal disorders); (2) methodology: study design information (e.g. randomized control trials), type of control group (e.g. treatment as usual, wait list, enhanced usual care) and statistical analysis (e.g. mediation analysis, structural equations or others); (3) intervention: type of CBT delivery, (e.g. individual, group, and self-help), professionals delivering the intervention (e.g. psychology or medical personnel), duration of the intervention and type of support (e.g. face-to-face or online support); and (4) mediators and outcomes: measurement tools and time of measurement (e.g. baseline, end of treatment, follow-up). Mediators were grouped in two categories: Cognitions (e.g. illness perception, catastrophizing, damaging beliefs), Behaviours and Emotions (e.g. fear avoidance, anxiety, depression, GI specific-anxiety, stress reactivity). Outcomes were organized as IBS symptoms severity or as psychosocial distress.

Statistical analysis

For each variable, standardized regression coefficients (β) for path a (i.e. the association between predictor and mediator), path b (i.e. the association between mediator and outcome), the indirect (path a*b) and total effects, path c (i.e. the association between predictor and outcome) were selected [25, 26]. The β coefficients and sample sizes were used to calculate a pooled effect size for the indirect (path a*b) and total effects (path c) [25].

The risk of publication bias was calculated using the Begg and Mazumdar's rank correlation test [27]. This test computes the rank order correlation (Kendall's tau b) between the treatment effect and the standard error (which is primarily driven by sample size) to identify whether large studies tend to be included in the analysis regardless of their treatment effect, whereas small studies would be more likely to be included when they show a relatively large treatment effect.

Analyses were conducted using Comprehensive Meta-Analysis V2.2.

Study quality assessment

The methodological quality of the selected studies was evaluated using a quality assessment scale [25]. The seven criteria included in the scale (e.g. inclusion of a theoretical

framework, psychometric characteristics and methods of data analysis, etc.) were rated with 0 (no) or 1 (yes) by two of the co-authors (MR and RM). The assessment is shown in Appendix 1 (Supplementary material).

RESULTS

A total of 699 studies were identified through databases and additional records searching. After removal of duplicates and screening of abstracts, 41 studies were selected for eligibility assessment, and 10 were identified for inclusion. The flowchart of the study is represented in Fig.1.

Of the initial 10 studies selected, only 6 articles included the statistical data needed for further analysis. A summary of study characteristics is presented in Table I.

Participants' characteristics

In all 6 studies included [15, 23, 28, 29, 30, 32], the majority of participants were women (73% or more in each study) ascertained from primary or secondary care, general practices or from online recruitment. Participants (total N = 638) mean age ranged from 33 to 40 years old. All patients were diagnosed with IBS; three studies [15, 29, 32] used Rome criteria (I, II or III) and three studies [23, 28, 30] did not report the diagnosis criteria used. Four studies reported a mean duration of the condition between 8 to 17 years [15, 28, 29, 30]. One study presented data on IBS subtypes (diarrhoea, constipation or mixed) [15].

Main effects

Analysis of the overall total effect

The results show a significant medium total effect size of CBT (r=0.323, p< 0.001). The distribution of effects proved to be significantly heterogeneous, Q(5)= 15.96, p<0.001, which indicates that moderators might play a significant role in the way CBT exerts its effect. The rank order correlation (Kendall's tau b) between the treatment effect and the standard error was non-significant, which indicates no publication bias (tau b= -0.20, p= 0.573).

Analysis of the overall mediated (indirect) effect

Fig 3 shows a significant overall mediated effect size (r=0.169, p<0.001). The distribution of effects was non-significantly heterogeneous, Q(5)= 2.97, p=0.704, yet due to the methodological diversity of the studies, we chose to perform our analysis using a random effects model. Further analysis revealed no publication bias (tau b= -0.46, p= 0.188).

The total effect of CBT as a function of outcome category

The total effect of CBT was significant for both categories of outcomes (i.e. IBS symptom severity and psychosocial distress), with a low-to-moderate effect on psychosocial distress (r=0.222) and a medium-to-large effect on IBS symptom severity (r=0.413). As seen in Table II, the total effect of CBT on IBS symptom severity is significantly higher than the total effect on psychosocial distress Q(1)=5.06, p=0.024.

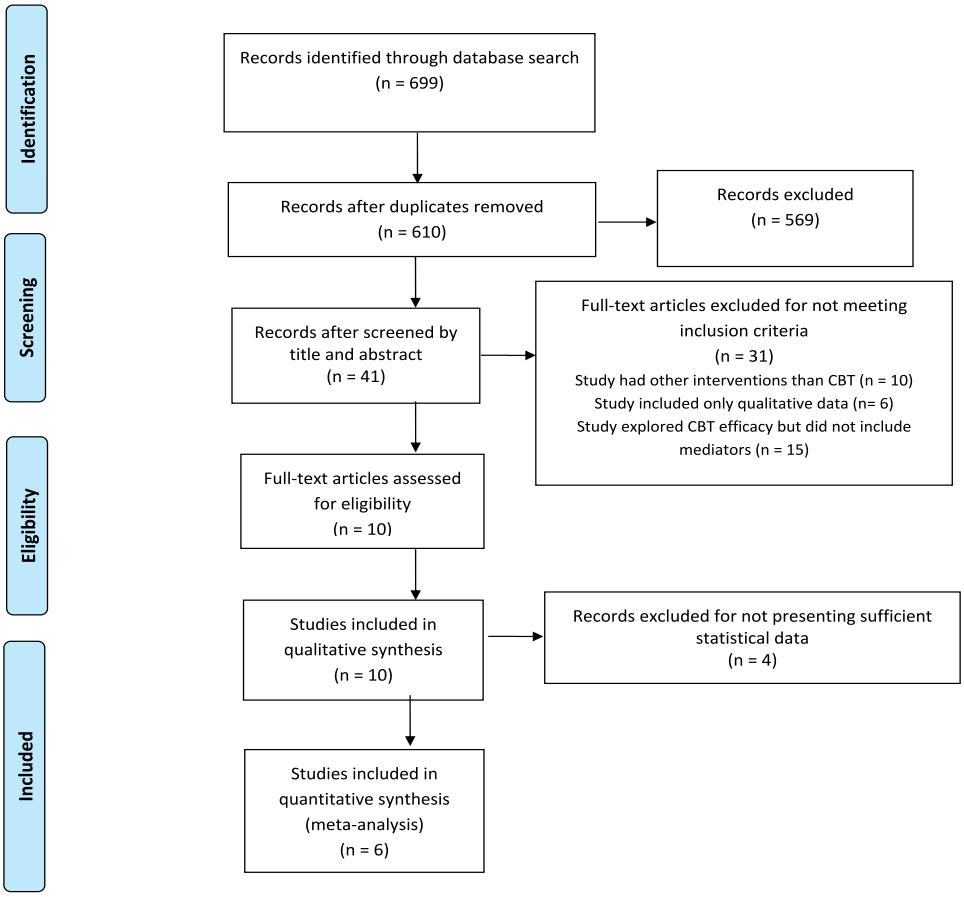

Fig. 1. PRISMA Flow Diagram

Table I. Study characteristics

Study	N analyzed % of females Mean age±SD	Diagnostic criteria	Control group	Type of intervention (type of delivery, duration, professional delivering the intervention)	Mediator	Time point	Outcome
Chilcot & Moss-Morris, 2013* [32]	64 73% 39 years±15.9	Rome I or II	TAU	CBT+TAU Self-management 7/8 weeks + 1hour face to face Health psychologist	Illness Perception Catastrophizing Damaging beliefs Fear avoidance Symptom attribution	Baseline post-treatment 5 to 8 months FU	IBS severity Social adjustment
Christensen et al., 2015* [28]	40 80% 36 years±6.4	NR	Enhanced usual care	CBT Group 16weaks; 3.5h/module Psychiatrist	Uncertainty Lack of control Negative consequences and emotional representation	Baseline during treatment post-treatment 12 months FU	Physical health Somatic symptoms Illness worry
Hunt et al., 2014 [5]	60 90% 36 years±12.6	Rome III	Wait list	CBT Self-management 6 weeks	Gastrointestinal specific catastrophizing Overall catastrophizing	Baseline post-treatment 3 months FU	GI symptom severity
Hunt et al., 2009 [1]	54 90% 38 years±12	Rome	Wait list	CBT Self-management 5 weeks Email therapist feedback	Catastrophizing Visceral sensitivity	Baseline post-treatment 3 months FU	GI symptom severity Quality of life
Jones et al., 2011 [22]	105 81% 42 years±11	Rome I	Routine clinical care Relaxation Therapy	CBT Individual face-to-face 8 weeks Gastroenterologist; Clinical psychologist	Anxiety Depression	Baseline during treatment post-treatment 6 and 13 months FU	Bowel symptom severity (Frequency, Distress, Dissability)
Lackner et al., 2007* [15]	147 82% 48 years±15	Rome II	Wait list; Psycho-education	CBT Group 10 weeks Clinical psychologist	Gastrointestinal global improvement Psychological distress	Baseline post-treatment	Quality of life
Ljotsson et al., 2013* [29]	195 79% 38 years±11.1	Rome III	ISM (relaxation, diet, stress-reduction)	CBT + mindfulness Self-management 10 weeks Online support Clinical psychologist or graduate psychology student	Gastrointestinal symptom-specific anxiety Stress reactivity	Baseline during treatment post-treatment	IBS symptom severity
Pedersen et al., 2016* [30]	43 79% 35.8 years±6.4	NR	Enhanced usual care	CBT Group 16weaks; 3.5h/module Psychiatrist	Symptom catastrophizing Distraction Distraction from pain Ignoring pain Experienced control	Baseline during treatment post-treatment 12 months FU	Change in physical health Change in social functioning
Reme et al., 2011* [23]	149 82% 33 years±8.6	NR	Mebeverine/ TAU	CBT+ Mebeverine Individual face-to-face 6 weeks Nurses	Behavior (avoidance behavior, toilet behavior) Cognitions(automatic thought and concerns regarding bowel habits)	Baseline during treatment post-treatment 1.5, 3,6 and 12 months FU	Work and social adjustment IBS symptom severity Anxiety
Wolitzky-Taylor et al., 2012 [31]	76 74% 39 years±13.5	Rome II	Attention control condition; CBT-Stress management; CBT-Intero-ceptive exposure	CBT Individual face-to-face 10 weeks Therapist	Visceral sensitivity	Baseline during treatment post-treatment 3 months FU	IBS symptom severity Quality of life Food avoidance

IBS: Irritable Bowel Syndrome; RCT: Randomized Clinical Trial; CBT: Cognitive-Behavioral Therapy; TAU: Treatment as Usual; NR: Not Reported. *Studies included in the meta-analysis

Moderation analysis

Moderation analysis for the total effect

The only characteristic of participants that had shown to significantly moderate the overall total effect was gender (i.e. percentage of females) (B= -0.036, p= 0.001). Data suggest that a high percentage of female participants seem to be associated with a lower overall total effect. Results should nevertheless be viewed with caution as the limited variability in gender in our

Tabel II. The analysis of the total effect of CBT as a function of outcome category (IBS symptom severity vs. Psycho-social distress)

Type of outcome	N	r	Inf (CI95%)	Sup (CI95%)	Z	p	Heterogeneity between categories		
							Q	df	p
IBS symptom severity	5	0.413	0.299	0.516	6.59	0.000	5.06	1	0.024
Psycho-social distress	5	0.222	0.092	0.344	3.33	0.001			

N: number of studies; r: Pearson Correlation; p: probability of the null hypothesis; CI95%: confidence interval with 95% probability; Z: the Z test.

data may have masked an effect. Other potential moderators (e.g. age, duration of condition, or recruitment) were not statistically significant.

As far as the intervention was concerned, one variable had a significant moderating role: the type of intervention delivery had a significantly medium effect for self-management delivery (r=0.491, p<0.001) and a significantly smaller effect for face-to-face delivery (e.g. group and individual therapy), (r=0.217, p<0.001). All other potential moderators investigated (e.g. duration of intervention, duration of face-to-face support and type of professionals delivering the intervention) were not statistically significant.

Moderation analysis for the mediated effect

Type of mediators

As shown in Table III, cognitions (r=0.115, p<0.001), behaviours and emotions (r=0.163, p< 0.001) were shown to have small but significant mediated effect sizes. No significant differences between the type of mediators on the mediated effect were found [(Q(1)= 1.624, p= 0.203)].

Type of outcomes

For both IBS symptom severity (r= 0.140, p< 0.001) and psychosocial distress (r= 0.132, p< 0.001), the mediated effect was small but significant. There are no significant differences of mediated effects as a function of the type of outcome (Q(1)= 0.04, p= 0.839).

For behaviours and emotions, the mediated effect on IBS symptom severity was small but significant (r=0.159, p<0.001); for cognitions the effect was small (r=0.113) and only marginally significant (p=0.054). When behaviours and emotions were tested as mediators, the mediated effect of CBT on IBS symptom severity represented 38.5% of the total effect, while 27.3% of the total effect was mediated by cognitions. There were no significant differences between the mediated effects generated by the two categories of mediators (Q(1)= 0.38, p= 0.536).

Both behaviours and emotions (r=0.158) as well as cognitions (r=0.141) generated significant mediated effects on psychosocial distress, with no significant differences between them (Q(1)= 0.05, p=0.825). Behaviours and emotions mediate 71.1% of the total effect of CBT on psychosocial distress and cognitions mediate 63.5% of the total effect. Table IV includes a summary of the results.

DISCUSSION

Our study looked at several types of CBT interventions for IBS (CBT protocol, CBT and mindfulness, CBT and relaxation therapy, etc.), types of delivery (face-to-face, group, self-management), control groups (wait list, TAU, relaxation therapy etc.) and statistical analyses (path analysis, latent growth model, hierarchical linear model, Barron and Kenny`s meditational analysis etc.). The results show that CBT is effective in alleviating the severity of IBS symptoms.

We also wanted to explore in more depth what are the mechanisms responsible for the CBT efficacy for IBS. We therefore looked at the mediated effect from the overall total effect. Our analysis revealed that 52% of the overall effect of CBT was mediated by changes in cognitions (e.g. illness perception, catastrophizing, symptom attribution, uncertainty, lack of control), emotions (e.g. stress reactivity, anxiety, depression) and behaviours (fear avoidance). Further analyses showed that CBT is significantly more effective for IBS symptom severity than psychosocial distress. Additionally, data showed that the total effect of CBT on both IBS symptom severity and psychosocial distress is mediated in a higher proportion by

Table III. The analysis of the mediated effect as a function of the type of mediators and as a type of outcomes

		N	r	Inf (CI95%)	Sup (CI95%)	Z	p	Heterogeneity between categories		
								Q	df	p
Type of mediators	Behaviour & Emotion	4	0.163	0.109	0.216	5.84	0.000	1.624	1	0.203
	Cognitions	4	0.115	0.064	0.165	4.43	0.000			
Type of outcomes	IBS symptom severity	4	0.140	0.084	0.195	4.86	0.000	0.04	1	0.839
	Psycho-social distress	4	0.132	0.079	0.183	4.90	0.000			

N: number of studies; r: Pearson Correlation; p: probability of the null hypothesis; CI95%: confidence interval with 95% probability: Z: the Z test.

Table IV. The analysis of the mediated effect upon each outcome as a function of mediator type (cognitions vs. behaviour & emotion)

Type of outcome	Type of mediators	N	r	Inf (CI95%)	Sup (CI95%)	Z	p	Heterogeneity between categories		
								Q	df	p
IBS symptom severity	Behaviour & Emotion	5	0.159	0.070	0.244	3.50	0.000	0.38	1	0.536
	Cognitions	4	0.113	-0.002	0.225	1.93	0.054			
Psycho-social distress	Behaviour & Emotion	5	0.158	0.065	0.248	3.30	0.001	0.05	1	0.825
	Cognitions	4	0.141	0.027	0.252	2.41	0.016			

N: number of studies; r: Pearson Correlation; p: probability of the null hypothesis; CI95%: confidence interval with 95% probability: Z: the Z test.

behaviours and emotions rather than by cognitions. These outcomes are best explained by looking at the protocol interventions used in the studies. For instance, after clarifying the IBS symptoms patients were encouraged to assess, monitor and manage their symptoms and then manage unhelpful thoughts [23, 28, 30, 32]. Patients were also encouraged to engage in exposure exercises and to challenge their fears [33]. Interventions seem to initially focus on targeting problematic behaviours and helping patients manage symptoms that in turn may change related cognitions. Our results are supported by previous studies showing how behavioural experiments and exposure exercises for IBS patients can increase day to day functioning, reduce severity symptoms and increase quality of life [6, 29, 34, 35].

Our moderation analyses suggested several hypotheses that would worth be further explored but did not suggest unequivocal moderators of change (e.g. duration of the condition, duration of CBT protocol, professionals delivering the intervention, etc.)

One of the main limitations of this study is the number of articles included. From 10 studies found to meet the inclusion criteria, only 6 provided sufficient data to perform the analyses. Another aspect that needs to be taken into account when interpreting the data is the heterogeneity of studies, which made it difficult to draw unequivocal conclusions. Irritable bowel syndrome is a syndrome diagnosed by symptom-based criteria and is a heterogeneous disorder with some patients having predominately psychological symptoms while others having biological signs, the response to any type of intervention might depend on the phenotypes of patients. It would be particularly useful for further studies to use clear IBS diagnosis criteria (e.g. Rome IV), include assessments of severity, detailed information about participants and CBT interventions implemented, as well as standard control groups, time point assessments and measures. More clarity in designing further studies could significantly reduce the variability of IBS studies, contributing to a better understanding of the mechanism of CBT for IBS.

Identifying mediators can have a significant role in improving our understanding of the psychosomatic mechanisms involved in IBS as well as the mechanisms of change we need to target when designing and implementing psychological interventions. By investigating why, how or when CBT works, we can explore the active ingredients of CBT when delivered to IBS patients. Knowing what the mechanisms of change are and what their role is in improving outcomes can help create more tailored CBT interventions.

Conflicts of interest: The authors declare that they have no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contribution: M.Radu.: collection of data, analysis and interpretation of data, elaboration of the manuscript; R.Moldovan: design of the study, analysis and interpretation of data, elaboration of the manuscript; S.P.: analysis and interpretation of data; elaboration of the manuscript; A.B.: supervision of research implementation; elaboration of the manuscript; D.D.: supervision of research implementation; manuscript elaboration.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://www.jgld.ro/wp/archive/y2018/n3/a10 and http://dx.doi.org/10.15403/jgld.2014.1121.273.bab

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Appendix 1.

	Chilcot& Moss-Morris, 2013	Christensen et al., 2014	Hunt et al., 2014	Hunt et al., 2009	Jones et al., 2011	Lackner et al., 2007	Ljotsson et al, 2013	Reme et al., 2011	Pederesen et al., 2016	Wolitzky-Taylor et al., 2012
1. Did the study cite a theoretical framework?	1	1	1	1	1	1	1	1	1	1
2. Were the psychometric characteristics of the mediator and outcome variables reported?	1	1	1	1	1	1	1	1	1	1
3. Did the study report a power calculation? If so, was the study adequately powered to detect mediation?	1	0	0	0	0	1	1	1	0	0
4. Were statistically appropriate/ acceptable methods of data analysis used?	1	1	1	1	1	1	1	1	1	1
5. Did the study ascertain whether changes in the predictor variable preceded changes in the mediator variable?	1	0	0	0	1	0	1	1	0	0
6. Did the study ascertain whether changes in the mediating variables preceded changes in the outcome variables?	0	0	0	0	1	0	1	1	0	0
7. Did the study control for possible confounding factors, e.g., baseline values?	1	1	1	1	1	1	1	1	1	1

Quality assessment (0= no; 1= yes)