REVIEW ARTICLE

Reconsidering the methodology of “stress” research in inflammatory bowel disease

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Abstract

Background and Aims: The goals of this paper are: 1) to critically review and analyze the methodology of the studies since 1990 linking stress to inflammatory bowel disease; and 2) to make recommendations for future research in this area of research. Methods: Articles were restricted to empirical reports in the English language with human subjects. Eleven empirical articles were able to answer “How is psychological stress related to inflammation and/or the expression or course of inflammatory bowel disease?” Results: Studies varied by choice of participant groups, method for classifying disease activity, choice of design, and definition and measurement of stress. Only half of the studies supported the hypothesis that stress affected IBD in some way. Conclusions: Current methodological limitations in the stress and gut inflammation research have made it difficult for us to ascertain the role of stress in inflammatory bowel disease. Authors provide a checklist of items to consider when designing future studies.

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KEYWORDS
Stress; Inflammatory bowel disease; Ulcerative colitis; Crohn’s disease; Methodology; Psychosocial

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1. Introduction

Historically, stress has been linked to the onset and maintenance of gastrointestinal symptoms. Since the 1930s, gastroenterologists and psychiatrists alike have implied that emotional life events or experiences are contemporaneously linked to intestinal inflammation.1–3 However, research in this area has been notoriously weak, with many studies uncontrolled, due, in part, to the early misconception that the “evidence” for this relation was so strong that no control groups were necessary.4 In the 1960s, research examining the interactions between psychosocial and biological factors in Inflammatory Bowel Disease (IBD) improved markedly with respect to scientific rigor. However, the subjectivity with which stress was measured remained a significant barrier to identifying the relations between stress and inflammation5 in both Ulcerative Colitis (UC) and Crohn’s Disease (CD).

While the basic science research supporting the role of stress in the inflammatory process in the gut is beyond the scope of this review, current literature supports the idea that stress has a direct role in the pathophysiology of IBD.7 Potential mediators of immune and neural-immune factors implicated in IBD include substance P, vasoactive intestinal protein, tumor necrosis factor, heat shock proteins, oxygen free radicals and oxidants, and endogenous glucocorticoids.6 While animal studies of gut inflammation and factors affecting the onset and maintenance of inflammatory bowel disease have consistently demonstrated the role of environmental stress in the disease process,53–55 these findings have not directly translated into research on human subjects. There are several methodological reasons for this, including uniquely human research issues such as finding a sufficient stressor, limitations of self-report, recall bias and the role of organic disease in the human perception of stress.

One of the main issues facing our current literature relating stress and inflammatory bowel disease that likely permeates other areas of psychosomatic medicine is a comprehensive, theoretically and practically sound definition of stress upon which to rest our assumptions regarding stress and disease. While biologists refer to factors such as heat, cold, restraint, and inadequate food supply as sources of stress and immunologists consider stress any stimulus that induces activation of the Hypothalamic–Pituitary–Adrenal (HPA) axis and sympathetic nervous system,6 social scientists are more often concerned with people’s interaction with the environment and the resulting emotional consequences. The paucity of studies adequately defining stress before determining its physiological effects leaves most of us feeling that stress can be anything to anyone and that it can contribute to just about any disease.9

2. Defining stress

From a social science perspective, the most rudimentary method of defining stress stems from a “response-based” view, such as that described by Hans Selye.10,11 From this viewpoint, stress can be considered a physiological response to a “stressor,” or an adverse circumstance in the environment leading to sympathetic nervous system activation, commonly known as the “fight-or-flight response.” This response-based approach is the most commonly adopted definition in medical stress research. Response-based measures ask primarily about symptoms, emotions, physiological changes and behaviors associated with a stressor. The Perceived Stress Questionnaire12 and the Perceived Stress Scale13 are examples of such measures. While valid and reliable, one disadvantage of a response-based approach to stress is that it often confounds stress with its consequence—answers on such scales may be related to the subjective feeling of stress after the response has already occurred.

Other definitions of stress are stressor-based14,15; in other words, looking at various types of events and attempting to determine which ones trigger an “adaptive effort to cope” by the organism. Those events requiring more effort are considered more stressful. This type of view is supported by life events checklists, such as those developed by Holmes and Rahe,15 and assumes that certain events are more “stressful” than others.16 One disadvantage of this definition is that it does not account for subjective experience—for one person, a divorce may be a relief of chronic tension in the household and for another person a devastating loss.

The most widely adopted conceptualization of stress by psychologists to date is the cognitive-transactional theory of stress.17,18 From this perspective, stress is defined as “a real or perceived imbalance between environmental demands required for survival and an individual’s capacity to adapt to these requirements.”19 Lazarus’ paradigm differs from the stimulus-based or response-based approaches described above in that it is no longer uni-directional or context free. Rather, stress is considered to be part of a sequential process that includes a) antecedents, which are individual difference variables such as one’s attitudes or beliefs, history with a stressor, or other demands; and b) mediators, which refer to coping skills, appraisals, social support and other variables that have immediate and direct effects on the situation. The theory allows for a large amount of variation in an individual’s repertoire of coping resources and vulnerabilities.19 Therefore, measurement of stress needs to take into account such variables. While there are no good measures to date that assess the entire context of a stressor(s), we can include multiple measures of stress and identified mediating variables in our studies. While certainly not an exhaustive list, some of the most commonly cited mediators of the stress...
response include coping, social support and perceived controllability. A review of stress research and theories of stress in health psychology can be found elsewhere. See Table 1 for a summary.

While there have been some recent reviews of the literature linking stress and IBD, these reviews have focused on either the neuro-immunological relations between stress and inflammation or have collapsed stress into a review of “psychological factors” that includes emotion, stress and the effects of psychological treatments. While the reviews do make excellent recommendations for future research, their broad scope has likely limited their impact on future research in this area.

The goal of this paper is to critically review and analyze the several studies linking stress to inflammatory bowel disease and to determine factors that may be important when designing future studies. We emphasize a cognitive-transactional model of stress, which is most commonly adopted by health psychologists, and accounts for additional factors influencing the relations between stress and disease. To prevent redundancy, we have chosen to simultaneously present our results and offer a discussion of the methodological issues and questions they raise.

3. Methods

Complete searches of Medline, PubMed, PsychInfo and PsycLit were performed using the following search terms: stress and intestine; stress and colitis, stress and Crohn’s, stress and bowel, life events and intestinal. Articles were restricted to empirical reports in the English language with human subjects. Studies were carefully chosen for methodological soundness and appropriateness of the main research question in our review, namely “how is psychological stress related to inflammation and/or the expression or course of inflammatory bowel disease?” Of the studies that met our search terms, eleven were empirical reports and directly measured stress and intestinal symptoms, therefore meeting our criteria for review (Table 2). Studies were excluded \( n=8 \) if they did not directly measure stress, only speculated about the role of stress in inflammatory bowel disease or focused primarily on psychopathology rather than on stress.

In order to better understand how the various studies went about determining outcome, we decided to compare and contrast methodology in these studies and discuss ways the methodology may have impacted the results. It became apparent that differences existed between the groups on the following methodological variables of interest and likely impacted outcome: choice of participant groups, method for classifying disease activity, choice of design (prospective, retrospective, cross-sectional) and definition and measurement of stress. Given the small sample size of articles appropriate for this review and the variability in outcome measures and design, this type of review does not lend itself to meta-analytic techniques, although analyses of effect size may be important and interesting at a later date.

4. Results and discussion

Of the eleven studies reviewed, six (55%) supported the hypothesis that stress affects IBD in some way. Two of the studies did not support this hypothesis, and three studies produced inconclusive results (Table 3).

4.1. Choice of participant groups

Four of the eleven studies reviewed included patients with Ulcerative Colitis (UC) only. In three out of four of these studies, the UC patients were in remission. One of the studies used a cross-sectional design, comparing patients who were both symptomatic and asymptomatic.

Two studies used patients with symptomatic Crohn’s Disease. Five studies used a mixed group of UC and CD patients, with 3 of these studies obtaining inconclusive results. To further complicate the picture, four out of the five studies using a mixed group of IBD also used patients with mixed disease status (active vs. remission). This practice of including mixed disease status confuses the effect that disease may have on recall and perception of stress and weaken power to detect differences.

Interestingly, only one study out of the eleven reviewed used a healthy control group. Use of appropriate control groups is essential for valid comparison. The use of control groups can help to identify the effects that chronic disease can have on symptoms and on perception of stress and its markers. For example, irritable bowel syndrome (IBS) patients who have chronic, relapsing GI symptoms and are known to be influenced by stress would be a good comparison group to assess the effects of chronic gastrointestinal symptoms without any inflammation. Comparing IBD patients to other groups of patients with inflammatory disorders with respect to inflammation levels and stress levels would also likely help us

### Table 1: Models of stress

<table>
<thead>
<tr>
<th>Model of stress</th>
<th>Description</th>
<th>Examples of measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response-based (Selye)</td>
<td>Stress is the response to an adverse circumstance leading to the “fight-or-flight” response</td>
<td>Perceived Stress Questionnaire; Perceived Stress Scale</td>
</tr>
<tr>
<td>Stressor-based (Dohrenwend and Dohrenwend)</td>
<td>Stress triggers an active effort to cope; events requiring more coping are more stressful</td>
<td>Life Events Checklist</td>
</tr>
<tr>
<td>Cognitive-Transactional (Lazarus and Folkman)</td>
<td>Stress is “a real or perceived imbalance between environmental demands required for survival and an individual’s capacity to meet those requirements”</td>
<td>None currently available; must use measures of mediating variables in addition to standard stress measures</td>
</tr>
</tbody>
</table>

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to better understand the mechanism by which stress acts on the body. For example, stress is also believed to influence the onset and course of rheumatoid diseases, including arthritis, lupus and fibromyalgia.29 Multiple sclerosis exacerbations have also been shown to be linked to recent stressful life events.30

The average number of study participants in the reviewed studies was 70(58), ranging from 10 to 200. None of the studies reported whether they had conducted a power analysis, or whether the study had adequate power to test their hypotheses. Future studies should use an adequate number of well-defined groups of patients with IBD (UC vs. CD; active vs. inactive) and compare the results with appropriate control groups such as patients with chronic inflammation to control for chronic inflammatory process and patients with chronic gastrointestinal symptoms to control for symptoms.

### 4.2. Classification of disease activity

Four of the eleven studies used an objective measure of inflammation/relapse in their patients. Seven studies used objective measures of inflammation such as unprepared flexible sigmoidoscopy and, in one case, rectal biopsy specimen.24 Two of the eleven studies did not use objective measures, but did rely on standardized measures of disease activity, such as the Crohn’s Disease Activity Index,31 (CDAI)26 or the Harvey–Bradshaw Index.27 Unfortunately, the other 2 studies used subjective measures of disease activity. Most often, a symptom diary based on the CDAI or a similar rating scale was used.

Clearly, there are some inherent problems with using subjective measurement of disease status. First, patients likely perceive the frequency and severity of their symptoms...
differently, thus introducing bias into the relations not only between perception of stress but with respect to perception of symptoms. Secondly, there is some evidence that inflammation in response to stress is present, even when the individual appears to be clinically asymptomatic, making it imperative to objectively measure the effects of stress. Future studies should use validated objective measures which may include clinical symptoms (like the CDAI), markers of the inflammatory process (like C-reactive protein) and/or tissue inflammation.

4.3. Choice of design

Nine of the eleven studies used a prospective research design, following participants for an average of almost 1 year [50.55 weeks (60.93)]. The average follow-up interval during the study was 5.7 weeks (7.46), with a range of 0–24 weeks. Two of the studies used a cross-sectional design, comparing asymptomatic patients in remission with symptomatic patients during flare-up on a variety of stress measures. Cross-sectional designs are probably no longer an appropriate methodology for answering questions about how stress influences disease—we now know enough about how a disease itself can exacerbate stress and therefore would never be able to determine directionality in a cross-sectional design. For these reasons, prospective research is more methodologically rigorous and the design of choice. It is important to decide upon a standardized time frame in which to measure stress and symptoms to ensure that our measurement of these variables best captures the course of the disease. We were disappointed to find that 5 of the 9 studies that monitored stress and inflammation prospectively used cross-sectional analyses, comparing people who relapsed over time with those who did not, again significantly limiting the types of conclusions that can be drawn from such studies.

4.4. Definition of stress

Only one of the eleven studies reviewed operationally defined “stress” before describing the choice of measurement. In that study, the authors simply defined stress as environmental events. Keep in mind, however, that the lack of good operationalized definitions is not just a problem in the gastroenterology literature. Future studies should carefully define stress prior to measuring its physiological effects. We recommend that the transactional model be considered the “gold-standard” for stress research. This model offers the most dynamic and complete picture of the stress response, allows for the differential effect of stress on individuals, and addresses other variables that interact with stress that could provide more explanatory power.

Two studies addressed these mediator variables, albeit in a limited way. One of the studies reviewed included a measure of coping. Another study included a short measure of social support and suggested that interventions aimed at improving support could have a favorable impact on health and disease activity.

4.5. Choice of stress measurement

Seven of the studies relied on the occurrence of major life events as their measure of stress. Four of the studies relied on the experience of “hassles” or minor annoyances as their primary outcome measure. Only 1 of the studies used both indices of stress. Given the complicated nature of stress, as described above, it is likely that neither approach to measuring stress fully addresses the complicated interaction between stress and disease activity. The lack of standardized measures results in the use of different measures in each study, making comparison across studies difficult. For example, in the 11 studies selected for this review, the investigators used 5 different measures of life events and 4 different measures of “hassles.” Therefore, conclusions drawn about the effects of stress on the course of IBD can be influenced by the type of measures (life events or hassles) used in these studies. In other words, the difference in the findings may represent methodological flaws or may indicate that each of these methods measures a different aspect of stress and thus provides a clue as to the mechanism of stress on inflammation and/or symptoms.

4.5.1. Studies that used life events as measure of stress

The majority of the standardized questionnaires that are used to evaluate the effects of major life events on psychosocial functioning originated in the study of psychiatric illness, such as depression and schizophrenia. Thus, it is not surprising that many of these questionnaires do not take into account the stress of having a chronic disease and how this may contribute to the experience of life events. For example, an exacerbation of Crohn’s disease or a scheduled surgery may result in work or financial stress, or in some cases, loss of a job. The cyclical nature of the disease can make it very difficult to determine the preceding stressor (chicken or egg) as many of the antecedents and consequences are intertwined.

The use of questionnaires that are not specific to health-related problems could also introduce bias into the findings. Some researchers have attempted to categorize types of stressors (i.e. health, interpersonal, etc.) to recognize this problem. While their findings have been overall inconclusive, the results did seem to support a modest statistical trend towards interpersonal stress experienced prior to participation.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Features of studies reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
<td>Number of studies</td>
</tr>
<tr>
<td>Concludes that stress affects disease activity in some way</td>
<td>6</td>
</tr>
<tr>
<td>Concludes that stress does not affect disease activity</td>
<td>2</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>3</td>
</tr>
<tr>
<td>Used a prospective design</td>
<td>9</td>
</tr>
<tr>
<td>Used a cross-sectional design</td>
<td>2</td>
</tr>
<tr>
<td>Used life events as stress measure</td>
<td>7</td>
</tr>
<tr>
<td>Used hassles/daily stress as stress measure</td>
<td>4</td>
</tr>
<tr>
<td>Used Ulcerative Colitis as model</td>
<td>5</td>
</tr>
<tr>
<td>Used Crohn's Disease as model</td>
<td>2</td>
</tr>
<tr>
<td>Used IBD as a model (both UC and CD)</td>
<td>4</td>
</tr>
<tr>
<td>Average follow-up period (weeks)</td>
<td>50.54 (60.93)</td>
</tr>
<tr>
<td>Average interval of measurement (weeks)</td>
<td>5.75 (7.46)</td>
</tr>
<tr>
<td>Average number of study participants</td>
<td>69.81 (57.76)</td>
</tr>
</tbody>
</table>
in the study and an increased risk of relapse. Further, health-related stress experienced at follow-up was the most significant type of stressor experienced, which reinforces the notion of measuring the impact of the disease on stress$^{25}$ and not just the impact of stress on the disease.

Another problem inherent in relying solely on the documentation of life events as a measure of stress is that life events are not all made equal, and certain life events may be more significant for some individuals than others. In other words, the sheer number of stressors does not necessarily reflect the level of stress in a person's life. Some have argued that once a significant stressor has occurred, additional stressors do not typically change symptom outcome. $^{36}$ If this is the case, studies that report "stress" summary scores do not always allow for adequate comparisons of groups. This may explain why there was only a weak relation between number of events and time to relapse in a recent study. $^{37}$ Along the same lines, dividing patients into "high" or "low" stress groups based on numeric cut-offs (i.e. average number of stressors over 6 months) may be problematic and result in inconclusive findings. $^{25}$

Perception of stress should always be taken into account as well. As discussed earlier, the mere occurrence of an event does not necessarily suggest that the event was stressful. Thus, having participants rate the impact of their stressor, which is the procedure described in the Life Experiences Survey $^{17}$ may be beneficial. This was done in some of the reviewed studies. $^{24,37-39}$

Further difficulty arises when one administers life events questionnaires retrospectively. Once a person has become ill, it is likely that they will have biased recall of the period of time prior to their illness, $^{40}$ possibly looking for an explanation for why they became ill. Further, altered eating, sleeping or medication use during illness can also affect stress levels and influence reporting. While the overall number of events may or may not remain the same, the perceived impact of them may be heightened due to a variety of psychological factors. $^{41}$ Finally, studies among depressed individuals suggest that people who are depressed and/or neurotic tend to have better cognitive access to past negative events. $^{42}$

Another difficulty arises when a mixed sample of symptomatic and asymptomatic patients is used and then compared on life events measures. Differences between groups may be related almost entirely to biased recall amongst the symptomatic group and not to the actual experience of life events. This may explain why 2 of the studies reviewed that used a mixed patient sample had inconclusive $^{43}$ or contradictory $^{46}$ findings. In a cross-sectional study comparing symptomatic and asymptomatic UC patients, $^{24}$ symptomatic participants were more likely to recall negative life events than asymptomatic patients. Interestingly, asymptomatic patients with abnormal rectal mucosa scored higher on perceived stress than asymptomatic patients with normal rectal mucosa. Unfortunately, an analysis between these two asymptomatic groups with respect to life events was not performed—this would have helped to clarify the role of life events in the inflammation process, controlling for the experience of symptoms.

In general, the reliability and therefore predictability of life events measures are low. $^{44}$ In a study where women were asked to monitor life events once a month for a 10 month period and then asked at the end of 10 months to report again the life events that occurred, only 25% of the events appeared at both points in time, and the latter list contained significantly fewer events. $^{45}$ This could explain the inconclusive findings in one study that asked participants to rate the amount of stress associated with each life event at the end of 1 year rather than as the events were occurring. $^{38}$ Other research has also suggested that retrospective data greater than 6 months are invalid. $^{46}$ Finally, without specific anchors, people tend to have difficulty sticking to a timeframe when reporting life events. In this sense, an interview approach $^{47}$ may yield more accurate information. However, this technique is time and labor intensive and relies on the judgment of yet another observer.

All of the studies reviewed assessed life events within the recommended 6-month time frame, with the average interval being 10 weeks (range 4 weeks through 24 weeks). The one study that assessed life events at the 6 month point used an interview approach to augment reliability. $^{39}$ This study also had the longest follow-up (up to 4 years). While it is better to administer life events questionnaires prospectively, it is very difficult to follow patients over significant periods of time. However, this would significantly improve the reliability of data since relapse during that time is more likely. Two of the studies reviewed $^{39,43}$ monitored past this 2-year timeframe.

Finally, it is important to control for (enter as covariates) other factors that may also be precipitating flare-ups, such as a change in diet, level of exercise, seasonal variations, smoking habit, alcohol or non-steroidal anti-inflammatory drug (NSAID) use. $^{38}$ There is also considerable symptom overlap between physical symptoms and markers of depression (reduced appetite, difficulty sleeping, low energy). This may explain the negative findings in a study looking at the relations between mood, stress and IBD symptoms reviewed. $^{43}$

### 4.5.2. Studies that used perceived daily hassles as measures of stress

While it has been more popular to look at stress from a life-events perspective, both for ease of cost and patient burden, there is some research that suggests the usefulness of daily stress monitoring and daily symptom monitoring. Inventories such as the Hassles Questionnaire. $^{48}$ designed to measure the cumulative effect of minor stressors, assume that people's lives are more affected by the accumulation of daily "hassles" than by the potentially more significant, but less frequent life events. Research has suggested that hassles and life events are only moderately correlated and that it is the hassles that seem to be more closely related to illness. $^{49}$ This relation may be mediated less by the daily hassles themselves as the effects that cumulated stress causes—increasing health compromising behaviors (smoking, alcohol consumption, weight gain) or causing negative mood. $^{50}$

From a statistical analysis perspective, however, linking daily hassles and disease activity is a very difficult thing to do. First, it is unclear how quickly "stress" acts on the gastrointestinal tract. Therefore, it is difficult to determine whether we should be focused on the same day/same symptoms approach, or account for a lag time, or add an accumulation of a week. It is also difficult to account for the effect of symptoms from the day prior. It is also very burdensome for a patient to monitor their daily stress for a period of time necessary to see a flare-up (about 1 year). There is even some evidence that monitoring of stress itself directly impacts the monitoring of symptoms. $^{51}$ The studies reviewed did use
statistically elegant time-series regression, pooled time series, or time-series analysis on 20 single cases. In this case, only one of the studies was cross-sectional. The burden of daily monitoring is likely the largest drawback to the study of daily stress on intestinal symptoms. Of the studies reviewed, the average number of days monitored was 93 (range 28 through 365). One way to reduce the burden of daily monitoring over a lengthy period of time is to have patients monitor one week out of a month over a year or more, such as described by Greene and colleagues. The main disadvantage of this approach is that it is likely to miss certain key stressors and their direct impact on key symptoms at any given time. Related to the problem of daily monitoring is the use of small samples (hard to get people to participate in these types of studies). The average number of participants in the studies reviewed was 13.67, not including the cross-sectional daily stress study which used a considerably larger sample.

Controlling for life events remains important in these types of studies as well. One must be careful to look for significant events that may affect the monitoring of daily hassles, not to mention inflammation linked to life events. One study controlled for the effects of life events in their 28-day prospective study and found that it was the daily stress, rather than life events that influenced symptoms. Of course, 28 days is a relatively short amount of time to be examining life events and the findings may have been different had participants monitored symptoms over a longer period of time. Overall, the findings in the 4 studies looking at daily stress in IBD suggested that daily stress does influence symptoms. One study found inconclusive results, likely because it was cross-sectional and used mixed UC and CD patients as well as inactive and active disease. The other 3 studies supported the role of daily stress in symptoms; one of which offered the caveat that daily stress affects symptoms for certain patients.

5. Conclusion

While there is some data and plenty of anecdotal reports of the effects of stress on IBD disease activity, we continue to lack a sound paradigm through which to approach this type of study with more depth and accuracy. With only about half of the research studies reviewed in the last 15 years suggesting an association between stress and IBD, and a literature with significant methodological issues muddying the waters in this area, we are still unable to draw any conclusions about the role of stress on inflammation in inflammatory bowel disease. This review has pointed out some of the reasons why we are unable to draw strong conclusions in either direction. See Table 4 for a “checklist” of things to consider in the designing of future studies.

References


