Citation for published version (APA):
A systematic review with meta-analysis of the role of anxiety and depression in Irritable Bowel Syndrome onset

Authors

Alice Sibelli
Health Psychology Section
Department of Psychology
Institute of Psychiatry, Psychology and Neuroscience
King's College London
5th floor Bermondsey Wing
Guy's Hospital Campus
London Bridge
London
SE1 9RT

Prof. Trudie Chalder
Professor of Cognitive Behavioural Psychotherapy
Department of Psychological Medicine
Institute of Psychiatry, Psychology and Neuroscience
King's College London
Weston Education Centre
Cutcombe Road
London
SE5 9RJ

Dr. Hazel Everitt
Associate Professor in General Practice
Primary Care and Population Sciences
University of Southampton
Aldermoor Health Centre
Aldermoor Close
Southampton
SO16 5ST

Paul Workman
Health Psychology Section
Department of Psychology
Institute of Psychiatry, Psychology and Neuroscience
King's College London
5th floor Bermondsey Wing
Guy's Hospital Campus
London Bridge
London
SE1 9RT

Sula Windgassen
Department of Psychological Medicine
Institute of Psychiatry, Psychology and Neuroscience
King's College London
Chronic Fatigue Research and Treatment Unit
Mapother House
De Crespigny Park
Denmark Hill
London
SE5 8AZ

Prof. Rona Moss-Morris* (Corresponding Author)
Professor of Psychology as Applied to Medicine
Health Psychology Section
Short title: The role of anxiety and depression in IBS onset.

Key words
Irritable Bowel Syndrome, Onset, Anxiety, Depression, Systematic Review, Meta-analysis

Abbreviations
IBS: Irritable Bowel Syndrome.
PI-IBS: post-infectious Irritable Bowel Syndrome.
GI: gastrointestinal.
HADS: Hospital Anxiety and Depression Scale.
DSSI: Delusion Symptom States Inventory.
SD: standard deviation.
N: sample number.

Funding information
This research received no specific grant from any funding agency, commercial or not-for-profit sector.

Conflict of interests
One of the authors of this review (RMM) was involved with two of the included papers (one used in the meta-analysis of anxiety/depression treated as categorical variables and the other one included in the meta-analysis of anxiety/depression treated as continuous variables). However, all the statistical analyses were conducted independently by AS. Five authors (AS, RMM, TC, HE, SW) are currently working on a Randomised Controlled Trial assessing the clinical and cost effectiveness of Cognitive Behavioural Therapy in refractory Irritable Bowel Syndrome funded by the Health Technology Assessment (HTA) Programme. No other conflicts of interest are declared.
Ethical standards

This research did not involve human or animal experimentation.

Word count: 5279 (only text, no references)
ABSTRACT

Background

It is well established that people with IBS have higher levels of anxiety and depression compared to controls. However, the role of these as risk factors is less clearly established. The aims of this systematic review were to investigate 1) whether anxiety and/or depression predict IBS onset 2) the size of the relative risk of anxiety versus depression in IBS onset. Sub-group analyses explored if methodological factors affected the overall findings.

Methods

Prospective cohort or case-control studies were included if they 1) focused on the development of IBS in population based or gastroenteritis cohorts 2) explored the effects of anxiety and/or depression at baseline as predictors of IBS onset at a future point. Eleven studies were included of which 8 recruited participants with a gastrointestinal infection. Meta-analyses were conducted.

Results

The risk of developing IBS was double for anxiety cases at baseline compared to those who were not: RR 2.38, 95% CI 1.58-3.60. Similar results were found for depression: RR 2.06, 95% CI 1.44-2.96. Anxiety and depression seemed to play a stronger role in IBS onset in individuals with a gastrointestinal infection although this could be attributed to other differences in methodology, such as use of diagnostic interviews rather than self-report.

Conclusions

The findings suggest that self-reported anxiety and depression provide a twofold risk for IBS onset. There is less support for the role of anxiety or depressive disorder diagnosed using clinical interview. These findings may have implications for the development of interventions focused on IBS prevention and treatment.
INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic functional gastrointestinal disorder associated with abdominal pain, bloating and change in bowel habit, with either predominantly diarrhoea, constipation or a combination of both (Spiller et al. 2007). A clinical diagnosis of IBS is based on the identification of positive symptoms through diagnostic criteria and the exclusion of organic diseases and alarm symptoms, such as unexplained weight loss and rectal bleeding (Manning et al. 1978; Drossman, 2006).

The prevalence of IBS ranges between 10 – 25% in community samples and it affects around 11% of the global population (Canavan et al. 2014; Lovell & Ford 2012). IBS has significant financial consequences, with direct costs per patient ranging from $1,562 to $7,547 per year, and indirect costs from $791 to $7,737 per year (Nellesen et al. 2013). Humanistic burdens of IBS include a negative impact on quality of life, social functioning and time off work (Spiller et al. 2007). Treatment for IBS relies on lifestyle advice, and medical and psychological therapies (Akehurst & Kaltenthaler 2001; Talley et al. 2015).

Current conceptualisations of IBS include the biopsychosocial model, which acknowledges the two-way communication between mind and body (Engel, 1980; Drossman, 1998; Tanaka et al. 2011). Psychological and social factors interact with physiological factors (e.g. intestinal inflammation, altered motility and bacterial flora) through the bidirectional communication between the central nervous system and the enteric nervous system (Jones et al. 2006; Surdea-Blaga et al. 2012). More specifically, the biopsychosocial model suggests that biological and psychosocial predisposing factors in early life, such as genetics, heredity, trauma, and parental illness behaviours, increase people’s susceptibility to develop IBS.

Precipitating factors (e.g. lack of social support, stressful life events, gut infection) can closely precede and trigger IBS. Perpetuating factors, such as anxiety, depression, negative perceptions of symptoms and illness behaviours contribute to the maintenance of symptoms over time (Hauser et al. 2014; Deary et al. 2007). Anxiety and depression are usually considered perpetuating factors of IBS symptoms but it is also possible that they act as predisposing or precipitating factors of IBS alongside other risk factors, such as an acute gastrointestinal (GI) infection (Stermer et al. 2006; Hamilton et al. 2009; Marshall et al. 2010; Spiller & Lam 2012).
Studies suggest that around 5% to 32% of patients develop IBS after GI infections (Thabane & Marshall, 2009) but this percentage may be higher as GI infections tend to be underreported by patients. It is still not clear whether post-infectious IBS (PI-IBS) is a different sub-group of patients suffering from IBS (Sundin et al. 2015). Research has found that a history of previous treatment of anxiety/depression is less correlated with PI-IBS than non PI-IBS (Dunlop et al. 2003). Therefore, exploring the role of anxiety and depression as risk factors of IBS in both GI samples and population based studies may contribute to understanding sub-group differences in IBS.

Although recent literature acknowledges the interplay between mind and body and describes the potential mechanisms underlying IBS pathophysiology (Stasi et al. 2012; Mayer et al. 2015), in clinical practice some doctors still conceive IBS as a sole somatisation of anxiety and depression (Dixon-Woods & Critchley, 2000; Bijkerk et al. 2003; Lacy et al. 2006). Indeed, patients feel that some doctors, because of their psychological view of the syndrome, do not take their symptoms seriously (Kennedy et al. 2003).

It is well established that individuals with IBS have higher levels of anxiety and depression compared to healthy controls (Henningsen et al. 2003; Fond et al. 2014). Cross-sectional analyses report a positive association between IBS symptoms and anxiety and depression (Masand et al. 1995; Mykletun et al. 2010; Phillips et al. 2013). However, these analyses cannot determine whether anxiety and depression increase the risk of developing IBS.

The purpose of this paper was to systematically review prospective studies investigating anxiety and depression as risk factors for the onset of IBS and to employ meta-analysis to understand the size of the effects. Quality assessment of studies was conducted to help understand any inconsistencies in data across studies. The research questions were: 1) are anxiety and/or depression significant predictors IBS onset? (i.e. do they increase the risk of developing IBS?) 2) what is the size of the relative risk of anxiety and depression in the onset of IBS? Sub-group analyses were also planned to explore if (a) population based vs GI samples (b) type of anxiety/depression measurements (c) IBS diagnostic criteria used and (d) length of follow-ups affected the overall findings. The length of follow-up can help to elucidate the temporal effect of anxiety/depression in the development of IBS by studying their role as potential precipitating factors in the short and long term.
METHODS

The findings of this systematic review are reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies. The process followed an a priori established protocol.

Search strategy and study selection

Electronic databases (MEDLINE - Ebsco, EMBASE - Ovid, Web of Science - ISI Web of Knowledge, CINAHL – Ebsco, and PsychINFO - Ebsco) were searched systematically for studies published between database start to the 18th of March 2015 by two authors (AS and PW). The reference lists of all eligible studies were also hand searched to identify further potential studies. MeSH terms relevant to anxiety, depression and Irritable Bowel Syndrome were used in the search. The search strategies for each specific database are shown in Appendix 1.

Study selection

Studies were included if they met all the following criteria: 1) prospective cohort or case-control studies that investigated anxiety and/or depression measured at baseline and their relationship with a new diagnosis of IBS at a future time point 2) population based studies or studies with individuals with a GI infection aged 16 years or over 3) studies that assessed anxiety and depression through validated psychometric measures or a structured clinical interview 4) studies that established a diagnosis of IBS at the endpoint (at least 3 months post-baseline) based on: published diagnostic criteria, adapted published diagnostic criteria or a multi-item symptom questionnaire.

Exclusion criteria for this review were: articles that were not empirical studies; dissertation and conference abstracts; studies that included a treatment condition; studies that included IBS patients as a sub-group of a larger sample, where the results were not presented separately from the other participants; sample with a primary GI diagnosis that was not IBS; cross-sectional studies. Retrospective studies excluded from this review were defined as: 1) studies that assessed anxiety and/or depression pre-IBS onset when the participants already
had IBS 2) studies that assessed anxiety and/or depression levels longer than 4 months after the onset of the GI infection 3) studies that retrospectively collected data from a database where the measures of anxiety/depression and the assessment of IBS were not standardised. Two authors (AS and PW) independently screened titles and abstracts for inclusion. Disagreements occurred for 10 out of 5454 abstracts screened (0.2%). A total of 93 full-texts were assessed for eligibility. Uncertainties regarding inclusion of studies were resolved through discussions between RMM, AS and PW.

**Data extraction**

Data extraction was conducted independently by two authors (AS and PW). Attempts were made to contact the authors by email where insufficient data were reported. Data were extracted from the included studies using a predefined Excel electronic template (see Appendix 2 for the variables extracted). Any discrepancies in data extraction were discussed between RMM, AS and PW.

**Quality assessment**

The methodological quality of the included studies was assessed independently by two authors (AS and SW) using an adapted version of the Black and Downs scale (Downs & Black, 1998) for observational studies. The adapted scale had an overall score of 29 points for the studies that included participants with gastroenteritis and an overall score of 27 for those studies with non-GI samples (See Appendix 3 for a detailed description of the scale and scoring). Inter-rater agreement for categorical scorings on each item of the adapted scale was assessed using Cohen's Kappa. An intraclass correlation coefficient was calculated to assess inter-rater agreement for the entire scale (i.e. using the overall numerical scores). Statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, New York).

**Quantitative synthesis**

To ascertain whether anxiety and/or depression increased the risk of developing IBS, we used the metan command in STATA 11 (StataCorp, College Station, TX, USA) to perform meta-analyses on relative risks as the effect measure. We derived the summary estimate
using a random effects model (DerSimonian and Laird) with the estimate of heterogeneity being taken from the Mantel–Haenszel model (Sterne et al. 2001; Harris et al. 2008). Ninety-five per cent confidence intervals (95% CI) were reported for each study’s relative risk and the pooled relative risk.

The heterogeneity was evaluated using the $I^2$ statistic, which provides a percentage of the variation attributable to the degree of differences between studies caused by factors other than sampling error. We used the following categories to interpret the levels of heterogeneity: low between 15%-50%, moderate between 50-75% and high for 75% or over (Higgins et al., 2003). Sub-group analyses were conducted to explore the potential sources of heterogeneity between studies: studies including individuals with a GI infection vs non-GI samples, anxiety/depression assessment, IBS assessment and follow-up period.

Since the studies used different cut-offs to determine anxiety and depression caseness at baseline, we also conducted meta-analyses of continuous measures of anxiety/depression if enough data were reported or provided by the authors. Additional studies providing only continuous data were also included in this analysis. The metan command was used to calculate standardised mean differences by the method of Cohen. Random effect models using the DerSimonian and Laird method were selected. Publication bias was assessed using funnel plots and the Egger test (Sterne & Harbord, 2004).

RESULTS
Search strategy and study selection
Eleven papers were included in this systematic review (see Figure 1 for the flow diagram of systematic literature searches).

INSERT Figure 1 approximately here

Overview of studies
Eight of the 11 studies recruited participants with a GI infection at baseline. From these 8 studies, two recruited hospitalised patients. The remaining three were population-based studies (see Table 1 for details of the included studies and Appendix 4 for details of the baseline characteristics of the each study).
Assessment of anxiety and depression

Nine studies used the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) at baseline to measure the levels of anxiety and depression (see details in Table 1). Nielsen et al. (2014) used an adapted version of the HADS scale, which consisted of 6 depression related items and 6 anxiety related items. Each item score ranged between 0 and 3 and the overall score for each sub-scale ranged from 0 to 18. Table 1 shows the cut-off scores adopted in each study for cases of anxiety and depression. Koloski et al. (2012) used 14 items from the Delusion Symptom States Inventory (DSSI) (Class I, Dysthymic disorders) to measure anxiety and depression (Bedford & Foulds, 1977). Talley et al. (2001) was the only study to use a defined mental health diagnosis using a modified version of the Diagnostic Interview Schedule (Robin et al. 1981).

Assessment of methodological quality

All the studies were of moderate quality except for Gwee et al. (1999) which had good quality (see Table 1 and Appendix 5 for the detailed scores). The quality assessment found that some studies presented common limitations: they did not report enough information to determine the external validity of the study; they did not apply a rigorous assessment to exclude participants with IBS at baseline; they failed to conduct a power calculation; nor did they control adequately for potential confounders.

There was complete agreement between the two raters when scoring the items of the scale across studies except for minor discrepancies on two items: 7 (item 9 from the original scale) and 17 (adapted item for this review). Cohen’s Kappa was 0.800 (standard error=0.186, p=0.01) for item 7 and 0.831 (standard error=0.156, p=0.000) for item 17, which indicated substantial agreement. The intraclass correlation coefficient of the adapted scale was 0.998 (95% CI 0.991-0.999, p=0.000), which showed high reliability. After discussion, full agreement was reached between the two raters and minor wording amendments were implemented to item 17.
Quantitative synthesis findings

Anxiety - categorical

Seven studies were included in this meta-analysis with a total sample of 4810 subjects. Three hundred and twenty five of these developed IBS at the end point and 4485 did not develop IBS (see Appendix 6 for details of the data extracted from each study). The length of the follow-ups ranged from 3 months to 8 years with a median of 6 months. Five studies recruited participants with a GI infection (Gwee et al. 1996; Borgaonkar et al. 2006; Nielsen et al. 2014; Moss-Morris & Spence 2006; Wouters et al. 2015) and 2 were population based studies (Talley et al. 2001; Nicholl et al. 2008) (see Table 1 for characteristics of the included studies).

The overall risk of developing IBS at follow-up was more than double for those subjects who met the criteria of anxiety caseness at baseline compared to those who did not (RR 2.38, 95% CI 1.58-3.60). The I² showed moderate heterogeneity between studies (70.9%) (p=0.002) (see Figure 2 for the forest plot).

Figure 2 shows that participants who met the criteria for anxiety caseness at baseline in the Wouters et al. (2015) study had five times the risk of developing IBS at the end point (RR 5.04 95% CI 3.01-8.45). Interestingly, this is the only study that recruited participants during or soon after an epidemic outbreak of infectious gastroenteritis. The inhabitants were informed about being exposed to the contaminated water by the local authorities, which may have increased the anxiety levels of this specific sample during the recruitment phase.

Furthermore, the Gwee et al. (1996) study showed the second highest risk of developing IBS (RR 3.69, 95% CI 1.97-6.90). Participants were recruited whilst hospitalised due to a GI infection and this may be the reason for the higher risk compared to most studies.

In contrast to the overall effect, two studies found that anxiety decreased the risk of IBS although these results were not statistically significant. Talley et al. (2001) showed a 26% reduced risk of developing IBS for the baseline anxiety cases (RR 0.74, 95% CI 0.31-1.76). This is the only study that used an adapted clinical structured interview schedule to assess
anxiety disorders and very long-term follow-up of 8 years. However, this study did not report if they excluded individuals with IBS at baseline. Borgaonkar et al. (2006) showed a 10% decreased risk of IBS onset for those participants with anxiety caseness at baseline (RR 0.90, 95% CI 0.18-4.48). In terms of the methodology, the mean time between the GI infection and the baseline measurements of anxiety was 46+-26 days. This suggests that for some participants anxiety was measured post-infection rather than at baseline.

**Sensitivity analysis**

We conducted the same meta-analysis for Anxiety - categorical excluding Talley et al. (2001) (ROME criteria, episodic anxiety) as the methodology and follow-up period were distinctly different from the other studies. The effect of anxiety was slightly stronger (RR 2.80, 95% CI 1.99-3.94). According to the I², the heterogeneity between studies dropped from 70.9% to 56% (moderate heterogeneity) (p=0.045).

We also conducted the same meta-analysis excluding Borgaonkar et al. (2006) as some of their participants completed the baseline measures post-infection. The relative risk of anxiety was slightly stronger (RR 2.51, 95% CI 1.66-3.82) and the heterogeneity remained practically stable (73.3%, p=0.002).

In summary, our meta-analysis showed that the overall risk of developing IBS at follow-up was double for those subjects who met the criteria for anxiety caseness at baseline compared to those who did not. The different sensitivity analyses showed similar findings.

**Depression - categorical**

Eight studies were included in this meta-analysis with a total sample of 5007 subjects. From these, 342 developed IBS at the end point and 4665 did not develop IBS. See Appendix 7 for details of the data extracted. The length of the follow-up ranged from 3 months to 8 years, with a median of 6 months. Six studies recruited participants with a GI infection (Gwee et al. 1996; Borgaonkar et al. 2006; Parry et al. 2005; Nielsen et al. 2014; Moss-Morris & Spence, 2006; Wouters et al. 2015) and 2 were population based studies (Nicholl et al. 2008; Talley et al. 2001) (see Table 1 for characteristics of the included studies).

The overall risk of developing IBS at follow-up was double for those subjects who met the criteria for depression caseness at baseline compared to those who did not (RR 2.06, 95% CI
The $I^2$ showed low heterogeneity between studies (48.40%) (p=0.06) (see Figure 3 for the forest plot).

INSERT Figure 3 here

As shown in Figure 3, the baseline depression cases in Parry et al. (2005) presented almost six times the risk of developing IBS (RR 5.57, 95% CI 2.79-11.16). This very high risk is probably due to the fact that 2 out of 2 participants with depression caseness at baseline developed IBS at the endpoint compared to 14 out of 96 in the non-depression group.

On the other hand, in Borgaonkar et al. (2006), the participants who met the criteria for depression caseness at baseline had their risk of developing IBS reduced by 45% (RR 0.55, 95% CI 0.03-9.26) although this was not statistically significant. The wide CI are probably explained by the fact that 0 out of the 16 depression cases at baseline developed IBS. As described above, the measurements of baseline depression were collected post-infection for some participants.

Sensitivity analysis
We conducted the same meta-analysis for Depression - categorical excluding Talley et al. (2001) (ROME criteria, episodic depression). The effect of depression was slightly stronger (RR 2.23, 95% CI 1.53-3.26). However, the heterogeneity remained practically stable from 48.4% to 46.1% (p=0.085). The aforementioned drop in $I^2$ for anxiety was due to the non-overlap of the CI for the Talley study with the pooled effect. However, the CI does overlap for depression and this is why the $I^2$ percentage does not change.

We conducted the same meta-analysis excluding Parry et al. (2005). The pooled RR still shows that depression is a predictor of IBS onset (RR 1.82, 95% CI 1.41-2.35). More importantly, the $I^2$ drops from 48.4% to 0% (p = 0.739).

We also conducted the same meta-analysis excluding Borgaonkar et al. (2006) as some of their participants completed the baseline measures post-infection. The relative risk of depression remained practically stable (RR 2.11, 95% CI 1.46-3.04) as well as the heterogeneity (52.2%, p=0.051).
In summary, our meta-analysis showed that the overall risk of developing IBS at follow-up was double for those subjects who met the criteria for depression caseness at baseline compared to those who did not. The different sensitivity analyses showed similar findings.

Anxiety - continuous
Five studies provided continuous data for anxiety. The Koloski et al. (2012) study was the only one not included in the previous meta-analyses where anxiety and depression were treated as categorical variables (see Appendix 8 for details of the data extracted and the forest plot). The results showed that there was a moderate effect of baseline anxiety as a predictor of IBS onset at follow-up. The pooled standardised mean difference was 0.62, 95% CI 0.39-0.84. The $I^2$ (51.00%) showed moderate heterogeneity between studies (p= 0.09).

Depression - continuous
Four studies provided continuous data for depression (see Appendix 9 for details of the data extracted and the forest plot). The results showed that there was a small effect of baseline depression as a predictor of IBS onset at follow-up. The pooled standardised mean difference was 0.32, 95% CI 0.16- 0.47. The $I^2$ (7.6%) showed low heterogeneity between studies (p=0.36).

Sub-group analyses
*GI infection vs no-GI infection*
For both anxiety and depression, the risk of developing IBS was higher in those studies that recruited individuals with a GI infection at baseline compared to population based studies (see Table 2 for detailed results). These results may be affected by the methodological differences of one of the no-GI infection studies (Talley et al. 2001), such as the use of a clinical structured interview to diagnose anxiety/depression and a longer follow-up length.

INSERT Table 2 approximately here

*Type of anxiety/depression assessment*
For both anxiety and depression, the risk of developing IBS was estimated to be higher when pooling studies that used the HADS compared to the one study that used a clinical diagnostic interview schedule (see Table 2 for detailed results). While this difference is not statistically reliable, it does suggest an interesting avenue for future research.

Type of IBS diagnostic criteria and follow-up length
Our sub-group analysis did not show clear patterns in terms of the IBS diagnostic criteria (ROME vs non-ROME) and length of the follow-ups (see Appendices 10 and 11 for forest plots).

Publication bias
Based on the funnel plots and the non-significant Egger test results for both anxiety (p=0.278) and depression (p=0.339), we concluded that there was no small-study effects (see Appendices 12 and 13 for detailed results).

DISCUSSION
The main purpose of this systematic review was to ascertain whether prior anxiety or depression raise the risk of developing IBS.

Summary of results
Our meta-analyses showed that the overall risk of developing IBS at follow-up was double for those subjects who met the criteria for anxiety caseness at baseline compared to those who did not, with similar results for those subjects who were depression cases at baseline.
When treated as continuous variables, the results showed that there was a moderate effect of baseline anxiety and a small effect of baseline depression as predictors of IBS onset at follow-up. However, these two analyses included 5 and 4 studies respectively and the results are only exploratory.
The sub-group analyses for anxiety and depression treated as categorical variables showed two findings: 1) for both anxiety and depression, the risk of developing IBS was higher in those studies that recruited individuals with a GI infection at baseline and 2) for both anxiety
and depression, the risk of developing IBS was higher in those studies that used the HADS compared to the one study that used a clinical diagnostic interview; however, this comparison between one study and the rest is not statistically reliable and needs to be confirmed in further studies using a psychiatric diagnosis.

**PI-IBS vs non PI-IBS cohorts**

Our sub-group analyses suggested that both anxiety and depression played a stronger role in the onset of IBS in individuals with a GI infection at baseline compared to population based studies. This could be attributed to other differences in methodology such as use of diagnostic interviews rather than self-report measures of depression and anxiety. However, it is possible that psychological factors have either a direct or indirect effect on the pathophysiology of PI-IBS. Wouters et al. (2015) proposed that anxiety may raise the risk of PI-IBS by directly increasing the susceptibility to develop a GI infection. Future research should move beyond animal models and explore the neurobiological mechanisms of the potential effects of depressive and anxious mood in the development of PI-IBS. It could also be argued that the severity of the infection may cause or aggravate distress during the gastroenteritis. Nevertheless, these results are relevant as they suggest that those individuals who present with anxious or depressive mood during a GI infection are at increased risk of developing PI-IBS at a future time point. Therefore, the identification of these risk factors during the acute phase may be important to decrease the chances of developing IBS in a specific group of patients. Though most of the included studies had GI samples, this does not rule out that psychological distress plays a role in IBS more generally. Our meta-analyses showed that baseline anxiety and depression were risk factors of IBS onset at a future time point in two out of three population based studies (Nicholl et al. 2008; Koloski et al. 2012) (See Figures 2 and 3 and Appendices 8 and 9 for detailed results). The only study that found conflicting results for anxiety presented substantial methodological differences: they used a psychiatric diagnosis of anxiety/depression and did not specify whether participants with IBS were excluded at baseline (Talley et al. 2001). Thus, future cohort studies should assess anxiety and depression through psychiatric diagnostic criteria as well
Implement strict exclusion/inclusion criteria in order to confirm the role of anxiety/depression as risk factors in IBS (not PI-IBS).

**Psychological distress vs psychiatric diagnosis**

Nine out of the eleven studies included in this review used the HADS to measure anxiety and depression levels (see Table 1 for details). Norton et al. (2013) found that, even though the HADS addresses the concepts of autonomic arousal (anxiety) and anhedonia (depression), it has a general psychological distress factor which represents a shared variance between symptoms of depression and anxiety. This suggests that the HADS should be best used as a total score measuring general psychological distress rather than two separate precise measures of anxiety and depression.

In relation to our meta-analyses data, this suggests that generalised psychological distress is a predictor of IBS onset rather than specific diagnoses of anxiety and depression. Indeed, the mean and SD of the HAD anxiety and depression sub-scales of the included studies were within normal or borderline abnormal ranges (see Appendix 14 for figures).

These findings highlight the potential importance of psychological distress, rather than psychopathology per se, in the development of IBS. Recent studies have attempted to explain the possible pathophysiological mechanisms linking distress to IBS through dysregulation of the brain-gut axis (Mayer & Tillisch, 2011). The autonomic nervous system response to stress or distress includes the release of corticotrophin releasing factor (CRF) via the hypothalamic-pituitary-adrenal-axis, which can 1) stimulate colonic motility via CRF1 receptors 2) increase the activation of mast cells in the colonic mucosa, which in turn can enhance both abdominal pain and mucosal permeability and 3) promote low-grade inflammation/immune activation via cytokine stimulation, particularly during a GI infection (Stasi et al. 2012; Spiller & Lam, 2012). Thus, psychosocial distress can directly or indirectly affect motility, abdominal pain, secretion and immune function of the bowels as well as the perception of visceral stimuli.

Future research should focus on the neurobiological mechanisms underlying IBS onset and the potential role that abnormalities in central pain processing and cognitive functioning play in IBS onset as these are mediated by anxiety and depression (Kennedy et al. 2012).
Anxiety and depression alongside other risk factors

Although our meta-analyses findings suggest that anxiety and depression are significant risk factors of IBS (i.e. two-fold increased risk), many of the included studies found that anxiety and depression were only two of a range of risk factors increasing the chances of developing IBS. Several of these studies explored the roles of other psychological factors including life events, perceived stress, negative illness beliefs, somatisation (tendency to report general somatic symptoms), hypochondriasis, illness behaviours (characterised mainly by avoidance behaviours, health seeking behaviours and all-or-nothing behaviours) in the onset of IBS (Gwee et al. 1999; Parry et al. 2005; Moss-Morris & Spence, 2006; Borgaonkar et al. 2006, Spence & Moss-Morris, 2007; Nicholl et al. 2008; Wouters et al. 2015). There was insufficient commonality across studies to incorporate these within a meta-analysis. However, it is worth noting that in multivariate analyses considering anxiety and depression alongside these factors as well as biological factors, distressed mood was only one of many risk factors for IBS. In some instances, the significant relationship between anxiety and depression and IBS onset disappeared (Gwee et al. 1999; Borgaonkar et al. 2006; Nicholl et al. 2008; Wouters et al. 2015).

One of the included studies found that exposure to two or more of the following factors identified 80.2% of all participants developing IBS: scoring in the highest third of the HAD Anxiety sub-scale and Estimated Sleep Problems Scale, and in the highest two-thirds of the Somatic Symptoms Checklist and Illness Behaviour Scale (Nicholl et al. 2008). Taken together, these findings argue against a simple somatisation hypothesis, and highlight that multiple factors in addition to baseline distress influence the development of IBS. These findings are in line with the biopsychosocial model, which suggests that genetics and environmental factors in early life may predispose to IBS and that cognitive, behavioural, emotional and biological/physiological factors (including GI infection) interact to precipitate and perpetuate symptoms and contribute to disability (Engel, 1980).

Implications for future studies

In order to understand in more depth the role of anxiety and depression in IBS onset, it is essential to conduct more prospective studies with individuals free of IBS at baseline with
large sample sizes ensuring a rigorous and standardised assessment of 1) IBS at baseline (to exclude participants with IBS) and at the endpoint 2) psychological distress and psychiatric diagnosis of anxiety/depression 3) a well-defined multifactorial set of biopsychosocial predictors, which are tied in with specific theories of IBS aetiology. Furthermore, several long-term follow-ups across the same sample would help to determine the incidence and prevalence of IBS within the same cohort at different time points, as well as help to distinguish between factors that predispose or precipitate the condition and those that perpetuate the symptoms. The clinical exclusion of organic diseases through adequate medical tests and assessments would also strengthen the methodological quality of research. Eight out of the 11 included studies were conducted with individuals with a GI infection and our findings may be more representative of PI-IBS and the IBS diarrhoea subtype. Ideally, future longitudinal studies would measure anxiety and depression before GI infection onset in order to explore their role as risk factors of PI-IBS rather than possible comorbidities that arise due to the presence of GI symptoms. However, studies such as these are extremely costly as they rely on broad population based samples. For those recruiting a GI infectious cohort, anxiety and depression should be assessed as closely as possible to the GI infection onset or during the acute phase. As some studies included in this review reported that the mean duration of acute symptoms ranged between 7.3 and 12.4 days from onset in the group that developed IBS, baseline assessments should ideally be conducted within this 1-3 week window. More population based studies are needed to confirm the role of anxiety and depression as predictors of IBS onset in non PI-IBS.

Implications for clinical practice
Promoting awareness about the potential role that anxiety and depression (or general distress) have on the development of IBS, in combination with biological factors and unhelpful illness cognitions and behaviours, may help to reduce the incidence of IBS onset in high risk individuals (e.g. severe symptoms during a gastroenteritis, chronic abdominal pain, recent adverse life events).
Although the results suggest that targeting distress in early interventions may be helpful, psychotherapies that are designed to target primary anxiety and depressive disorders may
not be the best treatments for IBS. Rather, treatments should focus on a range of factors which may perpetuate the syndrome including IBS related beliefs and coping behaviours, alongside negative mood. The language used by clinicians and health professionals to promote preventative psychological interventions would benefit from incorporating the notion that although distress (feeling anxious and/or depressed) increases the risk of developing IBS, this does not suggest patients have a mental health disorder rather than IBS. Distress, rather than psychopathology itself, seems to play a role in IBS onset and is one of a group of biopsychosocial risk factors which will be more or less significant in different individuals. Providing clear information to patients about the pathophysiological link between stress, anxiety, depression and the function of the bowel could improve the acceptance of behaviourally based treatments to prevent IBS, both amongst health professionals and patients.

Finally, better knowledge of the role of distress in IBS onset may have a positive impact on the way clinicians explain the illness to patients when they are diagnosed, improving their understanding and acceptance of the condition, especially in those patients who perceive IBS as the sole result of psychological factors.

**Strengths and limitations**

Several measures were taken to improve the reliability of the systematic processes of this meta-analytic review. Firstly, two authors conducted the electronic searches and assessed the abstracts and full text articles independently against the inclusion criteria. Secondly, data extraction was conducted independently by two authors. Finally, the quality of the studies was assessed by two authors and an inter-rater reliability score was calculated.

We evaluated the methodological quality of the included studies using an adapted version of a reliable tool for observational studies. Tailoring the quality assessment tool is advised in the Cochrane handbook (Higgins & Green, 2011) to best address the research aims of each systematic review. However, we cannot claim that the adapted tool is valid even if the inter-rater score showed high reliability. Furthermore, we cannot assume that each sub-scale contributes a similar weight to the overall quality of the studies.
Conclusions

To our knowledge, this is the first systematic review with meta-analysis that explored the role of anxiety and depression in the development of IBS using longitudinal studies with good quality designs. The findings suggest that anxious and depressed mood provide a twofold risk for the onset of IBS. There is less support for the role of a definitive diagnosis of an anxiety or depressive disorder. Although anxiety and depression were found to be risk factors of IBS onset, the findings suggest that they are not univariate causes of IBS. These findings may have implications for the development of interventions focused on IBS prevention and treatment. The role of negative affect should be considered alongside other psychological, behavioural and biological factors.
Legends for figures

**Figure 1.** Flow diagram of systematic literature searches

**Figure 2.** Forest plot: Anxiety – categorical

**Figure 3.** Forest plot: Depression – categorical
Acknowledgements

We are particularly grateful to Dr. Sam Norton for his valuable statistical advice.

TC receives salary support from the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed in this article are those of the authors and not necessarily those of the NIHR or the NHS.
References


meta-analysis. European Archives of Psychiatry and Clinical Neuroscience 264, 651-660.


<table>
<thead>
<tr>
<th>Study</th>
<th>Settings</th>
<th>GI Infection</th>
<th>N at baseline</th>
<th>Dx IBS at baseline</th>
<th>Time point of A/D collection</th>
<th>A/D category or cont</th>
<th>Dx IBS at follow-ups</th>
<th>N at follow-ups</th>
<th>N IBS+ at follow-ups</th>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gwee et al. 1996</td>
<td>Department of infectious diseases with acute GI infection, UK. Hospitalised patients</td>
<td>Different pathogens. Participants with negative stool tests included</td>
<td>86</td>
<td>ROME I. Exclusion of reported organic disease</td>
<td>During infection - 1 to 10 days after hospital admission</td>
<td>HADS – continuous and categorical (scores of 11 or more)</td>
<td>ROME I</td>
<td>75 out of 86</td>
<td>(87.21%) at 3 mths</td>
<td>Score=24/29 Category=moderate</td>
</tr>
<tr>
<td>Gwee et al. 1999</td>
<td>Department of infectious diseases with acute GI infection, UK. Hospitalised patients</td>
<td>Different pathogens. Participants with negative stool tests included</td>
<td>109</td>
<td>ROME I. Exclusion of reported organic disease</td>
<td>During infection - 1 to 10 days after hospital admission</td>
<td>HADS - continuous</td>
<td>ROME I</td>
<td>94 out of 109</td>
<td>(86.24%) at 3 mths</td>
<td>Score=26/29 Category=good</td>
</tr>
<tr>
<td>Moss-Morris &amp; Spence, 2006</td>
<td>Provider of community clinical diagnostic services for Auckland, New Zealand. Primary care</td>
<td>Campylobacter</td>
<td>835</td>
<td>Self-reported history of IBS. Exclusion of reported organic disease</td>
<td>During infection or acute phase</td>
<td>HADS - categorical (scores of 8 or more)</td>
<td>ROME I updated &amp; ROME II</td>
<td>775 out of 835</td>
<td>(92.81%) at 3 mths</td>
<td>Score=21/29 Category=moderate</td>
</tr>
<tr>
<td>Spence &amp; Moss-Morris, 2007</td>
<td>Provider of community clinical diagnostic services for Auckland, New Zealand. Primary care</td>
<td>Campylobacter</td>
<td>620</td>
<td>Self-reported history of IBS. Exclusion of reported organic disease</td>
<td>During infection or acute phase</td>
<td>HADS - continuous</td>
<td>ROME I updated &amp; ROME II</td>
<td>581 out of 620</td>
<td>(93.71%) at 3 mths</td>
<td>Score=22/29 Category=moderate</td>
</tr>
<tr>
<td>Borgaonkar et al. 2006</td>
<td>Positive stool culture from 3 health regions in Ontario, Canada</td>
<td>Different pathogens</td>
<td>191</td>
<td>Manning and ROME I. Exclusion of reported organic disease</td>
<td>Mean of 46+26 days from the GI infection</td>
<td>HADS - continuous</td>
<td>Manning or ROME I</td>
<td>99 out of 191</td>
<td>(51.83%) at 3 mths</td>
<td>Score=20/29 Category=moderate</td>
</tr>
</tbody>
</table>

**Table 1:** characteristics of individual studies
<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Culture sample</th>
<th>Pathogens</th>
<th>ROME/ROM III</th>
<th>Exclusion</th>
<th>Participants</th>
<th>Scoring Criteria</th>
<th>Positive Culture</th>
<th>Reported History</th>
<th>IBS Cases Identified</th>
<th>Follow-Up</th>
<th>Score</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parry et al. 2005</td>
<td>Northeast England. Positive bacterial stool culture from the microbiology laboratories of Northumbria Healthcare Trust</td>
<td>Different pathogens</td>
<td>122</td>
<td>ROME II</td>
<td>Exclusion of reported organic disease</td>
<td>Participants invited within 2 weeks from the stool sample</td>
<td>HADS - categorical (scores of 11 or more)</td>
<td>107 out of 122 (87.70%) at 6 mths</td>
<td>16 out of the 107 (14.95%) at 6 mths</td>
<td>Score=23/29</td>
<td>Category=moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nielsen et al. 2014</td>
<td>Culture positive samples from North Denmark region</td>
<td>Campylobacter</td>
<td>469</td>
<td>Reported history of IBS. Exclusion of reported organic disease</td>
<td>Participants invited as soon after stool sample was confirmed</td>
<td>Adapted version HADS with 12 items - Categorical (scores of 10 or more)</td>
<td>IBS cases were identified as those reporting abdominal pain and loose stools, in addition to at least one of the following within the last week: painful bowel movements, day-to-day variation in stool consistency, mucous in stools, sudden bowel movements, urge for new defecation shortly after defecation, flatulence and the need to loosen clothes after meals</td>
<td>300 out of 469 (63.97%) at 6 mths</td>
<td>56 out of 268 (20.90%) at 6 mths</td>
<td>Score=14/29</td>
<td>Category=moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wouters et al. 2015</td>
<td>Community-wide outbreak of gastroenteritis</td>
<td>Different pathogens. Participants with negative stool</td>
<td>968</td>
<td>ROME III</td>
<td>Exclusion of reported organic</td>
<td>During infection or acute phase</td>
<td>HADS Categorical (scores of 11 or more)</td>
<td>567 out of 968 (58.57%) at 1 year follow-up</td>
<td>58 out of 567 (10.23%) at 1 year follow-up</td>
<td>Score=21/29</td>
<td>Category=moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Follow-Up Period</td>
<td>Age of Participants</td>
<td>Methodology</td>
<td>Disease Definition</td>
<td>Rome II and Manning</td>
<td>Rome II</td>
<td>Manning criteria</td>
<td>Score</td>
<td>Category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>------------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>----------------</td>
<td>-------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talley et al. 2001</td>
<td>Longitudinal investigation of a complete cohort between April 1, 1972, and March-April, 2001 (Dunedin, New Zealand)</td>
<td>3 years</td>
<td>21 yrs old</td>
<td>Baseline</td>
<td>Modified version of the Diagnostic Interview Schedule</td>
<td>Rome II and the Manning criteria</td>
<td>992 (99.90%)</td>
<td>980 (98.69%)</td>
<td>20/27</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicholl et al. 2008.</td>
<td>Population-based study. Registers of 3 GPs (North West England)</td>
<td>8 years</td>
<td>15 mths</td>
<td>Baseline</td>
<td>HADS – categorical (3 categories)</td>
<td>Modified version of the Rome II criteria</td>
<td>2456 out of 5250 (46.78%)</td>
<td>86 of 2456 (3.50%)</td>
<td>19/27</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koloski et al. 2012</td>
<td>Population based study, electoral roll (Penrith, Australian)</td>
<td>8 years</td>
<td>12 yrs</td>
<td>Baseline</td>
<td>Delusion Symptom States Inventory (DSSI) – continuous</td>
<td>Rome II criteria</td>
<td>1002 out of 1775 (56.45% of the whole sample)</td>
<td>82 cases of IBS among the 626 free of FGID at baseline (13.10%)</td>
<td>19/27</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. The incidence percentages for this review were calculated taking into account the number of participants who developed IBS at the endpoint out of the total number of participants who completed the follow-up questionnaire.
2. This group includes those who met the Manning criteria as well.
3. They converted the HADS scores into three categories based on the distribution of the participants’ score.
Table 2: results of sub-group analyses for both anxiety and depression

<table>
<thead>
<tr>
<th>Sub-group analysis</th>
<th>RR (95% CI)</th>
<th>( I^2 )%, p value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI infection studies (Gwee et al. 1996; Borgaonkar et al. 2006; Moss-Morris &amp; Spence, 2006; Nielsen et al. 2014; Wouters et al. 2015)</td>
<td>2.74 (95% CI 1.73-4.34)</td>
<td>66.0%, p=0.019</td>
<td>The two no-GI infection studies had substantial differences in their methodology: 1) Diagnostic criteria - modified clinical structured interview schedule vs HADS 2) Follow-up length - presence of anxiety at 18 or 21 years old as the predictor of IBS at 26 years old (episodic anxiety) vs assessment of anxiety at baseline as the predictor of IBS at 15 months 3) Follow-up response rate - 98.69% vs 46.78%</td>
</tr>
<tr>
<td>No-GI infection studies (Talley et al. 2001; Nicholl et al. 2008)</td>
<td>1.54 (95% CI 0.40-5.88)</td>
<td>87.1%, p=0.005</td>
<td></td>
</tr>
<tr>
<td>HADS (Gwee et al. 1996; Moss-Morris &amp; Spence, 2006; Nicholl et al. 2008; Wouters et al. 2015)</td>
<td>2.90 (95% CI 1.89-4.46)</td>
<td>63.1%, p=0.028</td>
<td>Different cut-offs on HADS to classify anxiety caseness may have contributed to the between-study heterogeneity</td>
</tr>
<tr>
<td>HADS adapted (Nielsen et al. 2014)</td>
<td>2.35 (95% CI 1.49-3.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical interview (Talley et al. 2001)</td>
<td>0.74 (95% CI 0.31-1.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI infection studies (Gwee et al. 1996; Parry et al. 2005; Borgaonkar et al. 2006; Moss-Morris &amp; Spence, 2006;</td>
<td>2.25 (95% CI 1.32-3.83)</td>
<td>58.6%, p=0.034</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>Odds Ratio (95% CI)</td>
<td>Prevalence (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>No-GI infection studies</td>
<td>1.75 (95% CI 1.05-2.90)</td>
<td>35.7%</td>
<td>0.212</td>
</tr>
<tr>
<td>HADS (Gwee et al. 1996; Parry et al. 2005; Nicholl et al. 2008; Moss-Morris &amp; Spence, 2006; Wouters et al. 2015)</td>
<td>2.23 (95% CI 1.38-3.61)</td>
<td>55.5%</td>
<td>0.047</td>
</tr>
<tr>
<td>HADS adapted (Nielsen et al. 2014)</td>
<td>2.18 (95% CI 1.22-3.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical interview (Talley et al. 2001)</td>
<td>1.22 (95% CI 0.58-2.57)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>