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Stress and Exacerbation in Ulcerative Colitis: A Prospective Study of Patients Enrolled in Remission

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OBJECTIVE: We sought to determine whether psychosocial factors influence the course of ulcerative colitis, hypothesizing that high perceived stress among patients with inactive disease will increase the risk of subsequent exacerbation.

METHODS: Sixty-two patients with known ulcerative colitis were enrolled into a prospective cohort study while in clinical remission. Their perceived stress, depressive symptoms, and stressful life events were followed, along with potential confounders, for up to 45 months; exacerbation status was monitored for up to 68 months.

RESULTS: The 27 patients who experienced an exacerbation were compared with those who remained in remission. Having a score in the upper tertile on the long-term (past 2 yr) baseline Perceived Stress Questionnaire significantly increased the actuarial risk of exacerbation (hazards ratio = 2.8, 95% confidence interval 1.1–7.2). At any given study visit, high long-term stress tripled the risk of exacerbation during the next 8 months (risk for the three tertiles, 8.3%, 16.7%, and 26.2%, $p = 0.02$). Shorter sleep time, briefer remission, histological activity, and use of nonsteroidal antiinflammatory drugs, antibiotics, or oral contraceptives also increased the medium- and/or long-term risk of exacerbation, but adjustment for these variables did not eliminate the associations with stress. Exacerbation was not associated with stressful life events, depressive symptoms, short-term (past month) perceived stress, smoking, disease extent or duration, or severity of recent course.

CONCLUSIONS: Short-term stress does not trigger exacerbation in ulcerative colitis, but long-term perceived stress increases the risk of exacerbation over a period of months to years. (Am J Gastroenterol 2000;95:1213–1220. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Ulcerative colitis (UC) is a relapsing-remitting disease often characterized by striking swings between inflammatory activity and quiescence. The idea that psychological factors can influence these swings has a long history (1), and many gastroenterologists (2, 3) and patients (4, 5) continue to believe that stress can trigger exacerbations.

Despite the tenacity of the stress-exacerbation hypothesis, there is little evidence in its favor. The retrospective literature is mixed, some (6–8) but not all (9–13) controlled studies finding that UC patients recall increased life stress before exacerbations. Three studies have tracked disease activity and stress prospectively (14–16), and none of the three found stress unequivocally to predict subsequent activity. It might seem reasonable to conclude that the apparent sequential relation between stress and UC flares in some case-control studies arises not from a causal nexus but from the kind of recall bias that has been termed "effort after meaning," (17) the attempt to make sense of fluctuations in health.

Previous prospective studies may, however, have failed to detect a genuine association because of their choice of stress measures, subjects, or time scale. We developed a brief pencil-and-paper instrument, the Perceived Stress Questionnaire (PSQ), based on aspects of stress seen by gastroenterologists and patients as relevant to UC activity (18); typical items include, "You find yourself in situations of conflict" and "You believe you're in a hurry." The PSQ showed satisfactory psychometric characteristics (including a coefficient α of 0.90 and a test-retest reliability of r = 0.86), and correlated at an appropriately moderate level with measures of psychological distress and health status (18). When PSQ scores were studied in relation to endoscopic rectal inflammation among asymptomatic UC patients, a cross-sectional but double-blind model, subjects reporting higher levels of long-term stress were more likely to have abnormal endoscopy (19).

In the prospective study reported here, UC patients were enrolled in clinical remission and their exacerbation status, perceived stress levels, and potential confounders were monitored at length, to test the hypothesis that perceived stress has an adverse effect on disease course. Depressive symptoms and stressful life events were also examined, for comparison with previous studies.

MATERIALS AND METHODS

Patients seen between October 1990 and October 1994 by two of the Inflammatory Bowel Disease Clinic physicians at the Nuovo Regina Margherita Hospital, an inflammatory bowel disease referral center for south-central Italy, were asked to participate in the study if they had ulcerative colitis previously diagnosed on the basis of standard clinical, endoscopic, and histological criteria (20–22); had been in complete clinical remission for at least 2 months off systemic or local steroids, scoring 0 on a symptom scale of 0–8 (hematochezia or passage of mucus absent = 0, present <50% of the time = 1, present ≥50% of the time = 2; stools formed = 0, pasty = 1, liquid = 2; tenesmus absent = 0, occasional = 1, constant = 2; number of daily bowel movements 0–3 = 0, 4–5 = 1, ≥6 = 2) (19, 23); and were using oral or rectal 5–aminosalicylate or oral azulfidine in maintenance doses as sole therapy. Subjects who reentered stable remission after an exacerbation could be enrolled a second time.

Physician research associates (M.L.S., E.B.) described the purpose and design of the study to eligible patients, and obtained written consent from those agreeing to participate. They recorded year of diagnosis; disease extent; month of latest symptoms; number of courses of local or systemic corticosteroids and hospitalizations in the past 2 yr; and risk factors during the previous month: smoking (24), sleep time (25–27), respiratory infections (28), and use of oral contraceptives (29), nonsteroidal antiinflammatory drugs (30), or antibiotics (31).

Unprepared rigid proctoscopy was performed by experienced clinicians blinded to psychological findings (C.L., A.A.) and scored as no activity (0 = normal mucosa or chronic changes only), mild activity (1 = erythema, edema, minimal or no friability), moderate activity (2 = frank friability), or severe activity (3 = spontaneous bleeding, pus) (21). Rectal biopsy specimens were classified blind (A.M.) as showing histologically normal mucosa or inactive colitis (scored 0), minimal activity (scored 1), mild activity (scored 2), moderate activity (scored 3), or severe activity (scored 4) (22).

A psychologist (V.V.) administered the Paykel Life Experiences Interview (32), Recent (covering the past month) and General (covering the past 2 yr) forms of the Perceived Stress Questionnaire (PSQ) (18), and the Centers for Epidemiological Studies Depression Scale (CES-D) (33).

The study design is summarized in Figure 1. Subjects were scheduled to return every 6 months for a visit that included interim history, proctoscopy with biopsy, the Paykel interview, General PSQ, Recent PSQ, and CES-D. They were urged to return earlier if symptoms recurred. At each visit except the last they were given a packet of blank Recent PSQs to be completed monthly at home, with specific instructions that if they failed to complete the questionnaire during 1 month they should skip that PSQ rather than complete it retrospectively.

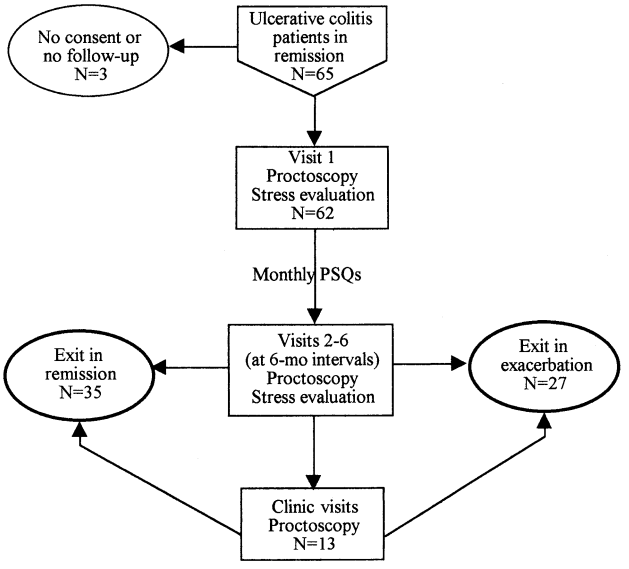

Figure 1. Study design: stress and exacerbation in ulcerative colitis.

Regular study visits and monthly PSQs continued for up to 45 months or until the patient experienced an exacerbation. For patients who were followed by the study physicians in the IBD clinic after the last psychological assessment, exacerbation status could continue to be monitored for up to 68 months. Exacerbation was defined as symptoms rated ≥1 that lasted ≥10 days and that were associated with at least one of two confirmation criteria: intensified therapy prescribed by a physician and/or rectal inflammation seen by study endoscopists. Positive findings were confirmed by repeating analyses against a series of more restrictive definitions of exacerbation, which either required both physician-intensified therapy and abnormal endoscopy (with a score of ≥1 or of ≥2) in addition to new symptoms, or required symptoms to be at a level of ≥2, ≥3, or ≥4. Subjects in exacerbation exited the study as of the date symptoms began, and any psychological data from that month onward were discarded.

This research was approved by the Nuovo Regina Margherita Hospital Ethics Committee.

Statistical Methods

Patients were classified on the basis of each Paykel Interview as having experienced or not experienced any contextually severe life event during the previous 6 months (17, 34). Severity of their recent course was roughly estimated by the number of courses of local or systemic corticosteroids plus twice the number of hospitalizations in the 2 yr before enrollment. Smoking, endoscopic activity, and histological activity were dichotomized as present or absent, and extent as proctitis/proctosigmoiditis *versus* extensive colitis.

The relation between dichotomous baseline variables and exacerbation was examined using survival analysis by the Kaplan-Meier nonparametric product limit method and analyzed using log-rank and proportional hazards methods to

Table 1. Characteristics on Enrollment of 62 Asymptomatic Subjects With Known Ulcerative Colitis

	All Subjects			By Course During Follow-Up					
				Continued Remission			Exacerbation		
	N	Mean ± SD or Number	Range or Percent	N	Mean ± SD or Number	Range or Percent	N	Mean ± SD or Number	Range or Percent
Age (yr)	62	38.8 ± 13.0	18–71	35	38.9 ± 14.0	18–71	27	38.7 ± 11.9	21–62
Male gender	62	33	53%	35	21	60%	27	12	44%
Disease duration (yr)	62	6.5 ± 6.0	0.25–35	35	7.6 ± 7.1	0.25–35	27	4.8 ± 3.9	0.5–15
Remission duration (months)	62	16.4 ± 15.9	2–70	35	19.0 ± 18.6	1–70	25	11.4 ± 11.1	1–38
Disease limited to rectum/sigmoid	61	25	41%	34	17	50%	27	8	30%
Severity of course in past 2 yr*	31	1.5 ± 1.8	0–7	18	1.1 ± 1.8	0–7	13	2.2 ± 1.8	0–7
Duration of present maintenance therapy (months)	61	14.2 ± 16.0	1–70	35	16.1 ± 18.6	1–70	25	11.4 ± 11.1	1–38
Any activity on proctoscopy	60	14	23%	33	9	27%	27	5	19%
Mild activity	60	12			8			4	
Moderate activity	60	2			1			1	
Any histological inflammation	26	3	11%	13	0		13	3	27%
Minimal inflammation	26	2			0			2	
Mild inflammation	26	1			0			1	
Rectal route for maintenance therapy	59	22	37%	33	15	45%	26	7	27%
Blue-collar head of household	57	16	28%	32	10	31%	25	6	24%
Family history of inflammatory bowel disease	35	5	14%	19	4	21%	16	1	6%
Current smoker	62	22	35%	35	15	42%	27	7	26%
Hours of sleep/day in past month	32	6.8 ± 1.1	5–10	18	7.1 ± 1.2	5–10	14	6.5 ± 0.8	5–8
Special risk factors in past month†	34	9	26%	19	3	16%	15	6	40%
General Perceived Stress Questionnaire (past 2 yr)	61	0.40 ± 0.17	0.03–0.84	35	0.37 ± 0.16	0.03–0.80	27	0.45 ± 0.17	0.17–0.84
Recent Perceived Stress Questionnaire (past month)	62	0.38 ± 0.16	0.01–0.80	35	0.34 ± 0.16	0.01–0.80	27	0.42 ± 0.16	0.11–0.69
Centers for Epidemiology Studies Depression Scale	55	16.3 ± 8.4	2–35	31	16.2 ± 8.5	2–35	24	16.4 ± 8.6	2–35
Severe life event during past 6 months	54	13	24%	30	8	27%	24	5	21%

* Courses of local or systemic corticosteroids plus 2 × the number of hospitalizations; † respiratory infection, nonsteroidal antiinflammatory drugs, antibiotics, oral contraceptives.

evaluate the univariate relationship between survival curves (35, 36). Continuous variables were examined by dividing the patients into tertiles and calculating coefficients for the relative hazard for higher levels as *versus* level 1. Adjustment for confounders was performed using multivariate analysis in proportional hazards models.

To examine the shorter-term predictive value of stress, the "pooling of repeated observations" technique was used: each observation period is treated as a mini-follow-up study, with risk factors at the start of the interval used to estimate the odds of exacerbation by the time of the next evaluation (37, 38). Because such analyses assume all intervals are equal in length (37) and because patient visits took place at intervals slightly longer than the planned 6 months, we took 8 months (243 days) as the uniform length of observation periods. Exacerbation status was thus determined during the 8 months after each study visit, and observations for all patients over multiple intervals were pooled into a single sample; exacerbations taking place longer than 8 months after the final stress evaluation were omitted from these analyses. Proportions of patients with exacerbation within 8 months were compared using χ^2, Mann-Whitney *U*, and *t* tests for dichotomous, ordinal, and continuous variables, respectively, using multiple logistic regression to adjust for confounders (37).

The percent of variance explained by logistic regression models was calculated from reduction in −2 log likelihood with respect to the null model.

Analyses were performed using Statview, EGRET, and SPSS statistical software. All *p* values were two-tailed.

RESULTS

Subjects

Sixty-five cases met the recruitment criteria. Two of them represented a single patient, who as per the protocol reentered the study after 9 months in remission after successful treatment of an exacerbation; the direction and significance of the results did not change if this patient's second enrollment was omitted. Two patients declined to participate, and one enrolled patient was lost to follow-up after the initial clinic visit, so the number of analyzable patients was 62, with a mean age of 38.8 ± 13.0 yr (all means are ± SD). Other baseline characteristics are reported in Table 1.

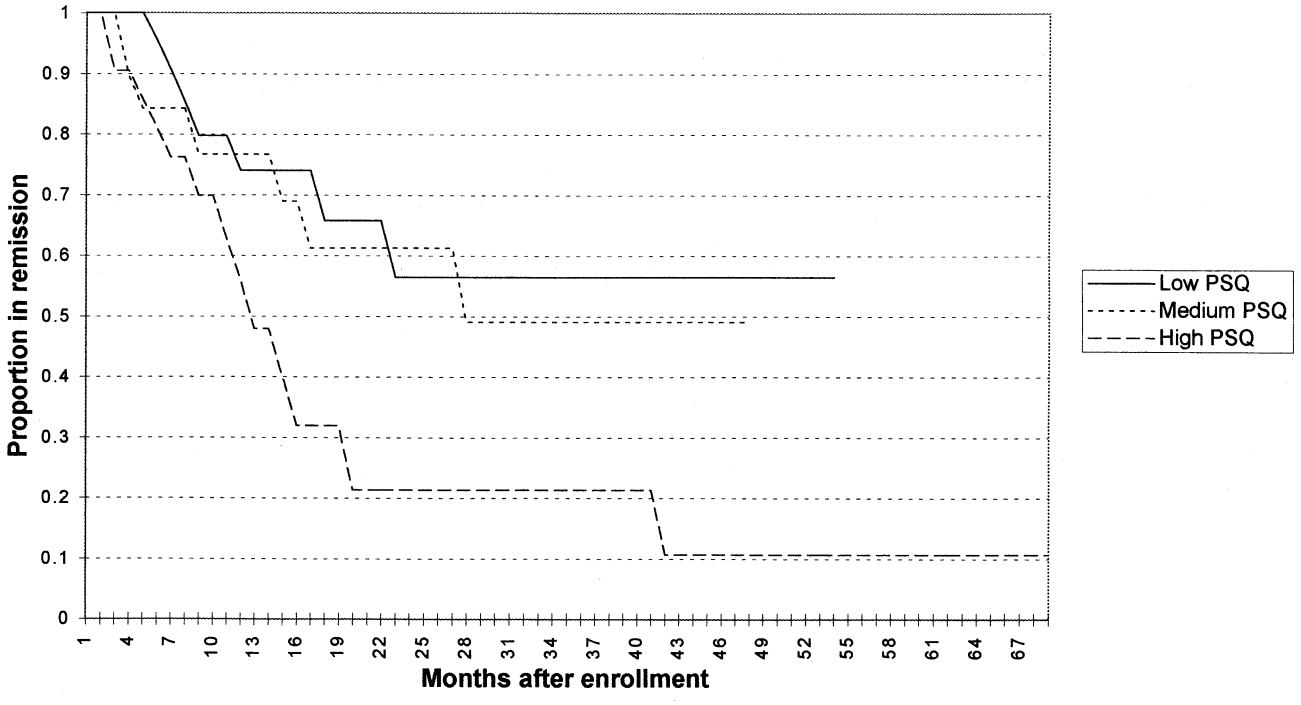

Figure 2. Kaplan-Meier analysis of cumulative rates of exacerbation in ulcerative colitis patients with high, middle, and low tertile scores on long-term Perceived Stress Questionnaire Scores (PSQ) at enrollment. Risk of exacerbation was higher among patients with high long-term stress levels than among those with low levels ($p = 0.03$ by log-rank test).

Outcomes

Subjects attended a mean of 2.9 ± 1.1 (range, 2–6) study clinic visits with psychological evaluation over a mean of 12.5 ± 8.4 months (range, 6–45). Total follow-up ranged between 3 and 68 months: a mean of 21.8 ± 17.4 months for subjects who exited the study in remission, and 11.7 ± 8.0 months for subjects with exacerbation.

Mean PSQ scores were similar to those of healthy subjects in the validation study (18). General PSQs were available for 95.0% of study visits, and Recent PSQs were available for 61.1% of the possible person-months.

Twenty-seven patients experienced an exacerbation, with a mean peak symptom score of 4.8 ± 2.0. Mean endoscopic scores were 1.5 ± 0.8 at postexacerbation visits (N = 23) *versus* 0.21 ± 0.44 during remission ($p < 0.0001$); mean histological scores were 2.2 ± 1.0 (N = 10) and 0.19 ± 0.56 ($p < 0.0001$) respectively.

Data Analysis

BASELINE CHARACTERISTICS *VERSUS* EXACERBATION: SURVIVAL ANALYSIS. Cumulative exacerbation rates were 43.6% for patients with a General Perceived Stress Questionnaire score in the low tertile at baseline, 56.2% for those in the middle tertile, and 89.4% for those in the high tertile (Fig. 2). The actuarial risk of exacerbation was significantly higher for the highest than for the lowest tertile, with a hazards ratio of 2.8 (95% confidence interval [CI] 1.1–7.2, $p = 0.03$).

Baseline histological inflammation and exposure to respiratory infections or medications were significantly associated with exacerbation on survival analysis, and there was a trend in this direction for sleep time (Table 2). Among patients with values for all these variables, the hazards ratio for high *versus* low baseline PSQ scores was 8.0 ($p = 0.01$) before and 4.5 ($p = 0.10$) after adjustment using a multivariate Cox model. Baseline stressful life events or depressive symptoms were not associated with exacerbation (Table 2).

CHARACTERISTICS AT EACH VISIT *VERSUS* EXACERBATION DURING THE NEXT 8 MONTHS. Four patients with exacerbations occurring >8 months after the last stress evaluation were considered to have completed that interval in remission, leaving 23 exacerbations for analysis.

General PSQ scores in the low, middle, and high tertiles at any given visit entailed a risk of 8.3%, 16.7%, and 26.2%, respectively, for exacerbation within 8 months ($p = 0.02$; Table 3); the univariate odds ratios (ORs) on logistic regression were 2.2 (CI = 0.57–8.5, $p = 0.25$) and 3.9 (CI = 1.1–13, $p = 0.03$) for middle and high tertiles, respectively, compared with the low tertile. Briefer remission duration (OR for 1 month = 0.97, CI = 0.94–0.99) and shorter recent sleep time (OR/h = 0.49, CI = 0.25–0.97) were significantly associated with exacerbation, but adjustment for these two variables, or for the full range of adjustment variables, did not eliminate the association between General PSQ and exacerbation (Table 4).

General PSQ tertile explained 8.0% of the variance in exacerbation occurrence. The model that further included

Table 2. Risk of Exacerbation Among Ulcerative Colitis Patients According to Baseline Characteristics: Univariate Analyses (Comparison of Kaplan-Meier Curves by Logrank Test and Cox Proportional Hazards Survival Analysis)

Variable	Hazards Ratio	95% Confidence Interval	Cox *p* (Logrank *p*)
General Perceived Stress Questionnaire			
Low tertile (reference group)	1.0		
Middle tertile	1.2	0.42–3.5	0.71 (0.71)
High tertile	2.8	1.1–7.2	0.03 (0.03)
Centers for Epidemiologic Studies Depression Scale			
Low tertile (reference group)	1.0		
Middle tertile	0.83	0.30–2.3	0.72 (0.69)
High tertile	0.99	0.36–2.7	0.98 (0.84)
Severe life event during past 6 months*	0.73	0.27–2.0	0.54 (0.54)
Disease duration			
<2.9 yr (reference group)	1.0		
2.9–7.8 yr	0.89	0.37–2.1	0.79 (0.65)
>7.8 yr	0.50	0.18–1.4	0.18 (0.17)
Remission duration			
<6 months (reference group)	1.0		
6–16 months	0.69	0.27–1.8	0.44 (0.94)
>16 months	0.53	0.20–1.4	0.19 (0.29)
Severity of course in past 2 yr			
Inactive (score = 0; reference group)	1.0		
Mild (score = 1–2)	1.9	0.48–7.9	0.35 (0.73)
Moderate-severe (score = 3–7)	3.0	0.66–14	0.16 (0.24)
Sleep time in past month			
>7 h/day (reference group)	1.0		
6.5–7 h/day	3.5	0.72–17	0.12 (0.37)
<6.5 h/day	4.2	0.78–22	0.09 (0.29)
Extensive disease*	1.5	0.65–3.5	0.33 (0.33)
Smoker*	0.73	0.30–1.8	0.49 (0.49)
Special risk factors in past month†	3.8	1.2–12	0.02 (0.01)
Any activity on proctoscopy*	0.64	0.24–1.7	0.37 (0.37)
Any histological inflammation*	5.6	1.3–24	0.02 (0.01)

* The reference group includes all subjects without the risk factor; † respiratory infection, nonsteroidal antiinflammatory drugs, antibiotics, oral contraceptives.

remission duration and sleep time explained 17.2%, and the one including all nonpsychosocial risk factors explained 20.3%.

Stressful life events, depressive symptoms, and Recent PSQ were not associated with exacerbation during the subsequent 8 months (Table 3), and mean monthly PSQ scores during the 3 months before exacerbations (N = 17) were no higher (0.40 ± 0.16) than the same patients' scores at baseline (0.38 ± 0.17).

ANALYSES USING ALTERNATIVE MEASURES. The *a priori* definition of exacerbation was a symptom score ≥1 confirmed by either physician-intensified therapy or an endoscopic inflammation score ≥1. In 24 of 27 symptom flares, not one but both confirmation criteria were present. Survival analyses using this stricter endpoint showed the hazards ratio for an upper *versus* lower tertile General PSQ to be 3.2 ($p < 0.03$), and 8-month exacerbation rates by tertile to be 6.3%, 11.1%, and 23.8% ($p < 0.02$). Using a still more rigorous definition of exacerbation (symptoms, physician judgment, endoscopic score ≥2), met by 10 subjects, exacerbation rates within 8 months were 0%, 8.3%, and 12.2% for the three PSQ tertiles ($p < 0.02$); the hazards ratio was not calculable because of empty cells. Significant associations persisted when analyses were limited to exacerbations with higher symptom scores (data not shown), as well as when the second remission of the single reenrolled patient was omitted (data not shown).

Analyses were repeated among subjects in endoscopic as well as clinical remission, excluding the 14 patients with initial endoscopy scores of >0. Exacerbation rates within 8 months were 7.1%, 13.8%, and 31.0% for the three PSQ tertiles ($p < 0.01$), and the hazards ratio for high *versus* low stress was 3.3 (CI = 1.2–8.7). When analyses were similarly limited to patients with normal baseline histology, exacerbation rates within 8 months were 0%, 16.7%, and 27.3% for the three PSQ tertiles ($p < 0.01$).

TEMPORAL PATTERNS OF PRE-EXACERBATION STRESS. Because stress levels did not rise just before exacerbation, monthly PSQs were examined during the 14 months leading up to exacerbations to investigate, in a exploratory fashion, the lag time between acute stress and subsequent disease activity. At all time points, these mean monthly PSQs were higher (range, 0.42–0.54) than the mean Recent PSQ score of nonexacerbation patients (0.35 ± 0.17), and there was a suggestion of a peak 8–11 months before symptoms began (mean during those months, 0.50 ± 0.16).

Table 3. Characteristics at Each Clinic Visit of Ulcerative Colitis Patients in Remission, in Relation to Exacerbation Within the Following 243 Days: Pooling of Repeated Observations

	Number of Observation Intervals	Percent of Intervals With Exacerbation	*p* (Mann-Whitney *U*)
General Perceived Stress Questionnaire			0.02
Low tertile	48	8.3%	
Middle tertile	36	16.7%	
High tertile	42	26.2%	
Recent Perceived Stress Questionnaire			0.57
Low tertile	43	11.6%	
Middle tertile	40	20.0%	
High tertile	41	17.1%	
Centers for Epidemiologic Studies Depression Scale			0.93
Low tertile	47	20.5%	
Middle tertile	37	10.8%	
High tertile	36	22.2%	
			(χ^2)
Severe life event during past 6 months	35	14.3%	0.81
No life event	77	18.2%	
Disease limited to rectum/sigmoid	51	13.7%	0.45
Extensive disease	78	20.5%	
Current smoker	38	13.2%	0.47
Nonsmoker	93	18.3%	
Special risk factors in past month*	26	23.1%	0.37
No special risk factors	76	13.2%	
Activity on proctoscopy	22	21.4%	0.74
Normal proctoscopy	86	16.5%	
Histological inflammation	10	20.0%	0.55
Normal biopsy	69	13.0%	
	Exacerbation	No Exacerbation	*p* (*t* test)
Hours of sleep/day during past month	6.3	6.9	0.04
Remission duration in months	17.4	28.0	0.04
Disease duration in yr	5.6	7.3	0.25

* Respiratory infection, nonsteroidal antiinflammatory drugs, antibiotics, oral contraceptives.

DISCUSSION

This prospective study of ulcerative colitis patients enrolled in remission found that long-term psychological stress, as measured by the General Perceived Stress Questionnaire, increased the risk of exacerbation. A patient who fell into the upper stress tertile on enrollment had a higher hazards ratio for exacerbation during the next several years than patients in the low tertile. A high PSQ score at any given visit more than tripled the risk of experiencing an exacerbation during the next 8 months. These associations could not be explained by confounding due to disease or patient characteristics.

The present findings are in line with a long anecdotal tradition (39–41) and with several case-control studies (6–8), but they contrast with previous prospective studies of UC (14–16). One reason for this discrepancy may lie in the approach to stress measurement. We used a perceived stress instrument (18) similar to final-common-pathway measures that have proved useful in other prospective studies of organic disease (42, 43). Previous ulcerative colitis studies

Table 4. Odds Ratios for Exacerbation Within the Following 243 Days According to Long-Term Perceived Stress (General Perceived Stress Questionnaire [PSQ] Score) at Each Clinic Visit by Ulcerative Colitis Patients in Remission: Univariate and Multivariate Logistic Regression, Limited to the 91 Visits for Which Data Are Available on All Variables

	No Adjustment Variables		With Significant Predictors*		With All Adjustment Variables†	
	OR	95% CI	OR	95% CI	OR	95% CI
Low tertile PSQ	1.0		1.0		1.0	
Middle tertile PSQ	3.5	0.59–21	3.2	0.52–20	2.6	0.40–17
High tertile PSQ	6.5‡	1.2–34	6.0‡	1.0–35	6.8‡	1.1–44

* Sleep time and remission duration; † sleep time, remission duration, disease duration, smoking status, respiratory infections, medication use, disease extension; ‡$p < 0.05$ for high *vs* low tertile; OR = odds ratio; CI = 95% confidence interval.

had instead concentrated on adverse life events, which may not coincide with the stress experienced by an individual, and on depressive symptoms, which are only one aspect of perceived stress; the present study replicated their findings by detecting no prospective association of these variables with exacerbation.

Previous researchers assessed stress over days to weeks, and looked for an effect within a month or two. The present study instead asked patients to report stress levels both for the previous month and over the previous 2 yr, and examined impact over months to years. It proved in fact to be chiefly long-term stress that affected disease course, with an effect over many months. Brief spurts in stress levels, or adverse life events, did not trigger exacerbations if they lacked a prolonged impact on perceived stress.

The importance of long- rather than short-term stress levels is plausible in terms of the probable mechanisms at play, which are likely to be different in the present study—which enrolled patients in remission and used clear-cut exacerbation as its endpoint—than in studies looking at symptom fluctuations among subjects enrolled with varying levels of disease activity. A direct effect of autonomic discharge on the already abnormal bowel motility of ulcerative colitis patients (44), irritable bowel syndrome superimposed on inflammatory bowel disease (45), might be involved in the short-term symptom activation by psychological stressors noted in the older literature (46, 47).

For exacerbation promotion, hyperactivation of the immune system is a more likely mechanism, because UC pathophysiology is thought to involve inadequate suppression of the immune response to luminal toxins (48). Immune deregulation seems to be a regular concomitant of stress (49), possibly through the mediation of autonomic nerves that innervate lymphoid tissue, and can result in stimulation as well as suppression (50–52). The temporal pattern of associations observed in this study, which suggested that stress-related exacerbations tend to develop only after many months, is consistent with the lengthy time scale that has been reported (53) for the evolution of the distinctive effects that chronic stress can have on the immune system (51, 52).

Caution must be observed in drawing etiological conclusions from the present study; for example, adherence to therapy, a potentially important behavioral mediator between stress and exacerbation, was not examined. The therapeutic implications are similarly unclear, as trials of insight-oriented psychotherapy (41) and stress-reduction techniques (54) have shown little effect on the course of the disease. None of the broad range of risk factors examined here, including perceived stress, explained by itself as much as 10% of the variance in exacerbation occurrence, and even a model including all of them accounted for barely 20%, a reminder that the determinants of UC fluctuations are still largely unknown.

Possible negative repercussions on patients may constitute, paradoxically, still another reason for caution. Ulcerative colitis was once considered a classic "psychosomatic" disease (40), and though in recent years scientific interest has shifted from its putative psychological causes to its distressing effects (55), many patients continue to believe themselves stigmatized and the severity of their disease undervalued due to overestimates of the importance of the psyche in determining colitis manifestations (56). Interactions between mind and body are the rule rather than the exception in disease processes (57, 58); recognition of these interactions should not lead to subtle forms of victim blaming.

We conclude that short-term stress does not trigger exacerbations among ulcerative colitis patients in remission, but that long-term ongoing stress increases the risk of experiencing an exacerbation over a period of months to years, independent of disease or patient characteristics. These findings reinforce the utility of the biopsychosocial model in understanding the origin and course of disease.

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