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Depressive symptoms in inflammatory bowel disease: an extraintestinal manifestation of inflammation?

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Summary

Depressive symptoms are reported by more than 20% of people with inflammatory bowel disease (IBD), while sleep difficulties and fatigue are even more common. Co-morbid depressive symptoms predict a poor IBD course, including increased risk of relapse and surgery, which is inconsistently improved by psychological treatments. Rather than being distinct systems, there is compelling evidence for bidirectional communication between gut and brain, driven by neural, metabolic, endocrine and inflammatory mediators. An emerging concept is that depressive symptoms may be mechanistically linked to excess inflammation and dysregulation of the gut–brain axis. Given the close link between the intestinal microbiota and host immune responses, patients prone to shifts in their intestinal microbiome, including smokers, those with poor diet and early life stress, may be exposed to exaggerated immune responses. Excess inflammation is associated with brain changes (depressive symptoms, fatigue, sleep difficulties) and worsening gastrointestinal symptoms, which are exacerbated by psychological distress. Equally, treatments both for depressive symptoms and IBD provide opportunities to break this cycle by reducing the causes and effects of inflammation. As well as addressing potential risk factors such as smoking and diet, treatments to alter the microbiome may reduce depressive symptoms. Observational evidence suggests that anti-inflammatory treatments for IBD may improve co-morbid depressive symptoms correlating with reduction in inflammation. With a growing range of treatments targeting inflammation centrally, peripherally and in the gut, IBD provides a unique model to understand the interplay between brain and gut in the pathogenesis of depressive symptoms, both in IBD and in the whole population.

Keywords: depressive symptoms, gut-brain-axis, inflammation, inflammatory bowel disease, microbiome

Introduction

Crohn's disease (CD) and ulcerative colitis (UC), together comprising inflammatory bowel disease (IBD), are long-term conditions characterized by a relapsing and remitting disease course. CD is associated with secondary progression with time, requiring surgical intervention in a significant proportion [1], but the factors influencing disease evolution are diverse and difficult to predict [2,3]. The disease course in UC is heterogeneous, including chronic–active or relapsing and remitting phenotype, but also a progressive disease course, necessitating urgent or emergency surgery [3,4].

Depressive symptoms include low mood, reduced enjoyment, increased fatigue, hopelessness and sleep difficulties [5]. Like IBD, depressive symptoms typically run a persistent or fluctuating course, and a significant proportion do not respond to standard therapy [6]. Notably, depressive symptoms occur in more than 20% of people with IBD, which is approximately two to four times more common than in the general population [7,8]. As well

as reduced quality of life, the co-morbidity of depressive symptoms and IBD is associated with poor biomedical outcomes, including increased risk of IBD relapse, hospitalization and surgery [9].

A psychological model would position depressive symptoms as a secondary reaction to the burden of IBD, including difficulties with coping, disability, pain, socially unacceptable symptoms and fear of complications [10–12]. In turn, the poor prognosis of depressive symptoms could occur through negative effects on self-care and treatment adherence [13,14]. However, this model alone provides limited opportunities to improve outcomes. For example, there is an inconsistent correlation between the severity of IBD and the prevalence of depressive symptoms [15,16], and depressive symptoms correlate variably with treatment adherence [17]. While conventional treatments for depressive symptoms (such as cognitive behavioural therapy) frequently improve depressive symptoms in people with IBD, this does not consistently improve biomedical outcomes [18]. There is therefore a need to identify novel targets to reduce the risk of depressive symptoms and their impact in people with IBD.

Despite its beneficial short-term effects in combating infection and enabling tissue repair [19], there is compelling evidence that chronically elevated inflammation has deleterious effects on multiple systems in the body, including the brain and the gut [20,21]. The role of inflammation in the pathogenesis of IBD is well established, in that cytokines drive intestinal inflammation and may also regulate extra-intestinal disease manifestations and systemic effects [21].

In this clinically focused review, we will argue that depressive symptoms are a further extra-intestinal manifestation of inflammation in people with IBD. After summarizing the epidemiology of the link between depressive symptoms and IBD, we will examine the evidence for inflammation as a cause of depressive symptoms or more commonly somatic symptoms such as fatigue. We will outline how dysregulation of the gut–brain axis may lead to an 'inflammatory depression', which fuels a vicious cycle of worsening IBD outcomes. Finally, we will argue that targeted anti-inflammatory treatments may improve co-morbid depressive symptoms in IBD, as well as providing a unique model for understanding the pathogenesis of depressive symptoms in the general population.

Epidemiology

The detection of depressive symptoms in IBD depends on the method of measurement. Clinical depression is a diagnosis made using a detailed diagnostic interview [22]. It requires the minimum of two of three 'core' symptoms of low mood, anhedonia (reduced enjoyment) and increased fatiguability, in addition to at least two other symptoms (see Table 1), for a minimum of 2 weeks' duration. Using this approach, the pooled prevalence of depression disorders in IBD is 15·2% [95% confidence interval (CI) = 9·9–20·5%] based on a meta-analysis of six estimates [8]. For the purpose of this review, the term 'depression' is therefore reserved for clinical depression only.

As diagnostic interview is time-intensive, most epidemiological studies of in IBD have instead measured depressive symptoms using self-report questionnaires, such as the Patient Health Questionnaire-9 (PHQ-9). With such questionnaires, a validated cut-off score (for example, ≥ 10 on the PHQ-9 [23]) is typically used to define cases of depressive symptoms. Unlike clinical depression, such an approach does not distinguish between 'core' depressive symptoms and other symptoms. Unsurprisingly, this approach leads to a higher pooled prevalence of depressive symptoms of 21·6% (CI = 18·8–24·3%) in people with IBD [8]. Notably, there appears to be a difference in depressive symptoms between CD and UC (25·3 *versus* 16·7%, respectively) and between active disease *versus* remission (40·7 *versus* 16·5%) [8]. Clinic-based samples are likely to have either or both more severe IBD and other co-morbidities.

Prospectively, there is recent evidence from large database research that a prior diagnosis of depression is associated with greater incidence of IBD over time [24]. However, no prospective studies have examined the incidence of depressive symptoms and IBD in the same population. Separately, early life stress [25,26] poor diet [27,28] and smoking [28,29] have been found to confer vulnerability to both conditions. Smoking is further known to worsen outcomes in CD but not in UC [30] and smoking appears to be disproportionately common in female CD patients [31]. This suggests that lifestyle factors may have a more important role in the depressive symptoms of CD than in UC.

The relationship between depressive symptoms and adverse outcomes in IBD has been inconsistently demonstrated. A meta-analysis of five small prospective studies found little association [32], while a subsequent 2-year prospective study found no association between depressive symptoms and worsening IBD activity [33]. However, the latter study used the Hospital Anxiety and Depression Scale, which does not capture any somatic symptoms such as fatigue and sleep disturbance. As discussed later, these symptoms may be most associated with inflammation.

By contrast, larger studies have nearly all reported strong associations between depression and a worse IBD course. In database studies, a pre-existing diagnosis of clinical depression is associated with adverse outcomes in IBD [34–36]. A recent high-quality prospective cohort study

Table 1. Diagnosis and treatment of clinical depression in people with chronic diseases

Diagnosis according to the International Classification of Diseases 10th edition (ICD-10)	Stepped care treatment model according to NICE guidelines [5]
Criteria	*Mild or subthreshold depression*
For at least 2 weeks (or less if symptoms are severe and of rapid onset), the following 2 core symptoms present	Group physical activity programme, group-based peer support or to low-intensity psychological interventions (e.g. group CBT or computerized CBT)
Low mood	Antidepressants if symptoms are persistent or unresponsive to above
Anhedonia (loss of interest and enjoyment)	
Low energy	
Plus at least 2 associated symptoms	*Moderate depression*
Reduced concentration and attention	Antidepressant medication (SSRI usual first-line) for minimum of 6 months; alternatives include mirtazapine, SNRI, tricyclics (caution because of toxicity in overdose)
Reduced self-esteem and self-confidence	High-intensity psychological therapy (e.g. individual CBT)
Ideas of guilt and unworthiness (even in a mild type of episode)	Combination of antidepressants and psychological therapy (most evidence-based)
Bleak and pessimistic views of the future	
Ideas or acts of self-harm or suicide	
Disturbed sleep	
Diminished appetite	
Severity	*Severe depression*
Mild depression defined with minimum 2 core symptoms and total of 4 symptoms (core or other)	As per moderate depression, but referral to specialist mental services recommended if risk of self-harm, suicide or severe self-neglect
Moderate depression defined with minimum 2 core symptoms and total of 6 symptoms	Specialist treatments may include augmentation with lithium, anti-psychotic medication or ECT
Severe depression defined with all 3 core symptoms and total of 8 symptoms. Psychotic symptoms (e.g. delusions, hallucinations) may or may not be present	

CBT = cognitive behavioural therapy; ECT = electroconvulsive therapy; ICD = International Classification of Diseases; NICE = National Institute for Health and Care Excellence; SNRI = serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

of 4314 patients with IBD over 2 years found significant associations between depressive symptoms and increased risk of multiple adverse outcomes, including relapse, hospitalization, requirement for biologicals and surgery [9]. Further, another prospective study of 2007 patients found that depressive symptoms expedited clinical recurrence [37]. Table 2 summarizes the associations between depressive symptoms and adverse outcomes in the largest prospective studies to date.

In sum, depressive symptoms are over-represented in people with IBD – especially in CD and in in-patients – although this is predominantly based on self-report measures. Moreover, the presence of depressive symptoms is associated with poor biomedical outcomes over time.

Inflammation as a link between depression and IBD

During the last two decades, a pathogenic role for inflammation has been advocated in mental illnesses, including depression, schizophrenia and bipolar disorders [20]. Meta-analyses have found that inflammatory cytokines, such as interleukin (IL)-6, and acute phase proteins, such as C-reactive protein (CRP), are associated with increased incidence of depressive symptoms over time [38]. Depressive symptoms are also associated with T cell activation, reflected in elevated concentrations of soluble IL-2 receptors (sIL-2Rs) and sCD8, as well as increased activation of effector T cell responses, including increased IL-2, interferon (IFN)-γ and IL-17 [39,40]. Therapeutically, anti-inflammatory treatments show promising effects on improving depressive symptoms in the general population [41]. Notably, people with early life stress are at increased risk of both increased inflammation and depression in later life [25].

As reviewed previously [40], there are many immune-inflammatory reactions implicated in both depressive symptoms and IBD, respectively, including increased concentrations of IL-1, sIL-2R, IL-6, IL-23 and CRP. However, the evidence specifically testing inflammation as a correlate

Table 2. Association between depression and biomedical outcomes in large longitudinal studies* of people with IBD

Outcome	Measure of depression	Crohn's disease	Ulcerative colitis
Readmission to hospital	Medical records coding of ICD depression diagnosis	OR = 1·89 (1·06–3·40) in children [35] and OR = 1·27 (1·07–1·50) in adults [34]	No increased odds in children [35] but OR = 1·35 (1·07–1·70) in adults [34]
	PHQ-8 score ≥ 5	RR = 1·3 (1·2–1·5) in adults [9]	RR = 1·3 (1·1–1·5) in adults [9]
Relapse**	PHQ-8 score ≥ 5	RR = 2·3 (1·9–2·8) in adults [9]	RR = 1·8 (0·9–1·7) in adults [9]
Recurrent disease***	HADS > 7	Reduced time to clinical recurrence in adults (P < 0·001) [37]	Reduced time to clinical recurrence in adults (P = 0·005) [37]
Requirement for biologicals	PHQ-8 score ≥ 5	RR = 1·8 (1·4–2·3) [9]	RR = 1·6 (1·1–2·3) [9]
Requirement for surgery	Medical records coding of ICD depression diagnosis	OR = 1·28 (1·03–1·57) in one cohort [36], RR = 1·3 (1·1–1·6) in another [9]	No increased risk of surgery in one cohort [36] but RR = 1·8 (1·2–2·6) in another [9]

*All longitudinal studies with ≥ 1000 patients were included and all results are adjusted for potential confounders.

**modified Harvey–Bradshaw Index ≥ 5 or Simple Clinical Colitis Activity Index > 2.

***any of: flare events or worsening of the disease (as established by physicians), fistulas and stenosis, anal fissure, abscess, IBD surgery, need for steroids or biologicals.

HAS = Hospital Anxiety and Depression Scale; ICD = International Classification of Diseases; OR = odds ratio (adjusted for confounders); PHQ = Patient Health Questionnaire; RR = relative risk (adjusted for confounders).

of depressive symptoms in patients with IBD is very limited. In a cross-sectional study of 11 IBD patients and nine controls, symptomatic IBD patients had the highest depressive and anxiety scores, as well as increased intestinal expression of IL-6 and IL-1β and serum IL-6 [42]. Prospective studies testing the directionality of inflammation and depressive symptoms in IBD are awaited.

Depressive symptoms or somatic symptoms?

In the general population, somatic symptoms associated with depression, such as fatigue and sleep disturbance, have been found to be more strongly associated with elevated inflammation than more cognitive symptoms, such as low mood and guilt [43–45]. Such somatic symptoms are experienced far more commonly in people with IBD than depressive symptoms overall: fatigue is reported by 44–86% of IBD individuals with active disease and 22–41% of individuals in remission [46], while 77 and 49% of those with active or inactive disease, respectively, experience poor sleep [47]. Importantly, self-report questionnaires can frequently identify patients as having depressive symptoms but whose clinical presentation is dominated by somatic symptoms, often in the absence of core symptoms of clinical depression [48]. Collectively, this suggests that for many patients being labelled as depressed, the 'depression' of IBD may, in fact, be characterized primarily by fatigue and sleep problems.

Within the IBD literature, a small number of cross-sectional studies have tested the association between inflammation and somatic symptoms. In a randomized controlled trial (RCT) of 98 patients with quiescent IBD and significant fatigue, solution-focused therapy (SFT) improved fatigue more than treatment as usual 3 months later, yet this effect was not sustained and SFT did not reduce CRP more than treatment as usual [49]. If fatigue is underpinned by elevated inflammation, these findings are unsurprising. In a cross-sectional study of 96 people with CD and 19 healthy controls, elevated inflammation, as measured using standard-sensitivity CRP and erythrocyte sedimentation rate (ESR), were strongly correlated with the first of two factors of the Pittsburgh Sleep Quality Index [50]. In a cross-sectional study of 131 patients with IBD, elevated CRP, also using a standard-sensitivity assay, was associated with 3·16 greater adjusted odds of poor sleep, although numbers were small [51]. In a recent cross-sectional study of 631 adults with IBD, the presence of significant fatigue was associated with marginally elevated CRP and ESR in UC patients but not CD [52]. However, these results are limited by nearly 40% missing data on inflammation and the standard-sensitivity CRP assay used.

Notably, the presence of fatigue and sleep is poorly explained by IBD disease severity alone. For example, in the Manitoba cohort of 312 patients, fatigue was greater in people with active IBD, yet fatigue was found to increase over time even for those in IBD remission [53]. Similarly,

in a secondary analysis of 1798 IBD patients in remission, poor sleep was associated with a twofold increase in risk of active disease over 6 months, although no association was seen in UC [54].

In summary, somatic symptoms are particularly common in people with IBD – occurring as part of a wider depressive illness or otherwise – and prospective research is needed to test inflammation as a potential cause of such symptoms.

The gut–brain axis

Rather than being distinct systems, there is compelling evidence of bidirectional communication between gut and brain, including neural, metabolic and endocrine mediators that interact critically with inflammation [55]. From brain to gut, stress causes colitis through sympathetic nervous system activation and mast cell activation in animal models of IBD, which is accentuated in those exposed to early life stress [56]. In humans, stress leads to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, with concomitant increase in HPA axis activity and peripheral inflammation [57]. This may be due to a reduced sensitivity of the immune system to the immunoregulatory action of cortisol, as well as possibly to direct proinflammatory signalling in the periphery by cortisol [57], particularly in females [58]. Immediate sympathetic activation occurs after integration of stress signals at the paraventricular nucleus of the hypothalamus, from where neurones project to innervate immune tissue in the gut [59]. Stress further exerts proinflammatory effects on the gut and periphery and leads to increased intestinal permeability [60,61].

From gut to brain, increased intestinal permeability is thought to lead to both increased inflammation and depressive symptoms. For example, increasing serum concentrations of lipopolysaccharide (LPS), a proxy marker of intestinal permeability [62], have been found to produce a dose-dependent increase in both anxiety and depressive symptoms, correlating with increasing serum cytokine concentrations [63]. Individuals with mood disorders have also been found to have a higher concentration of circulating antibodies to microbial products, including LPS [64], as well as elevated zonulin and fatty-acid binding protein-2, markers of mucosal barrier function [65]. This suggests that circulating microbial products in the context of a 'leaky gut' may contribute to increased peripheral inflammation and mood disorders.

This bidirectional axis leads to a vicious cycle of increasing inflammation, which can in turn communicate with the brain to lead to depressive symptoms. For example, inflammatory cytokines activate the HPA axis, fuelling a vicious cycle of increased oxidative stress in the brain [66]. Inflammatory cytokines activate the tryptophan–kynurenine pathway through activation of the enzyme indoleamine-2,3-dioxygenase (IDO), leading to reduced production of serotonin and increased production of tryptophan catabolites such as kynurenine, which have neurotoxic properties [67]. As with depressive symptoms, the serum kynurenine/tryptophan ratio is elevated in people with IBD and has been found to correlate with disease activity and with inflammatory markers [68,69]. The effects of inflammation on the brain appear to be more pronounced in females [70].

Aetiologically, perturbations in gut microbiota composition – so-called gut dysbiosis – are known to influence intestinal permeability [61], providing a potential shared aetiology for depressive symptoms and IBD. In IBD, gut dysbiosis has been extensively described [71,72] and disease remission can be achieved using faecal microbiota transplantation [73]. Lifestyle behaviours, such as poor diet and smoking, have adverse effects on gut microbiota [30,74]. Meanwhile, psychological stress alters the community structure of the gut microbiota in animal models [75], which may be mediated through inflammatory pathways [76]. Moreover, the composition of the microbiota directly influences host immune responses both qualitatively and quantitatively, and both within and outside the gut. For instance, in mice, intestinal colonization with segmental filamentous bacteria is required for T helper type 17 (Th17) responses [77], and immunomodulatory responses, such as IL-10 production driven by regulatory T cells, are induced by clusters of Clostridia and species such as *Bacteroides fragilis* [78,79].

In humans with depressive symptoms, gut dysbiosis has been found to correlate with severity of depressive symptoms in cross-sectional studies [80,81], and there is evidence from small RCTs that probiotic therapies to alter gut microbiota may reduce depressive symptoms over time, which correlates with reduction in inflammation [82].

Overall, there is evidence of a bidirectional axis between brain and gut, underpinned by stress and gut dysbiosis, and leading to a vicious cycle of elevated inflammation in the brain, periphery and gut. This provides various opportunities to break this cycle therapeutically, as discussed below.

Inflammation as a novel target for depressive symptoms in IBD

In IBD, rates of disease complications, including the need for surgery, appear to have declined in recent years, due in part to improved understanding of the biology and epidemiology of IBD, and earlier

recognition and diagnosis facilitating earlier intervention with more potent biological agents [3,4]. Among these, the anti-tumour necrosis factor (TNF) agents transformed the paradigm of care for appropriate patients after their introduction more than a decade ago [83,84]. Although anti-TNF agents can neutralize soluble TNF, in IBD their probable mechanism of action is through binding membrane-bound TNF [85] and inducing apoptosis in proinflammatory T lymphocytes, thereby decreasing levels of T cell-derived proinflammatory cytokines and reduction in active inflammatory cells in the intestinal tissue [85].

Anti-TNF agents demonstrated initial promise as a novel treatment for depressive symptoms in the general population. In a placebo-controlled trial of 60 patients, inhibition of TNF did not improve depressive symptoms after 12 weeks. However, in a subset (n = 21) with high baseline CRP, the remission rate was greater in the intervention group [86]. Conversely, in a network meta-analysis in people with rheumatoid arthritis, anti-TNF therapy showed weaker effects on depressive symptoms compared to other biologicals such as anti-IL-6 [87]. In a retrospective study of 69 patients with IBD, anti-TNF therapy was associated with significant reduction in PHQ-9 depression scores regardless of IBD disease response, and changes in PHQ-9 were strongly correlated with changes in CRP [15]. In a prospective observational study in IBD, patients starting anti-TNF (n = 49) improved in overall depressive symptoms and sleep over 14 weeks, although data were missing for the majority at follow-up [88]. By contrast, a meta-analysis of 23 RCTs found that fatigue was significantly increased with anti-TNF-α therapy in people with IBD [89]. Suggesting that fatigue in particular may be mediated through other pathways.

Vedolizumab is a newer biological agent specific for the integrin $\alpha_4\beta_7$, which acts by blocking the trafficking of activating lymphocytes to the gut. In this way, it is an effective and specific treatment for IBD and provides an important test of the gut–brain axis in depressive symptoms by blocking the gut specifically. Vedolizumab is generally regarded as a safe and effective intervention [90], and in one observational study, patients starting vedolizumab (n = 111) experienced a reduction in depressive symptoms and sleep over time [88]. Replication of these findings in parallel with changes in inflammation is awaited.

Anti-depressants are a first-line treatment for moderate or severe depression, and selective serotonin reuptake inhibitors (SSRIs) are most commonly used due to their efficacy and favourable side-effect profile [5]. Notably, SSRIs have some effects in reducing inflammation [91], while tricyclics may have even greater anti-inflammatory effects [92]. To date, however, only one RCT in IBD has tested an anti-depressant for depressive symptoms in people with IBD [93], and measures of inflammation were not analysed.

Summary: theoretical framework

Fig. 1 outlines a conceptually attractive model by which inflammation may link depressive symptoms and IBD. The evidence suggests that depressive symptoms, fatigue or sleep problems provide a biomarker for an aggressive form of IBD that is underpinned by an unfavourable microbiome, which leads to over-active immune pathways. Vulnerability may be conferred by female sex, early life stress and lifestyle behaviours. In turn, psychological distress leads to further dysfunction of the axis and increased intestinal permeability.

At the same time, this inflammation model presents several opportunities for intervention. First, psychological therapies can help to reduce levels of IBD distress, thereby reducing effects on the HPA axis and inflammation. Anti-depressant therapies can help to reduce inflammation and may restore HPA axis function. Systemic anti-inflammatory treatments, such as biological cytokine antagonists, can help to reduce the effects of inflammation on the brain. Finally, interventions to alter the gut microbiota and gut-specific anti-inflammatory treatments can reduce upstream effects of the gut on driving the gut–brain axis and inflammation. For such interventions, greater benefit is likely the earlier it targets the natural course of the disease pathway. For example, blocking the causes of inflammation is likely to produce more sustained benefits than simply limiting its effects, while treatments to address underlying vulnerability to the effects of inflammation – such as reducing early life stressors, poor diet and smoking – may have the greatest potential for prevention.

Future directions

In epidemiology, prospective observational studies are needed that combine detailed profiling of inflammation (including cytokines, high-sensitivity CRP and markers of T cell immunity), measures of depressive symptoms (including clinical depression, self-report depressive symptoms and detailed measures of somatic symptoms) and their associations with IBD outcomes. Such research would be illuminated by mechanistic studies testing the interactions between stress and gut microbiome with inflammation in the depressive symptoms of IBD.

Despite several studies of psychological therapy in paediatric and adult IBD [18,94], there has been no RCT of anti-depressant pharmacotherapy in people with IBD.

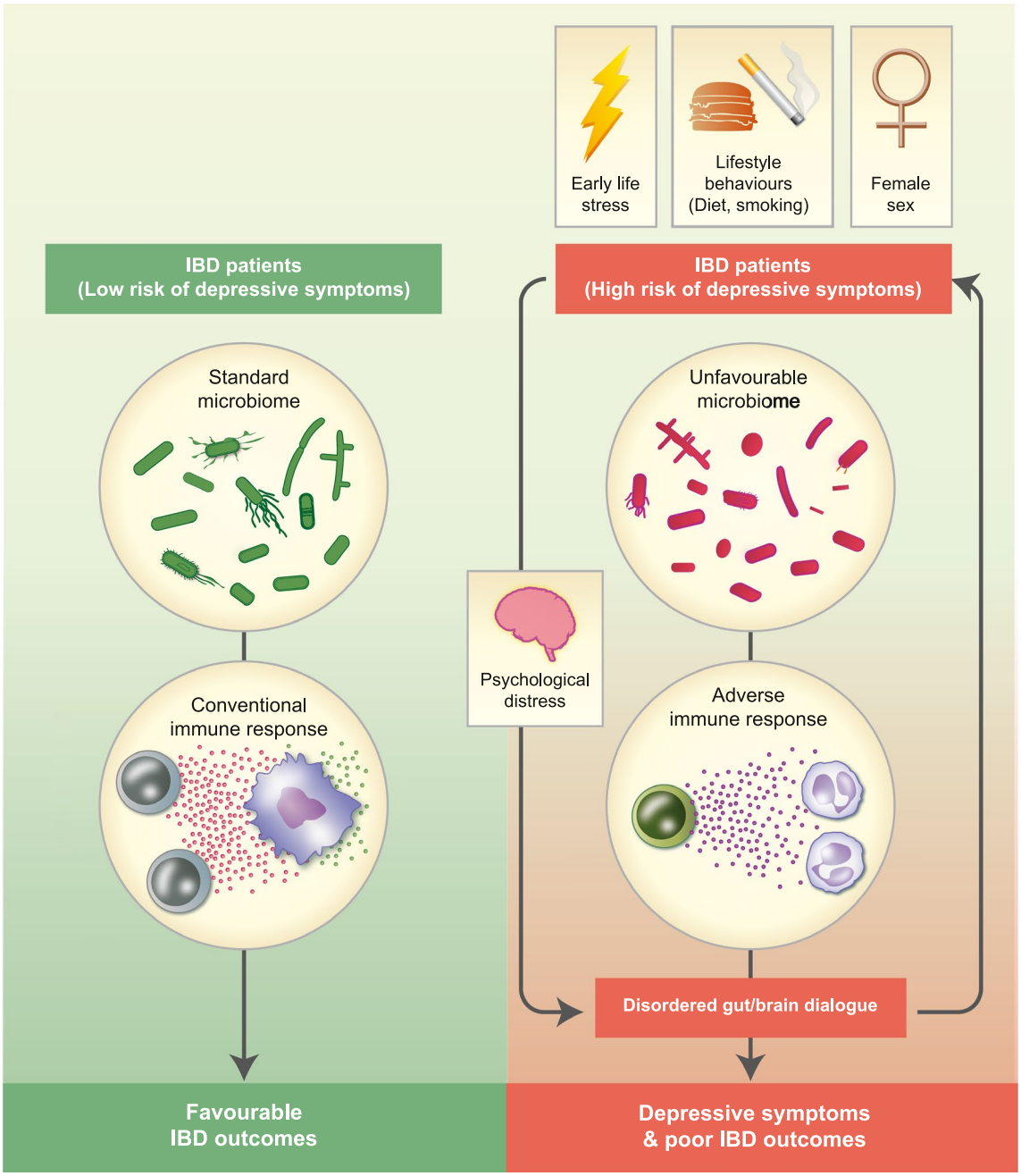

Fig. 1. Pathways towards an inflammatory depression and its adverse impacts in inflammatory bowel disease (IBD). In predisposed individuals – such as females, smokers and those experiencing early life stress – changes to the gut microbiome occur, which leads to exaggerated or adverse immune responses. The result is a vicious cycle of worsening inflammation, particularly through interleukin (IL)-6- and IL-1β-related pathways, which is associated with worsening gastrointestinal symptoms and depressive symptoms – an 'inflammatory depression' – exacerbated by psychological distress. The presence of depressive symptoms thereby denotes significant dysfunction of the gut–brain axis, leading to a worse course of IBD in these patients.

RCTs of standard anti-depressants are needed to test both their potential, and limits, in both reducing inflammation and improving IBD outcomes. As well as patients with severe gut dysfunction, experiments should recruit people with IBD remission, in order to help disentangle the effects of inflammation on gut and brain. Studies could be further enhanced by a comparison group of depressed patients with different chronic disease.

As well as in IBD, the gut–brain axis is thought to be important in the pathogenesis of depressive symptoms in general. In people with depressive symptoms, the wide range of anti-inflammatory treatments in IBD – including immunomodulators, systemic biologicals and gut-specific biologicals – provide unique opportunities to alter the gut–brain axis at different points. Studies testing systemic- and gut-specific agents in depression would help to define the most effective points at which inflammation can be modified to break the cycle of worsening depressive symptoms and IBD outcomes. Changes in depressive symptoms could be tracked over multiple time-points against changes in peripheral inflammation, gut inflammation and even central inflammation. Finally, comparison with other chronic inflammatory conditions would help to define whether there is a somatic subtype of depression that is driven by inflammation and seen across inflammatory conditions.

Summary

Depressive symptoms are a common co-morbidity in people with IBD and are associated with a worse course of IBD, which is incompletely explained by psychological factors alone. Fatigue and sleep disturbance are particularly common, whether as part of a broader depressive illness or not. Inflammation provides a promising shared origin for both depressive symptoms and poor IBD outcomes. Specifically, changes to the gut microbiome occur in high-risk groups, which leads to exaggerated immune responses. Excess inflammation is then associated with both worsening depressive symptoms and gastrointestinal dysfunction. Established treatments for both depressive symptoms and for IBD provide opportunities to break this cycle by reducing both the causes and effects of inflammation. With a range of treatments targeting inflammation centrally, peripherally and in the gut specifically, IBD provides a unique disease model for understanding the interplay between brain and gut in the pathogenesis of depressive symptoms, both in IBD and in the whole population.

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Disclosure

None.

Author contributions

C. D. M. and N. P. conceived the manuscript. All authors contributed to the first draft of the manuscript and all authors revised the manuscript for important intellectual content.

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