Effect of psychosocial stressors on patients with Crohn's disease: threatening life experiences and family relations

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Background and aims Threatening life experiences and adverse family relations are major psychosocial stressors affecting mental and physical health in chronic illnesses, but their influence in Crohn's disease (CD) is unclear. We assessed whether these stressors would predict the psychological and medical condition of CD patients.

Methods Consecutive adult CD patients completed a series of instruments including demography, Patient Harvey–Bradshaw Index (P-HBI), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), short-form survey instrument (SF-36), brief symptom inventory (BSI), family assessment device (FAD), and list of threatening life experiences (LTE). Associations of FAD and LTE with P-HBI, SIBDQ, SF-36, and BSI were examined by multiple linear and quantile regression analyses.

Results The cohort included 391 patients, mean age 38.38 ± 13.95 years, 59.6% women, with intermediate economic status. The median scores were as follows: P-HBI 4 (2–8), FAD 1.67 (1.3–2.1), LTE 1 (0–3), SF-36 physical health 43.75 (33.7–51.0), SF-36 mental health 42.99 (34.1–51.9), and BSI-Global Severity Index 0.81 (0.4–1.4). The SIBDQ was 47.27 ± 13.9. LTE was associated with increased P-HBI in all quantiles and FAD in the 50% quantile. FAD and LTE were associated with reduced SIBDQ ($P < 0.001$). Higher LTE was associated with lower SF-36 physical and mental health ($P < 0.001$); FAD was associated with reduced mental health ($P < 0.001$). FAD and LTE were associated positively with GSI in all quantiles; age was associated negatively.

Conclusion CD patients with more threatening life experiences and adverse family relations were less healthy both physically and mentally. Physicians offering patients sociopsychological therapy should relate to threatening life experiences and family relations. Eur J Gastroenterol Hepatol 00:000–000

Introduction

Crohn's disease (CD) is a common form of inflammatory bowel disease (IBD). Although the etiology of CD remains unknown, it is widely accepted that it results from an inappropriate immune response that occurs in genetically susceptible individuals as a result of a complex interaction among environmental factors, microbial factors, and the intestinal immune system [1]. In addition, psychological factors play an important role in the physical and mental functioning of all patients with chronic illnesses, including CD. Among the major psychological stresses in an individual's life are threatening life experiences and adverse family relationships.

Threatening life experiences include a number of issues, such as serious illness or injury in oneself or a close relative, death of a close relative or friend, separation in marriage or other close associations, altercations with friends and neighbors, loss of employment, financial crisis, and trouble with the police. These experiences impact on physical and mental health [2,3]. In a large study of various populations and controlling for mental illness, it has been shown that stressful life events have a significant relationship with a variety of physical illnesses [4]. Although there is no evidence that stress is a primary cause of IBD, several studies have shown that patients with IBD experience increased stress and threatening life experiences before disease exacerbations. Perceived stress, negative mood, and major life events were trigger variables significantly associated with flares of IBD in a study of 704 patients in Manitoba, Canada, over a 12-month follow-up period [5]. IBD patients have been reported to perceive a strong relationship between adverse life events and the course of their IBD [6]. Furthermore, there was a significantly greater proportion of stressful life events among IBD patients with persistently active versus inactive disease, with stress in the family being identified as the most common stressor [7]. Threatening life experiences and chronic stress increase the likelihood of relapse in patients

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with quiescent IBD [8]. Various pathophysiological mechanisms have been suggested by which stress can affect the gastrointestinal immune and inflammatory responses [9,10]. To date, there is insufficient understanding of the role of stressful life events in large community cohorts of CD patients not limited specifically to periods of disease onset or exacerbation.

The term ‘family relations’ includes such topics as members of the family supporting each other in times of crisis, the ability to communicate about sad issues and discuss fears and concerns, making decisions together, planning family activities together, and getting along together. The postulated role for poor family relations as a stressor in CD patients is based on the theory of social capital, defined as ‘the ability of actors to secure benefits by virtue of membership in social networks or other social structures’ [11–13]. This indicates the ability of individuals to overcome life’s difficulties and challenges by using social support. The three main avenues of social support are the family, social institutions, and peers [12,14,15]. Social support has two essential effects: the main effect of benefitting the individual in regular (not stressful) periods and the buffering effect, which mitigates the negative impact of life stressors on the individual’s adjustment during stressful periods. The biobehavioral model emphasizes the role of family support and postulates that both the patient’s reaction to disease and his/her long-term general physical health are influenced by innate psychological strengths and weaknesses and the family’s relationship with the patient [16]. The study of family relations and IBD has hitherto been limited to pediatric patients, where it was shown that good family communication and agreement contributed toward reduced patient psychological distress and better management of the disease [17–22]. However, to date, little is known about the association of family functioning with respect to the medical and psychological condition of adult patients with CD.

Given the expected prominent association of threatening life experiences and poor family relations with the well-being of CD patients, the aim of this study is to examine the association of these two psychosocial stressors with the medical and psychological health of adult patients with CD. To the best of our knowledge, such an examination has not been carried out to date in CD patients.

Patients and methods

Cohort

Our study forms part of a broader ongoing socioeconomic study of CD in the Israeli adult patient population (age 18 years and older) aimed at determining the social and psychological stressors of patients and the economic burden of disease. There were two methods of patient recruitment. Patients with a confirmed CD diagnosis by clinical history, examination, and appropriate endoscopy, radiology, and endoscopy, per ECCO Statement 2B [23], were recruited on a consecutive basis when presenting for follow-up, or for acute (nonhospitalized) care, at the Out-Patient Gastroenterology Departments of five participating university-affiliated tertiary care hospitals located in the north, south, east and west of Israel (Rambam Health Campus, Tel Aviv Medical Center, Soroka Medical Center, Shaare Zedek Medical Center, Tel Hashomer Medical Center). These patients were provided the option of completing the questionnaires on paper or online (one option only) in their own time at home. Patients were also canvassed on the website of the patients’ association ‘The Israel Foundation for Crohn’s Disease and Ulcerative Colitis’ and completed the questionnaires online. Although we could not confirm the diagnosis of CD in these patients as we had no access to their medical records, we assumed that individuals who were registered members of the Foundation would be confirmed CD cases as was the assumption with patients recruited from the Crohn’s and Colitis Foundation of America for an internet-based cohort [24]. Patients were eligible to participate irrespective of the duration or the severity of their illness, and irrespective of their treatment and surgical (if any) history.

Data collection

This was a cross-sectional study and data collection was carried out from July 2013 to June 2015. Patients were asked to report on a variety of sociodemographic characteristics including sex, year of birth, education, place of birth, economic status (patient’s opinion on a scale of 1–5, where 1 = very poor and 5 = very rich), marital status and number of children, religion and religiosity, and current smoking habit.

Patients reported their clinical data, which comprised current medications, anytime surgery for CD, and hospitalizations for CD in the past year. Data on comorbidities including psychological and psychiatric illness were collected from the patients recruited at the hospitals. Patients filled in the Patient Harvey–Bradshaw Index (P-HBI) [25]. This clinical measure of the activity of disease was specifically designed for patients with CD. It consists of four items reflecting the previous day’s symptoms and signs of CD; the question on the physician’s assessment of the possible presence of an abdominal mass in the original HBI [26] is removed in the P-HBI, making the questionnaire suitable for completion by the patients themselves. A total score less than 5 indicates disease remission, a score of 5–7 indicates mild disease, a score of 8–16 indicates moderate disease, and a score of higher than 16 indicates severe disease.

We used self-administered instruments to measure the patients’ health-related quality of life, psychological stress, threatening life experiences, and family relations.

Short Inflammatory Bowel Disease Questionnaire [27]

This instrument, which measures disease-specific quality of life in IBD, has physical (systemic and bowel symptoms), social, and emotional dimensions. It consists of 10 items: each item refers to the last 2 weeks and is rated on a 7° scale (1 = all the time, 7 = never). The total score ranges from 10 to 70. A higher value indicates a better quality of life. The scale was shown to be reliable and valid among Israeli patients who participated in an EpiCom study of IBD epidemiology unrelated to the present research [28]. The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was rated as a ‘well-established’ measure of assessment and showed good test–retest reliability and responsiveness in a recent review of disease-specific health-related quality of life measures [29].

MOS 36-item short-form survey instrument [30]

This generic quality of life measure is comprised of 36 items divided into eight domains, which in turn are grouped as the Physical Health Summary Score (physical functioning, role-physical, bodily pain, general health) and the Mental Health Summary Score (vitality, role-emotional, social functioning, mental health). Responses refer to the past 4 weeks. The range of the Physical or Mental Health Summary Score is 0–100. A higher number indicates a better quality of life. The scale is sensitive to changes in the quality of life in CD patients responding to biologic therapy [31] and was validated in the Israeli adult population [32].

Brief symptom inventory [33]

This instrument is a measure of psychological stress in the past month. It consists of 53 items that assess nine symptomatic dimensions or subscales: depression, somatization, obsession-compulsive, interpersonal sensitivity, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism on a 0–4 scale. Participants rate the extent to which they have been bothered (0 = 'not at all' to 4 = 'extremely') by various symptoms: a higher score implies more distress. The brief symptom inventory (BSI) yields a global summary score (the mean of all of the subscale scores) called the General Severity Index (GSI), with a 0–4 range. In a nationwide sample of 510 healthy Israeli adults (aged 35–65 years, 51.4% women), the mean score of GSI was 0.71 ± 0.63 in men and 0.74 ± 0.56 in women, which in fact was 2.4 times higher than the USA norm [34].

McMaster family assessment device [35]

This measure includes 12 statements that assess the respondent's perceptions of functioning and malfunctioning in the family and of thes different ways in which the family members communicate with each other. The patient's responses refer to the day of completion of the questionnaire and are marked on a 1–4 scale (1 = strongly agree with the statement, 4 = do not agree at all). Higher scores imply more problems in family functioning. A cut-off score of 2.0 distinguishes between healthy and unhealthy family functioning, where a higher score indicates problematic functioning [36].

List of threatening life experiences [37]

This questionnaire measures the amount of negative life experiences in the individual's experience over the last 6 months. The questionnaire consists of a set of 12 life event categories with a long-term contextual threat; each item is answered as 'yes, happened to me in the last 6 months' or 'no, did not happen'. The possible range of responses is 0–12; a higher score indicates exposure to more threatening life experiences. In the nonclinical population, the reported median score of exposure to threatening life experiences during the last year was 1 [38].

Statistics

All data collected by paper and internet questionnaires were pooled in a single database. Patients whose data were deemed eligible for analysis were required to have filled in all 12 questions of family assessment device (FAD) and all 12 questions of list of threatening life experiences (LTE); patients with any missing values were excluded. Descriptive statistics were used to document the results as means ± SD for normally distributed variables; medians (minimum–maximum) and interquartile range (IQR) were used where the probability distribution was not normal. A univariate analysis was carried out to determine the effect of sex and family status on P-HBI, SIBDQ, short-form survey instrument (SF-36), and GSI, and the correlations between P-HBI, SIBDQ, SF-36, and GSI with age, economic status, FAD, and LTE. We used the Mann–Whitney test, *t*-test, and Spearman correlations to test the significance of associations depending on the type of distribution of the data. We then examined the impact of threatening life experiences and the role of family relations on the physical and mental health of patients with CD using multiple linear regression analysis, incorporating variables found to be significant in the univariate analysis. For variables that were not normally distributed, we used multiple linear regressions while modeling the natural logarithm transformations of dependent variables. Furthermore, when transformation did not yield normal distributions, we used multivariable quantile regression for different percentiles [39]. We used regression equations to examine the impact of FAD, LTE, and other variables on disease severity (P-HBI), quality of life (SIBDQ and SF-36), and psychological stress (GSI), which were all treated as dependent variables. Data analyses were carried out using SPSS Statistics 22 for Windows (IBM Corp, Armonk, New York, USA), and the quantile regressions on STATA 12 (StataCorp LP, College Station, Texas, USA). *P* values of less than 0.05 indicated statistical significance for all analyses. All patient data were treated anonymously in terms of patient identity and the source of the data in the final analysis, except that the paper and electronic data were separated before the final analysis to determine whether important differences existed between these two methods of case ascertainment that could bias the final results.

Ethical considerations

The Ethics Committees of all the participating hospitals approved the study and both forms of patient recruitment. The patients attending at the various hospitals signed an informed consent form before receiving the questionnaires. Patients completing the questionnaires electronically on the web-site were informed specifically of the purpose of the study and that their data would be used in the study; they did not supply identifying information or e-mail addresses and were deemed to have agreed to participate in the study.

Results

Demographics and clinical data

A total of 579 patients submitted paper or internet questionnaires. However, 188 patients were excluded as they failed to fill in all 12 questions of LTE and all 12 questions of FAD. Excluded patients were similar in age to the 391 valid patients (37.37 ± 14.94 vs. 38.38 ± 13.95 years, respectively), but there were relatively more women (73.0

vs. 59.6%, respectively, $P=0.003$). The median P-HBI (IQR) was 4 (2–6) among excluded and 4 (2–8) among valid patients ($P=0.329$). SIBDQ and SF-36 scores were similar in the excluded and valid patients. Surgical rates and treatments were not different between these groups.

The final cohort of 391 individuals included 279 (71.4%) patients who completed the paper questionnaire and 112 (28.6%) patients who filled in the internet questionnaire. These groups were similar in age (39.20 ± 14.54 years for paper, 36.32 ± 12.17 years for internet, $P=0.188$) and disease activity P-HBI [median (IQR): 4 (2–8) and 5 (3–9), respectively, $P=0.058$]. In the final cohort, the mean age was 38.38 years, the majority of patients were women, and over half were married or living with a partner (Table 1). Most patients (96.1%) were Jewish and 2.8% were Moslem Arabs. The cohort had a moderate self-declared socioeconomic status, with median 3 on a scale of 1 (lowest) to 5 (highest), and 66.8% were working. In the final cohort, 45.3% of patients reported receiving biologic medication, 33.8% had a history of CD-related surgery, and 25.3% had been hospitalized for CD in the previous year. The median P-HBI of the final cohort was 4, showing that about half of the patients were in a state of disease remission; the range was 0–29 (Table 1). In terms of comorbidities in the patients recruited from the hospitals, it was found that 5.1% of cases had minor illnesses (depression and/or anxiety) and one patient reported having a mild manic state not usually requiring medication.

Psychosocial instruments

The results of the FAD, LTE, SF-36, and GSI questionnaires, expressed as medians, are shown in Table 1; the SIBDQ data were normally distributed and are described as the mean ± SD. The median FAD score was 1.67 (range 1–3.8), indicating a low to moderate level of disturbed family functioning. The median LTE score was 1 (range 0–12). Although half the patients experienced 0 or 1 event in the past month, the other half reported up to 12 such events.

Table 1. Patient characteristics and results of questionnaires (*N* = 391)

Demographics	
Female sex [*n* (%)]	233 (59.6)
Married/partnered [*n* (%)]	239 (61.1)
Age (years) [mean (SD)]	38.38 (13.9)
Median (min–max) (IQR)	34.5 (18–79) (28–45)
Economic status [median (min–max) (IQR)][a]	3 (1–5) (3–4)
Self-administered questionnaires	
Patient Harvey–Bradshaw Index (P-HBI) [median (min–max) (IQR)]	4 (0–29) (2–8)
Family assessment device [median (min–max) (IQR)]	1.67 (1–3.8) (1.3–2.1)
Threatening life experiences [median (min–max) (IQR)]	1 (0–12) (0–3)
Short Inflammatory Bowel Disease Questionnaire [mean (SD)]	47.27 (13.9)
Short-form 36	
Physical health [median (min–max) (IQR)]	43.75 (10.3–62.4) (33.7–51.0)
Mental health [median (min–max) (IQR)]	42.99 (15.4–64.2) (34.1–51.9)
General Severity Index [median (min–max) (IQR)]	0.81 (0–3.2) (0.4–1.4)

Family assessment device (FAD): range 1–4, higher scores indicating worse family relations; list of threatening life experiences (LTE): range 0–12, higher scores indicating more negative life events; Short Inflammatory Bowel Disease Questionnaire (SIBDQ): range 10–70, higher scores indicate a better quality of life; MOS 36-item short-form survey instrument (SF-36), Physical Health and Mental Health Summary Scores: range 0–100, a higher score indicates a better quality of life; General Severity Index (GSI) of the brief symptom inventory: range 0–4, a higher value indicates a higher level of psychological stress.

IQR, interquartile range; max, maximum; min, minimum.

[a] Economic status (self-declared on a scale of 1–5, where 1 = very poor and 5 = very rich).

Two health-related quality of life measures were analyzed. Using the CD-specific SIBDQ instrument, the mean score was 47.27. The generic SF-36 Physical Health and Mental Health Summary Scores showed medians of 43.75 and 42.99, respectively. The median GSI score of 0.81 showed a relatively low level of psychological symptoms in the cohort.

Univariate analysis

In the univariate analysis (Table 2), the median (IQR) P-HBI was 4.0 (2–8) in men versus 4.0 (1–7) in women ($P=0.034$). Furthermore, the values of SIBDQ and SF-36 physical health were also significantly higher among men. The median SF-36 mental health scores were similar in women and men. The GSI was significantly greater in patients who were single or divorced. Although women had a higher median GSI than men, the difference was not statistically different. There were significant correlations of P-HBI with lower economic status, poorer family relations, and more life-threatening experiences (Table 2). SIBDQ correlated positively with the economic status of the patients and negatively with FAD and LTE. SF-36 physical health and mental health were correlated positively with economic status and negatively with age, FAD, and LTE. The GSI correlated negatively with age and economic status and positively with FAD and LTE. We found that the SF-36 and SIBDQ scores were correlated; the correlation coefficients were 0.687 for mental health and 0.713 for physical health.

We also examined the clinical parameters of hospitalization, surgery, and treatment with biologic medication in the univariate analysis. Of these, only hospitalization showed any significant associations. These associations were with P-HBI ($P<0.01$), SIBDQ ($P<0.01$), SF-36 physical health ($P<0.01$), and SF-36 mental health ($P<0.04$), but not GSI. As hospitalization had collinearity with LTE, this variable was not used in the following regression analyses.

Regression analysis

Using regression equations, we examined the impact of FAD, LTE, and other variables on disease severity (P-HBI), quality-of-life scales (SIBDQ and SF-36), and psychological stress (GSI) in the cohort, which were the dependent variables in the models. Quantile regression analysis for selected percentiles of P-HBI (Table 3) indicated that LTE was associated positively with disease severity in all the quantiles and the regression coefficient actually increased progressively as the quantile became greater. Economic status was associated with a reduced P-HBI at the 50% quantile and sex was associated negatively with P-HBI in the 25% quantile. FAD was associated with P-HBI in the 50% quantile.

Regression analysis for SIBDQ showed that age, male sex, and economic status were all significantly positively

Table 2. Associations between P-HBI, SIBDQ, SF-36 physical and mental health, GSI, and sociodemographic and clinical factors: univariate analysis

	P-HBI	
Characteristics	Median (min–max) (IQR)	*P*-value[a]
Sex		
Female	4.0 (0–20) (2–8)	0.034
Male	4.0 (0–29) (1–7)	
Family status		
Couple	4.0 (0–26) (2–8)	NS
Single	4.0 (0–29) (2–7)	
	Correlation coefficient	*P*-value[b]
Age	0.029	NS
Economic status	−0.259	<0.01
FAD	0.129	<0.05
LTE	0.226	<0.01

	SIBDQ	
Characteristics	Mean (SD)	*P*-value[c]
Sex		
Female	45.8 (13.7)	<0.01
Male	49.4 (14.1)	
Family status		
Couple	48.2 (13.8)	NS
Single	45.7 (14.1)	
	Correlation coefficient	*P*-value[b]
Age	0.076	NS
Economic status	0.380	<0.01
FAD	−0.291	<0.01
LTE	−0.327	<0.01

	SF-36 physical and mental health			
	Physical health		Mental health	
Characteristics	Median (min–max) (IQR)	*P*-value[a]	Median (min–max) (IQR)	*P*-value[a]
Sex				
Female	41.63 (10.3–62.4) (31.3–49.9)	0.034	41.79 (16–64.2) (33.2–51.6)	NS
Male	46.45 (16.3–61.2) (37.1–53.1)		44.09 (15.4–63.5) (35.6–52.4)	
Family status				
Couple	41.14 (10.3–62.4) (34.1–51.1)	NS	44.61 (15.4–63.5) (34.4–52.0)	NS
Single	42.38 (10.3–61.6) (31.6–49.8)		40.63 (17.0–64.2) (32.4–51.9)	
	Correlation coefficient	*P*-value[b]	Correlation coefficient	*P*-value[b]
Age	−0.103	<0.01	0.232	<0.01
Economic status	0.297	<0.01	0.343	<0.01
FAD	−0.104	<0.05	−0.386	<0.01
LTE	−0.331	<0.01	−0.297	<0.01

	GSI	
Characteristics	Median (min–max) (IQR)	*P*-value[a]
Sex		
Female	0.85 (0–3.1) (0.4–1.5)	NS
Male	0.72 (0–3.2) (0.4–1.4)	
Family status		
Couple	0.69 (0–3.1) (0.3–1.3)	<0.01
Single	0.98 (0–3.2) (0.5–1.6)	
	Correlation coefficient	*P*-value[b]
Age	−0.147	<0.01
Economic status	−0.348	<0.01
FAD	0.462	<0.01
LTE	0.394	<0.01

P values are two tailed.

Economic status is self-declared on a scale from 1 (very poor) to 5 (very rich).

FAD, family assessment device; GSI, General Severity Index of the brief symptom inventory; LTE, list of threatening life experiences; max, maximum; min, minimum; NS, not significant; P-HBI, Patient Harvey–Bradshaw Index; SF-36, MOS 36-item short-form survey instrument; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

[a] Mann–Whitney test used.

[b] Spearman rank correlation used.

[c] Independent *t*-test used.

associated with increased quality of life in this disease-specific measure, whereas FAD and LTE ($P<0.001$) showed strong negative associations (Table 4). Notably, the R^2 change was the greatest for economic status. A multiple linear regression analysis for log-transformed SF-36 was carried out. Age and LTE showed significant negative associations with SF-36 physical health; by contrast, sex and economic status showed positive associations with physical health (Table 5). Age, sex, economic status, and family status were all associated positively with SF-36 mental health, whereas FAD and LTE were associated negatively with mental health (Table 5). In terms of the quantile regression analysis of the GSI, both FAD and LTE showed highly significant associations across all four quantiles, with the regression coefficients being higher for FAD (Table 6). Age and economic status were associated negatively with GSI at the 25, 50, and 75% quantiles. Family status showed no association with GSI. When we separated the patients with LTE score 0–1 versus LTE score of more than 2, the significance of our findings remained present only at the score of more than 2.

In addition to the above methods, we also carried out a logistic regression analysis; the results were similar to those obtained with the multiple quantile regression analysis.

Discussion

We have examined the impact of threatening life experiences and family relations on the medical and psychological condition, and health-related quality of life, of a large cohort of adult CD patients in Israel. Our principal finding was that patients with better socioeconomic status, fewer threatening life experiences, and better family relations tend to do better in their disease both physically and mentally. These patients had a higher quality of life by the SIBDQ and SF-36 scales, and less psychological stress as measured by the GSI. Patients with fewer threatening life experiences had less disease activity as shown by the P-HBI score. We also found that women had a higher disease activity score than men, and a lower score for SIBDQ and SF-36 physical health.

The relationship between threatening life experiences causing mental stress and the physical health of patients has been studied in diverse medical conditions [40,41]. Severe illness is a prime source of acute or chronic mental stress. It has been shown that the psychosocial factors that are important in influencing the health of CD patients include sex, economic level, ethnicity, and perceived stress. Thus, it was found that psychological stress was associated positively with relapse of CD in a Canadian cohort of 101 patients [41]. Perceived stress was associated significantly with reduced quality of life by the SIBDQ measure in CD patients [42]. Stress has a negative effect on quality of life in CD patients, and is associated with exacerbation of symptoms [6,7,43]. In a study of 80 IBD patients from the UK, 45% of patients cited stressful life experiences as the dominant trigger leading to exacerbation of their illness, whereas anxiety was listed by only 8% [44]. However, current perceived social support was an important independent contributing factor toward the postsurgical quality of life in 86 CD patients in Canada; the authors recommended assessing the degree of social support in screening patients awaiting surgery [45]. In a large

Table 3. Results of quantile regression for selected percentiles of Patient Harvey–Bradshaw Index ($N=383$)

Variables	Regression coefficient (P-value)			
	25%	50%	75%	90%
Age	−0.03 (0.153)	0.01 (0.698)	−01 (0.646)	0.07 (0.275)
Sex (male)	−0.97 (0.022)	−0.86 (0.168)	−0.65 (0.411)	−2.61 (0.073)
Economic status	−0.62 (0.067)	−1.01 (0.002)	−1.19 (0.061)	−0.23 (0.841)
Family status (single)	−0.68 (0.123)	−0.65 (0.372)	−1.17 (0.097)	−1.69 (0.252)
Family assessment device	0.61 (0.068)	0.93 (0.014)	0.20 (0.818)	−0.65 (0.560)
Threatening life experiences	0.27 (0.050)	0.46 (0.019)	0.71 (0.001)	0.84 (0.006)

Table 4. Results of multiple linear regression for Short Inflammatory Bowel Disease Questionnaire score* ($N=383$)

Variables	Standardized regression coefficient	Unstandardized regression coefficient	R^2 change	P-value
Age	0.104	0.104	0.007	0.026
Sex (male)	0.123	3.502	0.021	0.006
Economic status	0.258	4.331	0.151	<0.001
Family status (single)	0.065	1.865	0.000	0.173
Family assessment device	−0.174	−4.553	0.037	<0.001
Threatening life experiences	−0.246	−1.757	0.049	<0.001

*Adjusted R^2 0.253, model significance <0.001.

Table 5. Results of multiple linear regression for log-transformed SF-36: physical health and mental health summary scales ($N=383$)

Variables	Standardized regression coefficient	Unstandardized regression coefficient	R^2 change	P-value
Physical health*				
Age	−0.144	−0.003	0.022	0.003
Sex (male)	0.141	0.084	0.026	0.003
Economic status	0.179	0.063	0.077	<0.001
Family status (single)	−0.004	−0.003	0.002	0.931
Family assessment device	0.032	0.017	0.000	0.519
Threatening life experiences	−0.280	−0.042	0.064	<0.001
Mental health**				
Age	0.271	0.006	0.058	<0.001
Sex (male)	0.096	0.057	0.012	0.028
Economic status	0.216	0.075	0.118	<0.001
Family status (single)	0.119	0.071	0.003	0.011
Family assessment device	−0.276	−0.150	0.081	<0.001
Threatening life experiences	−0.187	−0.028	0.028	<0.001

*Adjusted R^2 0.191, model significance <0.001.
**Adjusted R^2 0.300, model significance <0.001.

Table 6. Results of quantile regression for selected percentiles of the Global Severity Index ($N=383$)

Variables	Regression coefficient (P-value)			
	25%	50%	75%	90%
Age	−0.00 (0.042)	−0.01 (0.005)	−0.01 (0.034)	−0.01 (0.077)
Sex (male)	−0.02 (0.737)	−0.04 (0.648)	−0.10 (0.211)	−0.09 (0.501)
Economic status	−0.12 (0.006)	−0.20 (<0.001)	−0.13 (0.014)	−0.08 (0.316)
Family status (single)	−0.01 (0.832)	−0.12 (0.140)	−0.11 (0.299)	−0.15 (0.306)
Family assessment device	0.39 (<0.001)	0.50 (<0.001)	0.58 (<0.001)	0.60 (<0.001)
Threatening life experiences	0.09 (<0.001)	0.12 (<0.001)	0.17 (<0.001)	0.14 (<0.001)

Norwegian study in healthy persons, with adjustment for age, sex, education, and income, negative life experiences were significantly associated and explained 22.3% of the variance in psychological distress [46]. The association between threatening life experiences and subsequent poor physical functioning was found in multiple countries, including Israel, and was independent of mental disorders [4]. Our results in CD patients are broadly in agreement with these foregoing studies linking stressful life events and the patients' medical condition. It is unclear, however, how stressful life events affect the medical condition of CD patients in terms of altered physiology in the gut, and this requires further investigation.

The importance of good family relations in promoting mental health in both healthy and sick individuals has been the subject of several studies. In a large study of middle-aged individuals in the USA, negative family interactions were shown to predict poor biobehavioral reactivity for anxiety and depression and allostatic load [16]. In other words, in the dysfunctional family, there is failure to support the individual in his/her reaction to disease, which leads to increased stress in the individual. The authors further suggested that disordered bodily function should prompt a search for underlying psychological stress. Poor family functioning was identified as a cause of stress in Iranian female teenagers [47]. Family functioning has been studied in CD and IBD, but these investigations were limited to the pediatric population. Thus, a cohort of youths with CD, half of whom were in clinical remission, was found to show more behavioral and emotional symptoms, particularly depression and anxiety, and these were compounded by family dysfunction (affective involvement by FAD) in some 30% of parents [48]. In another study, 25% of families with children affected by IBD reported difficulties across domains of family functioning [49]. Our study is the first to report the role of family functioning in adults with CD. Our results are consistent with those of the pediatric studies, but clearly much more needs to be researched until the subject is fully understood.

Here, we report that there were significant correlations of age with SF-36 physical and mental health, and with the GSI measure of psychological stress in our cohort. Economic status correlated with P-HBI, SIBDQ, SF-36, and GSI. There are few reported studies on the association of CD with age, demographic, and economic variables. Previous studies in the pediatric age group suggested that several sociodemographic factors, including age, sex, education, and economic status, affect the psychological condition of CD patients [4,5]. Individuals in poor economic straits, not unexpectedly, show more anxiety than those who are better off, and this affects their medical and mental health [50,51]. Socioeconomic deprivation did not influence the severity of CD in a French study, presumably because there is easy access to healthcare facilities in that country [52]. In Israel, all patients have public health insurance by law and healthcare access is generally easy and affordable. Nonetheless, we found that patients with a low economic status reported more severe disease by the P-HBI. With respect to causality, it could be speculated that the burden of having a more severe form of CD prevents those patients from holding better-paying jobs or pursuing higher education. However, in a USA study, economically disadvantaged Black patients with CD reported more difficulty in receiving health care, but their disease was no more severe than White patients with higher incomes [53]. The role of economic status in society in relation to perceived disease activity therefore requires further investigation.

The strengths of our study relate to the cohort, which was large, community based, and country-wide, and the use of advanced statistical methods of handling data that are not normally distributed. Our study, however, has certain limitations. We have carried out a cross-sectional study, and thus we can only present and discuss correlations among factors and not causality. Our patients were almost all Jewish and westernized; therefore, the correlations and associations may be different in Arab and Asian populations. The lack of data on comorbidity in the internet-recruited patients is another limitation, although it is reasonable to assume that they too would have only 5% of patients with mild psychological disturbance, a figure that is unlikely to bias our results. Future studies should address these limitations and consider the use of longitudinal designs to determine the directionality of the observations.

We have used advanced statistical methods in our calculations, while appreciating that their use in epidemiology and medicine is relatively new. The quantile regression [39] models the relationship between independent variables and the conditional quantile (percentile) of quantitative dependent variables. Standard linear regression models, however, describe and estimate the relationships between independent variables and the conditional mean of dependent variables, and require normality of dependent variables and homoskedasticity. This can impose a severe restriction on the analysis of epidemiologic data as such data are often skewed. The central tendency of such data cannot be expressed properly by the mean and is better presented as the median value, as was the case with much of our data. Using quantile regression analysis, we were able to establish the relationships between independent variables and any given conditional percentile of any quantitative outcome, and thus observe dynamic changes in regression coefficients among the different quantile points and obtain a more complete picture of the interrelationships between the variables in our research.

Our study has several important implications for physicians treating CD patients. It is important to examine not only the medical condition of these patients but also their recent and past emotional state, paying special attention to threatening life experiences and family relations as shown here. Furthermore, study of the potential associations between family interactions and the health of CD patients is important because this may lead to counseling interventions for adult patients and their family members on how to manage the disease from the psychological perspective. Clinicians at present do not ask patients about threatening life experiences and family problems, and psychological strategies still have no place in disease management in busy IBD clinics. IBD departments should consider incorporating social support services for individuals reporting adverse family relations and significant exposure to threatening life experiences. We agree with a recent roadmap to the future of practice [54] that this should be part of a comprehensive management plan for such affected patients. The degree of benefit to patients and whether this measure will be cost-saving remain to be determined.

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Conflicts of interest

There are no conflicts of interest.

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