The Influence of Stress on the Development and Severity of Immune-Mediated Diseases

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ABSTRACT. Evidence that psychological stress can increase inflammation and worsen the course of immune-mediated inflammatory disease (IMID) is steadily accumulating. The majority of data supporting this hypothesis come from studies in patients with inflammatory bowel disease (IBD). While there is no evidence to suggest that stress is a primary cause of IBD, many, although not all, studies have found that patients with IBD experience increased stress and stressful life events before disease exacerbations. Further, the disease itself can cause psychological stress, creating a vicious cycle. In addition to reviewing the epidemiological evidence supporting a stress-IMID relationship, this article also briefly discusses how stress-related changes in neural, endocrine, and immune functioning may contribute to the pathogenesis of immune diseases, IBD in particular. The effects of different pharmacological and nonpharmacological interventions, including stress management and behavioral therapy, on stress, mood, quality of life (QOL), and activity of the underlying IMID are also summarized. (J Rheumatol 2011;38 Suppl 88:43–7; doi:10.3899/jrheum.110904)

Key Indexing Terms:
STRESS QUALITY OF LIFE INFLAMMATORY BOWEL DISEASES
RHEUMATOID ARTHRITIS PSORIASIS

Stress, which can be defined as a threat or a perceived threat to an organism's homeostasis, carries numerous health-related adverse effects[1,2]. Historically, psychological stress has been linked to the functioning of the gastrointestinal (GI) system[3]. Since the 1930s, both gastroenterologists and psychiatrists have implied that emotional life experiences might be associated with intestinal inflammation[3,4]. Since then, and despite methodological difficulties, substantial advances have been made in elucidating the relationship between stress and inflammatory bowel disease (IBD) activity, and the mechanisms by which this occurs. Several studies have also evaluated the effects of pharmacological and particularly nonpharmacological therapies on psychological stress and disease activity and course.

PSYCHOLOGICAL STRESS AND IBD — OBSERVATIONAL STUDIES

Despite numerous anecdotal reports of the effects of stress on GI functioning, it has taken several decades to clarify the influence of psychological stress on the development and severity of IBD and other immune-mediated inflammatory diseases (IMID). This is partly due to methodological limitations in this area of research. Studies testing the hypothesis that stressful events are associated with IBD are difficult to design and conduct because:

- They require a long study period to allow for a sufficient number of events to occur for correlation testing
- A high degree of patient compliance is required for the recording of life events and symptoms
- The definition of what comprises stress and a stressful life-event is variable
- There are interindividual differences in stress perception
- Some researchers have studied mixed groups of patients with ulcerative colitis (UC) and Crohn's disease (CD)
- A wide range of outcome measures has been used
- In several reports, statistical methods have been suboptimal

Thus, available studies differ in design, participants' characteristics, methods of classifying disease activity, and duration of followup.

Goodhand, *et al*[1] analyzed 13 studies that evaluated the influence of stress on relapse in IBD. Of these, 9 supported the hypothesis that stress and/or adverse life events worsened disease activity, and 4 reported no effect.

A prospective study of 62 patients with UC found that chronic psychological stress, measured by the Perceived Stress Questionnaire (PSQ), increased the risk of exacerbations of the disease[5]. Patients who fell into the upper stress tertile on enrolment had a higher hazard ratio for exacerbation during the subsequent 5 years than those in the low tertile (Figure 1). Further, a high PSQ score at any visit more than tripled the risk of disease worsening during the next 8 months.

Multivariate time-dependent analysis involving 101 patients with CD showed that those who had low levels of stress and who were identified as using low-avoidance

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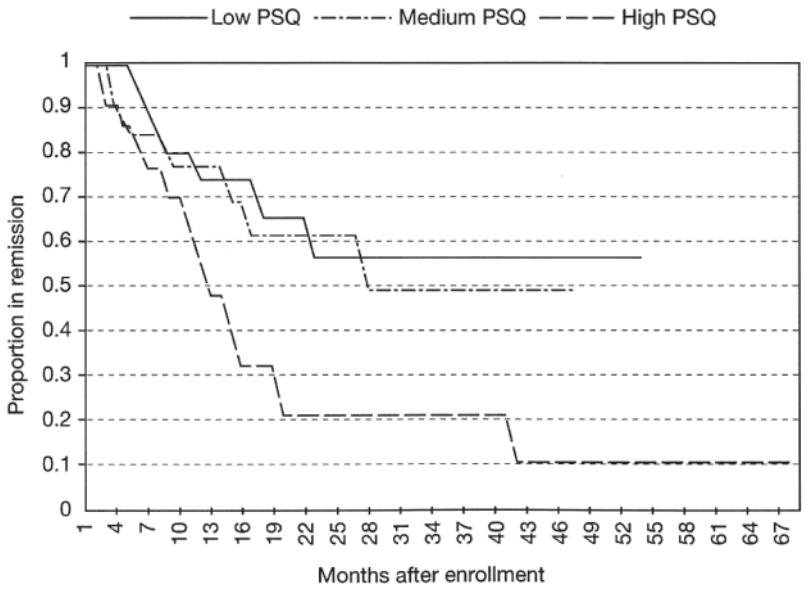

Figure 1. Rates of exacerbation in patients with ulcerative colitis according to high, middle, and low tertile scores on longterm Perceived Stress Questionnaire (PSQ) at enrolment. Risk of exacerbation was higher among patients with high PSQ levels than among those with low levels ($p < 0.03$ by log-rank test). Reprinted with permission from Macmillan Publishers Ltd.; Levenstein S, *et al*. Am J Gastroenterol 2000;95:1213-20.

methods using the Coping Inventory for Stressful Situation Avoidance subscale were least likely to relapse during the study period[6]. On the other hand, patients with either high stress-low avoidance, high stress-high avoidance, or low stress-high avoidance scores had higher likelihood of relapse (Figure 2). That study highlighted the importance of psychological stress in induction of relapse in CD, and suggested that patients' coping methods may affect relapse rates.

A recent prospective study, using a population-based IBD sample and directly comparing potential risk factors for disease flare, found that the rates of major life-related stressful events, high perceived stress, and negative mood were significantly different between those who experienced flare and those who were in remission (Table 1)[7]. Further, the flare group was more likely to have had a major stressful event in the 3-month period before the relapse ($p = 0.01$). Based on a numeric rating scale to describe the stress impact of these events (i.e., 0 = not at all stressful to 10 = extremely stressful), the flare group reported a higher total stress impact of major events (7.2 vs 4.9; $p < 0.01$) compared to those without flare.

The finding that stress might lead to disease exacerba-

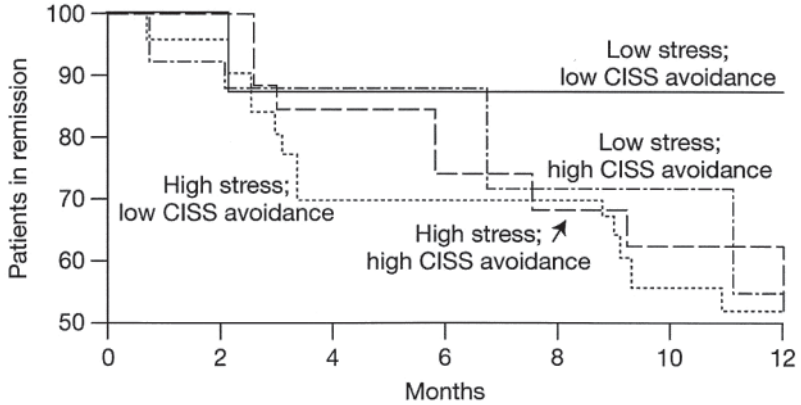

Figure 2. The stress-avoidance coping interaction. Most recent score (14–35 days prior to relapse) on Coping Inventory for Stressful Situation (CISS) avoidance subscale and risk of Crohn's disease relapse. At Months 0 and 12, respectively, n = 30 and 5 for high stress-high avoidance coping curve, n = 23 and 9 for high stress-low avoidance coping curve, n = 26 and 5 for low stress-high avoidance coping curve, and n = 19 and 26 for low stress-low avoidance coping curve. Reproduced from Bitton A, *et al*. Gut 2008;57:1386-92, with permission from BMJ Publishing Group Ltd.

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Table 1. Stress as a trigger for relapse in inflammatory bowel disease (IBD). Adapted from Bernstein CN, *et al*. Am J Gastroenterol 2010;105:1994-2002.

Stress	Flare, %	Remission, %	Bivariate OR (95% CI)
Major life stress event	56.4	43.5	1.69 (1.13–2.54)
High perceived stress	51.7	29.2	2.63 (1.72–4.01)
High negative mood	43.0	30.7	1.73 (1.13–2.66)

tions in patients with IBD prompts the question of whether stress affects response to treatment. Persoons, *et al*[8] determined that the presence of a major depressive disorder at baseline predicted a lower remission rate (odds ratio = 0.166, 95% confidence intervals 0.049–0.567, p = 0.004) in patients receiving episodic infliximab treatment (5 mg/kg), and the period of time before needing retreatment with infliximab was reduced (p < 0.001).

IMMUNE AND INFLAMMATORY RESPONSES TO EXPERIMENTAL AND ACUTE PSYCHOLOGICAL STRESS

Psychological stress is a subjective experience that is difficult to evoke and to objectively define in a controlled experimental environment. One of the methods used to assess the effects of stress on human GI function is the dichotomous listening test, in which different types of music are played simultaneously into each of the subject's ears at the same time as they take an IQ test. When applied for 50 minutes to patients with UC, this experimental stress test has been shown to increase production of systemic and rectal mucosal inflammatory cytokines and mediators thought to be important in the pathogenesis of IBD[9].

PATHOGENESIS OF STRESS-RELATED CHANGES IN THE GI TRACT

Although the underlying mechanisms by which psychological stress can affect immune function at both systemic and gut mucosal levels are yet to be fully understood, recent evidence points to changes in the hypothalamic-pituitary-adrenal (HPA) axis (Figure 3)[9]. Production of corticotropin-releasing factor (CRF) by the hypothalamus, stimulated by stress, promotes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH stimulates production of cortisol, the principal glucocorticoid, from the adrenal cortex[9,10]. Activation of the autonomic nervous system in response to stress causes stimulation of the sympathetic, and inhibition of the parasympathetic nervous systems, which communicate through the brain-gut axis with the nervous system in the gut, also known as the enteric nervous system.

The enteric nervous system not only controls and regulates the motility, exocrine and endocrine functions, and microcirculation of the GI tract, but also interacts directly with the mucosal immune system. Nerve fibers of the autonomic nervous system create tight effector junctions with lymphocytes and macrophages[9,11]. Further, receptors for hormones and neuropeptides of the HPA axis such as ACTH, corticosteroids, substance P, and CRF are found on various inflammatory cells. The effects of stress on the immune and inflammatory systems are multifactorial, and depend on both the intensity of the stressor and the duration of the stressful event[12].

THE INFLUENCE OF STRESS ON RHEUMATOID ARTHRITIS AND PSORIASIS

Both psychological distress and personality variables have been shown to be involved in the disablement process in rheumatoid arthritis[13]. There is also evidence, mainly from case-control studies, that stress might trigger psoriasis[14,15].

According to a recent study involving 169 outpatients with psoriasis and 169 matched controls, 54% of patients with psoriasis experienced at least one stressful event (47% for onset, 64% for recurrence), compared with 20% of controls (p < 0.0001)[14]. Family issues were mentioned by 43% of psoriatic patients, personal problems by 26%, and job/financial difficulties by 32%. All 3 types of stressful event were significantly more common in patients with psoriasis compared to controls. Similarly, Naldi, *et al*[15] found stressful life events to be a risk factor for a first episode of acute guttate psoriasis.

THERAPEUTIC IMPLICATIONS

If psychological stress affects the natural history of IBD, then stress-reduction therapies might have beneficial effects. Unfortunately, appropriately designed controlled studies are difficult to conduct in a blinded manner. Further, results of published studies should be interpreted with caution as they have used different patient populations, measures of disease activity, and psychological approaches[1,9].

Unfortunately, there have been no good trials of the effects of pharmacological treatments, such as antidepressants, in IBD. Of several trials using psychotherapy, including cognitive behavioral therapy, a minority suggested any improvement in the course of patients' IBD, although several did indicate an improvement in their psychological status[1,16,17,18,19,20,21,22,23,24,25,26,27,28,29]. However, using a retrospective case note review, Wahed, *et al*[30] recently compared the course of IBD in 24 patients during the year before (Year 1) and the year after (Year 2) referral for supportive outpatient psychological counselling to 24 matched IBD controls. Patients receiving counselling had significantly fewer relapses and outpatient attendances, and lower steroid and other relapse-related medication use during Year 2 compared to Year 1. There were no differences in any of these outcomes between Years 1 and 2 in the control group (Figure 4). Thus, IBD-focused counselling might improve not only psychological well-being but also the course of IBD in individuals with psychological stress.

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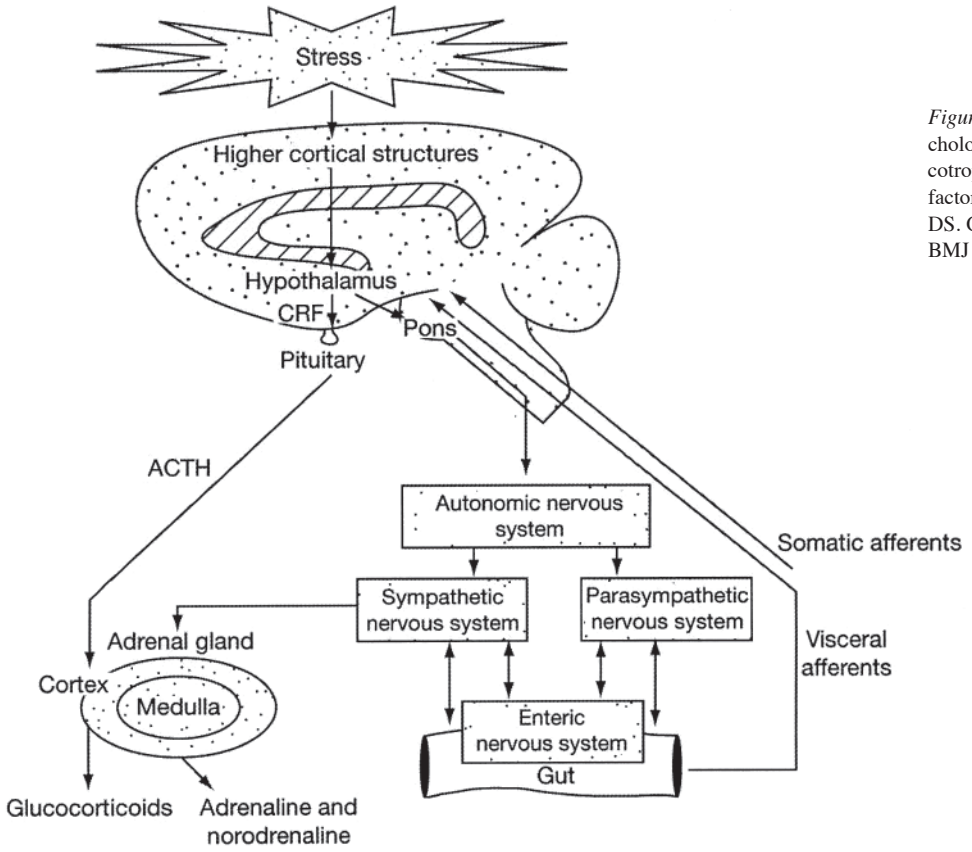

Figure 3. Pathways mediating the effects of psychological stress on the gut. ACTH: adrenocorticotropic hormone; CRF: corticotropin-releasing factor. Reproduced from Mawdsley JE, Rampton DS. Gut 2005;54:1481-91, with permission from BMJ Publishing Group Ltd.

Reductions in disease activity achieved with antiinflammatory, immunomodulatory, and anti-tumor necrosis factor therapies improve quality of life (QOL) and possibly mood in patients with IBD. For example, a subanalysis of patient-reported outcomes from the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) study demonstrated that maintenance with adalimumab provided sustained improvement in health-related QOL in patients with moderate to severe CD up to Week 56[31].

CONCLUSION

Although the 2-way interconnections between psychological stress and IMID need further definition, psychological stress does appear to play a role in the natural history of some, if not all, IMID. Additional well designed studies are needed to clarify the mechanisms underlying the stress-IMID relationship, in the hope that they can be used to devise new therapeutic approaches. In the meantime, identifying and addressing the needs of patients with psychological stress and maladaptive coping strategies may influence not only their quality of life and mood, but potentially alter the course of their chronic inflammatory disease.

REFERENCES

1. Goodhand JR, Wahed M, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? Exp Rev Gastroenterol Hepatol 2009;3:661-79.
2. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171-9.
3. Keefer L, Keshavarzian A, Mutlu E. Reconsidering the methodology of "stress" research in inflammatory bowel disease. J Crohns Colitis 2008;2:193-201.
4. Murray CD. Psychogenic factors in the etiology of ulcerative colitis and bloody diarrhea. Am J Med Sci 1930;180:239-48.
5. Levenstein S, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C, et al. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. Am J Gastroenterol 2000;95:1213-20.
6. Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut 2008;57:1386-92.
7. Bernstein CN, Singh S, Graff LA, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. Am J Gastroenterol 2010;105:1994-2002.
8. Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment Pharmacol Ther 2005;22:101-10.
9. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. Gut 2005;54:1481-91.
10. Goyal RK, Hirano I. The enteric nervous system. N Engl J Med 1996;334:1106-15.
11. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 1995;345:99-103.
12. Straub RH, Dhabhar FS, Bijlsma JW, Cutolo M. How psychological stress via hormones and nerve fibers may exacerbate rheumatoid arthritis. Arthritis Rheum 2005;52:16-26.

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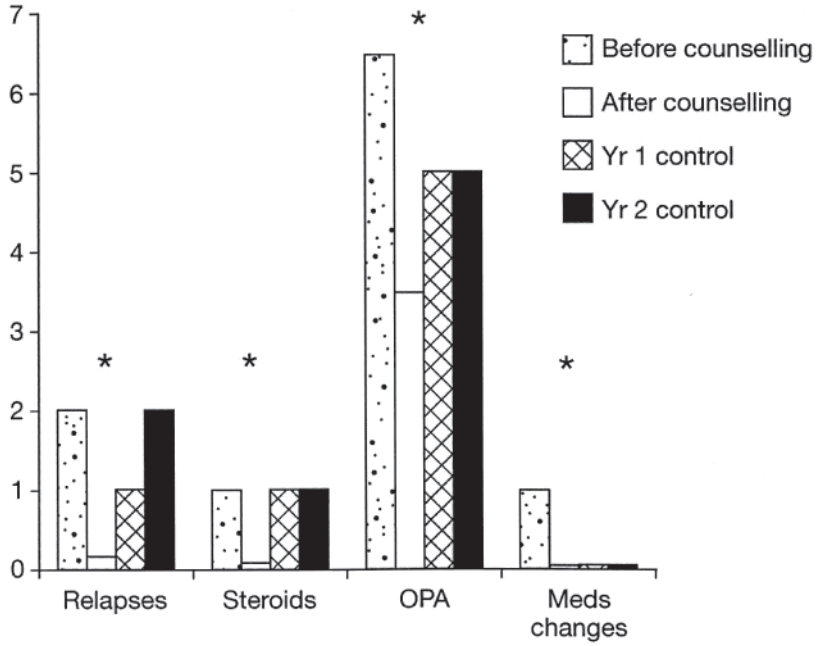

Figure 4. Effect of counselling on IBD[30]. *Statistical significance. OPA: outpatient attendance.

13. Bai M, Tomenson B, Creed F, Mantis D, Tsifetaki N, Voulgari PV, et al. The role of psychological distress and personality variables in the disablement process in rheumatoid arthritis. Scand J Rheumatol 2009;38:419-30.
14. Manolache L, Petrescu-Seceleanu D, Benea V. Life events involvement in psoriasis onset/recurrence. Int J Dermatol 2010;49:636-41.
15. Naldi L, Peli L, Parazzini F, Carrel CF; Psoriasis Study Group of the Italian Group for Epidemiological Research in Dermatology. Family history of psoriasis, stressful life events, and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: results of a case-control study. J Am Acad Dermatol 2001;44:433-8.
16. O'Connor JF, Daniels GE, Flood C, Karush A, Lepore M, Moses L. An evaluation of psychosomatic patients: A proposed methodological approach. Proc Annu Meet Am Psychopathol Assoc 1964;52:194-201.
17. Jantschek G, Zeitz M, Pritsch M, Wirsching M, Klör HU, Studt HH, et al. Effect of psychotherapy on the course of Crohn's disease. Results of the German prospective multicenter psychotherapy treatment study on Crohn's disease. German Study Group on Psychosocial Intervention in Crohn's Disease. Scand J Gastroenterol 1998;33:1289-96.
18. Maunder RG, Esplen MJ. Supportive-expressive group psychotherapy for persons with inflammatory bowel disease. Can J Psychiatry 2001;46:622-6.
19. Deter HC, Keller W, von Wietersheim J, Jantschek G, Duchmann R, Zeitz M; German Study Group on Psychosocial Intervention in Crohn's Disease. Psychological treatment may reduce the need for healthcare in patients with Crohn's disease. Inflamm Bowel Dis 2007;13:745-52.
20. Deter HC, von Wietersheim J, Jantschek G, Burgdorf F, Blum B, Keller W; German Study Group on Psychosocial Intervention in Crohn's Disease. High-utilizing Crohn's disease patients under psychosomatic therapy. Biopsychosoc Med 2008;2:18.
21. Milne B, Joachim G, Niedhardt J. A stress management programme for inflammatory bowel disease patients. J Adv Nurs 1986;11:561-7.
22. Schwarz SP, Blanchard EB. Evaluation of a psychological treatment for inflammatory bowel disease. Behav Res Ther 1991;29:167-77.
23. Mussell M, Böcker U, Nagel N, Olbrich R, Singer MV. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. Scand J Gastroenterol 2003;38:755-62.
24. García-Vega E, Fernandez-Rodriguez C. A stress management programme for Crohn's disease. Behav Res Ther 2004;42:367-83.
25. Elsenbruch S, Langhorst J, Popkirowa K, Müller T, Luedtke R, Franken U, et al. Effects of mind-body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. Psychother Psychosom 2005;74:277-87.
26. Langhorst J, Mueller T, Luedtke R, Franken U, Paul A, Michalsen A, et al. Effects of a comprehensive lifestyle modification program on quality-of-life in patients with ulcerative colitis: a twelve-month follow-up. Scand J Gastroenterol 2007;42:734-45.
27. Díaz Sibaja MA, Comeche Moreno MI, Mas Hesse B. Protocolized cognitive-behavioural group therapy for inflammatory bowel disease. Rev Esp Enferm Dig 2007;99:593-8.
28. Szigethy E, Kenney E, Carpenter J, Hardy DM, Fairclough D, Bousvaros A, et al. Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. J Am Acad Child Adolesc Psychiatry 2007;46:1290-8.
29. Szigethy E, Craig AE, Iobst EA, Grand RJ, Keljo D, DeMaso D, et al. Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. Inflamm Bowel Dis 2009;15:69-74.
30. Wahed M, Corser M, Goodhand JR, Rampton DS. Does psychological counseling alter the natural history of inflammatory bowel disease? Inflamm Bowel Dis 2010;16:664-9.
31. Loftus EV, Feagan BG, Colombel JF, Rubin DT, Wu EQ, Yu AP, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. Am J Gastroenterol 2008; 103:3132-41.

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