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Observations and Research

The Comorbidity of Patient-Reported Crohn's Disease Activity and Depression: The Role of Health Behavior Mediators

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Background: Longitudinal research reveals a unidirectional relationship between a nonsomatic symptom of depression, a negative view of the self, and later reported Crohn's disease (CD) activity. We evaluated whether health behaviors mediated this association using a longitudinal design.

Methods: We studied 3304 adult volunteers with a self-reported diagnosis of CD who completed a baseline survey that included demographics, CD activity, a symptom-specific index of depression, and measures of physical activity, smoking, and sleep quality. Crohn's disease status and the cognitive index of depression were also measured 6 and 12 months after the baseline evaluation. We specified single-mediator and multiple-mediator models to elucidate the depression–disease activity relationship.

Results: Among 2395 females and 909 males, we found a significant mediation effect for activity level ($P < .001$) after adjusting for age, sex, and body mass index. There was no evidence that sleep quality and smoking are significant single mediators. When we considered multiple mediation models, smoking and less activity partially mediate the depression–CD association.

Conclusions: Smoking and lower levels of physical activity are potential mediators of the unidirectional association between a nonsomatic symptom of depression—a negative view of the self—and patient-reported CD activity. Evaluating and treating specific symptoms of depression may reduce the frequency of CD exacerbations.

Lay Summary

This study investigated whether depression changes health behaviors and results in increased Crohn's disease activity. Findings show depression seems to worsen Crohn's disease by increasing harmful behaviors such as smoking and decreased physical activity but are not large single mediators.

Key Words: depression, Crohn's disease, health behavior, mediators

Background

Crohn's disease (CD) is an autoimmune disorder with gastrointestinal and extraintestinal manifestations and well-known psychological comorbidity.[1] Epidemiological studies of the comorbidity of CD and psychological factors have focused primarily on the mood of patients with existent CD. The study of the depression–CD relationship is important because several lines of research show that depression is associated with negative patient-reported experiences, including lower quality of life,[2] medical nonadherence,[3,4] use of more services, and more expensive services.[5]

There is mounting evidence to support the notion that the relationship between CD activity and depression may be reciprocal in nature.[6,7] Not only do CD symptoms cause depressive symptoms, but the reverse may also be true with depression leading to worsening CD activity and symptoms. This bidirectional relationship may be mediated by neuroendocrine pathways including the hypothalamic–pituitary–adrenal axis and other pro-inflammatory effects of depression. Although the results suggest that there is a bidirectional connection between CD in remission at baseline and depression, more research is required to understand the complexity of the association between CD and depression. For example, a longitudinal study revealed that there is a unidirectional relationship between depression when measured in terms of a nonsomatic depressive symptom and subsequent patient-reported changes in CD.[8] The study's findings have been tested to evaluate the possibility of reverse causality as an explanatory factor.[9] There was no

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evidence to support the alternative hypothesis that higher levels of depression, that is, a negative view of the self, are caused by earlier CD activity, resulting in increased patient-reported CD activity in a bidirectional relationship. From the limited data available, it appears that there may be conflicting findings on the dynamic connection between depression and CD, depending on the research methodology employed.

Our research aimed to explore if health behaviors mediate the connection between depression and CD, particularly when depression centers on a negative view of the self. Our study's main hypothesis is that depression affects a person's health habits, which then has a negative effect on their self-reported CD activity. Prior research has demonstrated that depression is associated with smoking,[33] sleep quality,[34] and physical activity,[35] and we considered these health behaviors as candidate mediators. This theory suggests that individuals with CD may have negative self-perceptions, which can lead to a psychological vulnerability that impacts their reported CD activity due to negative health behaviors. This psychological vulnerability can create a harmful feedback loop in which an increased negative view of the self leads to poor self-care, such as reduced physical activity, smoking, and sleep disturbances, ultimately resulting in increased CD activity.[8]

Methods

Study Sample

Participants (N = 3307; 2397 females, 910 males) were recruited nationally through the Crohn's and Colitis Foundation of America's (CCFA) email roster, social media, and at educational and fundraising events. Inclusion criteria included the age of 18 years, a self-reported diagnosis of IBD, access to the Internet, and the ability to complete informed consent and surveys in English. After enrollment, participants completed surveys at baseline and at 6-month intervals to capture health behaviors, treatments, and patient-reported outcomes. A brief description of CCFA Partners is described in earlier research reports.[10] In this analysis, we included IBD Partners participants with a diagnosis of CD and complete data for the baseline, 6-month follow-up, and 12-month follow-up surveys.

Measures

Depression was measured using the NIH's Patient-Reported Outcomes Measurement Information Systems (PROMIS) 4-item form on depression.[11] The short form was composed of 4 Likert-type 5-point items measuring the frequency of negative view of the self (I felt hopeless, I felt helpless, I felt worthless), and negative mood (I felt depressed) during the previous 7 days. Psychometric analyses of the PROMIS short Depression Scale show internal consistency and dimensionality consistent with viewing the scale as principally measuring 1 depressive symptom, a negative view of the self.[12,13] For all PROMIS measures, the t-score for the standardized population is 50 with an SD equal to 10. Higher scores represent more of the concept being measured. The primary predictor was this measure of depression at baseline.

Disease activity was measured at baseline, 6 months, and 12 months by the short Crohn's Disease Activity Index (sCDAI),[14] a patient-reported measure. Disease activity was modeled as a continuous sCDAI score where higher scores are correlated with more disease activities. The sCDAI was developed to provide a shortened and simplified CD Activity Index using patient self-reports. The primary outcome was disease activity as measured by this form at 12 months.

All potential mediators were measured at the 6-month follow-up. Sleep quality was measured with a subset of 4 questions from the NIH's PROMIS 4-item sleep quality questionnaire.[15] Subjects were asked if over the past 7 days: (1) Their sleep quality was good,[2] their sleep was refreshing,[3] they had a problem with their sleep,[4] and they had difficulty falling asleep. Responses were scored on a 5-point Likert scale. The sum of scores was normalized to a t-score with a mean of 50 and an SD of 10. The lower the score the better the quality of sleep. Smoking status was defined as current smoking or not. Physical activity/exercise was measured with the Godin leisure-time activity index to assess exercise behavior.[16] The weekly leisure activity score is calculated by the following formula: Weekly leisure activity = (9 × strenuous) + (5 × moderate) + (3 × light) for at least 15 minutes each time.

Statistical Analysis

Continuous variables were summarized using the median, 25th, and 75th percentiles, and categorical variables were summarized using percentages. Pearson correlations were used to estimate the bivariate associations between depression, disease activity, and 3 prespecified mediators.

Single and multiple mediation models were considered using the baseline, 6-month, and 12-month follow-up data. Depression at baseline was the predictor of interest, mediators were assessed at 6 months, and disease activity at 12 months was the outcome. To establish and estimate the mediation effect, we utilized the 4 steps originally outlined by Barron and Kenny.[17] First, we tested that there was a significant effect of depression at baseline with disease activity at 12 months to establish there was an effect to be mediated. Second, we estimated the correlation between depression at baseline and each of the potential mediators measured at 6 months. Third, we tested if each of the mediators at 6 months was associated with disease activity at 12 months while controlling for disease activity at baseline. Fourth, the mediation package in R was used to estimate various quantities for causal mediation analysis, including average causal mediation effects (indirect effect), average direct effects, proportions mediated, and total effect.[18] This step involves combining estimates from the mediator model (mediator at 6-month outcome, depression at baseline the predictor) and estimates from the outcome model (disease activity at 12-month outcome, mediator at 6 months and depression at baseline as predictors of interest, and controlling for disease activity at baseline) efficiently and with appropriate standard error estimates.[19] In the mediation and outcome models, we also considered adjusted models that additionally controlled for age, body mass index (BMI), and sex. Linear models were assumed for all mediation and outcome models, except for the smoking status mediation model which used logistic regression. For single mediation models, confidence intervals (CIs) and significance tests were estimated nonparametrically using Bootstrap with 1000 replications. Multiple mediation models were estimated using structural equation models and fit in Stata. We include the multiple mediation model results as a companion to the single-mediator models to evaluate the robustness of the findings to different

model assumptions. Most notably, the structural equation model assumes normality, allows for correlation among the mediators, and does not adjust for baseline disease severity or other covariates. All models were prespecified and the results are presented regardless of statistical significance.

For single-mediator models with significant mediation effects, we conducted additional sensitivity analyses to evaluate the impact of unmeasured confounding on the estimated mediation effect.[20] This analysis estimates the magnitude of the unmeasured confounding that would need to be present for the estimated mediation effect to be no longer significant. The sensitivity analysis can be used to assess the robustness of the findings to the violation of sequential ignorability, the crucial identification assumption necessary for the estimates to be valid. The analysis proceeds by quantifying the degree of sequential ignorability violation as the correlation between the error terms of the mediator and outcome models and then calculating the true values of the average causal mediation effect for given values of this sensitivity parameter, rho. The original findings are deemed sensitive if the true effects are found to vary widely as a function of rho.

Results

Baseline descriptive statistics for the subjects completing baseline, 6-month follow-up, and 12-month follow-up are compared to subjects excluded due to incomplete information in Table 1. Included subjects were predominantly female (72%) and White (95%) with a median age of 43 and BMI of 24. The median duration of the disease was 18 years before study entry. Compared to excluded subjects, the included subjects were slightly older and more likely to be White. Bivariate associations between baseline depression (predictor of interest), the 3 putative mediators (smoking, physical activity, and sleep quality), and disease activity are presented in Table 2. Results in the first column of Table 2 establish the first and second steps necessary for being able to test mediation effects. First, there is an effect to be mediated as there was a significant association of baseline depression with disease activity at 12 months (r = 0.32, P < .001). Second, the proposed mediators are plausible in that there are significant associations of baseline depression with smoking (r = 0.13, P < .001), activity (r = –0.14, P < .001), and sleep (r = 0.04, P < .05) at 6 months. Bivariate correlations among mediators were small, ranging between –0.07 and 0.03.

Table 1. Characteristics of the included and exclude subjects at baseline.

Characteristics	Included (N = 3307)	Excluded (N = 12 202)
Sex		
Male	28%	29%
Female	72%	71%
Race		
White	95%	92%
Other	5%	8%
Age (years)	43 (30–56)	41 (30–53)
Age at diagnosis (years)	25 (19–36)	26 (19–36)
Body mass index	24 (22–28)	24 (22–28)
Current smoker	7%	8%
Activity level	24 (9–39)	Missing
Sleep disturbances	52 (50–52)	Missing
Depression	52 (41–57)	Missing

Continuous variables summarized as Median (25th percentile–75th percentile).

Results from separate, single mediation models are summarized in Table 3. For each of the mediators, the average causal direct effect (ACDE) is the adjusted regression coefficient of depression at baseline on disease activity at 12 months controlling for the mediator and baseline disease activity. For activity level, the ACDE was 0.89 indicating that controlling for activity, a 1-point increase in depression score is associated with a 0.89-unit increase in future disease activity. Our hypothesis was that in addition to the ACDE, depression affects future activity levels which in turn affects future disease activity, which is presented as the average causal mediated effect (ACME) in Table 3. The Total Effect is the sum of the ACDE and ACME, and the percent mediated is the ACME divided by the Total Effect. We found a significant mediation effect for activity levels (P < .001) and estimate that 6.8% (95% CI, 2.9%–13%) of the effect of depression on disease activity goes through physical activity when adjusting for only baseline disease activity. If we additionally adjusted for age, sex, and BMI, the proportion mediated remained significant (4.7%, 95% CI, 0.9%–11%). In sensitivity analyses, the mediated effect would be null if rho is 0.06. For sleep quality (P = .41) and smoking (P = .89), there is no evidence that these variables are significant single mediators. For sleep quality, we can also rule out large mediation effects as the upper limit of the 95% CI was only 2% mediated.

When we considered a multiple mediation model estimated using structural equations, similar results were found for activity and sleep quality, but smoking was also a potential mediator. Results from the multiple mediation models are shown in Figure 1. The estimated Total Effect of depression at baseline on disease activity at 12 months was 2.90 (P < .01), so for every 1-point increase in depression score, disease activity increased by 2.90. The total effect of 2.90 was partitioned into 3 paths that go through the mediators (the sum of the 3 paths was 0.25, 9% mediated) and a path that does not involve the mediators (2.65, 91% not through the mediators). Of the total mediation effect of 0.25 units, 0.11 was mediated through activity (P < .01; 3.7% mediated) 0.14 through smoking (P < .01; 4.7% mediated), and 0.01 through sleep quality (P = .44; 0.2% mediated), that is, smoking and less activity mediates depression. Baseline depression was related to the mediators such that a 1-point increase in depression score was associated with a 0.014-point increase in sleep disturbance, a 0.35% increase in the probability of smoking, and a 0.32-unit decrease in activity levels at 6 months. The mediators were associated with disease activity at 12 months. A 1-point increase in sleep disturbance was associated with a 0.36-unit increase in disease activity, a smoker had on average 39.65 points higher disease activity than a nonsmoker, and a 1-point increase in physical activity decreased disease activity by 0.34 units.

Discussion

As far as we know, this study is the first to explore whether health behaviors could be mediators for the comorbid relationship between a nonsomatic aspect of depression and later

Table 2. Bivariate Pearson correlation coefficients among depression, mediators, and disease activity.[1–5]

Variable	1	2	3	4	5
1. Depression, baseline	—	—	—	—	—
2. Smoking, 6 months	0.13**	—	—	—	—
3. Activity, 6 months	−0.14**	−0.07**	—	—	—
4. Sleep, 6 months	0.04*	0.03	0.02	—	—
5. Disease activity, 12 months	0.32**	0.16**	−0.13**	0.02	—

Correlations not provided (dashes) if the correlation is 1 or redundant. Column header labels omitted for brevity and correspond to numbered rows.
*$P < .05$;
**$P < .001$.

Table 3. Regression coefficients from separate, single causal mediation models of depression at baseline on disease activity at 12 months.

Mediator	Effect	Estimate	Lower CI	Upper CI	*P* value
Smoking	ACME	−0.02	−0.10	0.13	.89
	ACDE	0.89	0.55	1.23	<.001
	Total effect	0.87	0.55	1.25	<.001
	Prop. mediated	−1.8%	−15%	15%	.89
Activity	ACME	0.06	0.00	0.07	<.001
	ACDE	0.89	0.53	1.22	<.001
	Total effect	0.96	0.85	1.29	<.001
	Prop. mediated	6.8%	2.5%	14%	<.001
Sleep	ACME	0.01	−0.01	0.02	.41
	ACDE	0.93	0.60	1.28	<.001
	Total effect	0.94	0.60	1.28	<.001
	Prop. mediated	0.6%	−0.7%	2.0%	.41

ACME, average causal mediated effect, baseline depression with disease activity through mediator.
ACDE, average causal direct effect, baseline depression with disease activity *not* through mediator.
Total Effect: ACME + ACDE, baseline depression with disease activity at 12 months, all pathways.
Prop. Mediated: Proportion of total effect of depression on disease activity going through the mediator. ACME/ Total Effect.

patient-reported CD activity. Consistent with the hypothesis that health behaviors may be mediators of the relationship between depression and patient-reported CD activity, physical activity and smoking were mediators. The result begins to fill the gap in our understanding of how a nonsomatic depressive symptom—a negative view of the self—may contribute to the worsening of CD albeit patient-reported. Specifically, CD patients with negative views of the self at baseline were physically less active and more likely to smoke at 6 months, and more likely to report increased CD activity at 12 months. These findings are highly clinically relevant, as they suggest that identification and treatment of depression, specifically an improvement in the view of the self, may set in motion more healthy behaviors and lead to better CD control over time.

Our study is novel since it employed a measure specifically crafted to circumvent physical manifestations of depression; depression was measured as a negative view of the self. Other studies have used a symptom-specific approach to the measurement of depression to study the comorbidity of CD and depression,[21] which is appropriate given its phenotypic heterogeneity.[22] Studies have found a bidirectional relationship by using anhedonia as a specific symptom in the depression subscale of the Hospital Anxiety and Depression Scale (HADS) questionnaire.[23] HADS questionnaire depression subscale items are *I still enjoy the things I used to enjoy*; *I can laugh and see the funny side of things*; *I feel cheerful*; *I feel as if I am slowed down*; *I have lost interest in my appearance*; *I look forward with enjoyment to things*; *I can enjoy a good book or radio or TV program*. These different approaches to studying the comorbidity of CD and depression indicate that the comorbidity depends on why CD and depression are thought to co-occur. In studying health behaviors as possible mediators, we found that negative views of the self can stimulate risk factors for CD exacerbations through health behaviors leading to epigenetic and neuroendocrine pathways through to determinates of CD activity.[24] Health behaviors have previously been considered as playing a part in understanding the relationship between depression and inflammation.[25] However, until recently, studies on depression and CD focused on the degree of association between the 2 health problems, rather than how specific depressive symptoms affect mechanisms that bring about change in CD activity. This study highlights the importance of exploring how different depressive symptoms are linked to intervening processes and self-reported CD activity. Focusing on CD patients' health behaviors could greatly improve their quality of life.

Depression and CD comorbidity will be better understood by studying diverse depressive symptoms, health behaviors, and epigenetic and immunological processes that mediate some of the relationships between a symptom-specific aspect

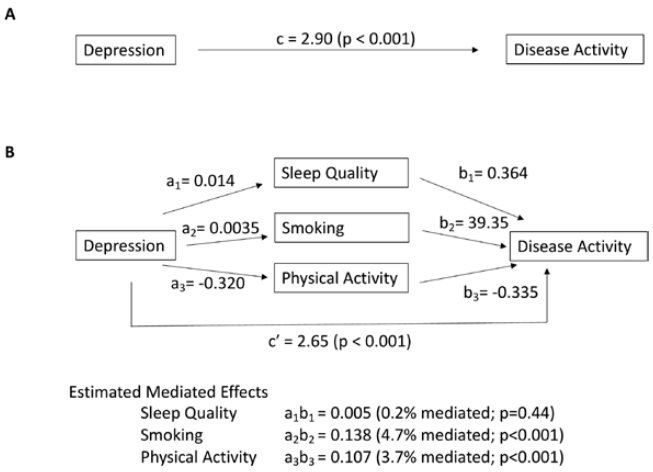

Figure 1. Multiple mediation model path diagram and estimates from structural equations model. Part A shows the total effect of depression at baseline on disease activity at 12 months is that, per 1-unit increase in depression, disease activity increases by 2.90. Part B shows the associations of depression at baseline, mediators at 6 months, and disease activity at 12 months. Individual mediation effects are found by multiplying *a* by *b* for each mediator. Of the 2.90 total effect, 0.005 went through sleep, 0.138 went through smoking, and 0.107 went through activity. Summing these 3 values, a total of 0.250 (8.6% mediated), when through the 3 mediators.

of depression and patient-reported CD activity. Over time, these interacting processes may have identifiable consequences that represent a heightened vulnerability to increased disease activity. Advances in understanding the comorbidity of depression and CD need to include a more detailed examination of the vulnerability underlying the exacerbation of CD. In addition, greater concern for the clinical measurement of CD activity is also warranted so as to include more detailed access to patients' experience of their CD activity.

A significant advantage of the study was implementing an action theory that supported the proposed mechanisms and explained why the exposure was expected to impact the suggested mediators, although epigenetic and immunological mechanisms were not measured. We used a longitudinal design with 3 prospective time points, thus allowing us to appropriately incorporate the temporal ordering of all measures in the modeling of mediation.[26] We used a survey methodology that avoided sampling bias associated with clinical samples. We used a measure of depression that accords well with a developmental analysis of the manifestation of depressive symptoms.[27,28] We also analyzed sCDAI as a continuous variable to minimize type 2 error associated with the common practice of dichotomizing the distribution of the outcome measure.[29,30]

The present study has several potential limitations that may limit the conclusions. We controlled for baseline disease activity, age, BMI, and sex, but other variables could confound the observed associations. One limitation that can be corrected in future research is the generalizability of the sample. The present sample consisted of subjects who were disproportionately highly educated, White women who remained in the cohort for the baseline assessment, 6-month follow-up, and 12-month follow-up. We do not know if the CD patients were taking antidepressants or psychotherapy and their experience of stress, and CD diagnosis was self-reported. As to the research design, future studies should have more assessment intervals and the intervals need to be briefer. Obtaining finer views of the relationship between patients' view of the self, health behaviors, and disease activity will provide a better picture of one of the psychosocial elements causally related to CD exacerbations.[31] The inclusion of biomarkers of epigenetic and immunologic processes will be immensely useful in understanding how health behaviors impact CD. Examination of the impact of age and illness duration will also be informative about the dynamics of comorbidity of depression and CD over time. Finally, a more precise estimation of the magnitude of mediation, that is, the size of indirect effects, can be obtained by reducing measurement error with multimethod measurements of depression, health behavior, and disease activity.[32]

In conclusion, depression-related health behaviors influence change in patient-reported CD activity and represent a liability for the exacerbation of CD. As depression is relatively treatable, particularly a negative view of the self, efforts to improve the screening, diagnosis, and treatment of this common comorbidity may have a profound impact on health behaviors and on the mental and physical health of patients with CD.

Author Contributions

L.S.G. and J.C.S. had full access to all the data in the study and took responsibility for the integrity of data and the accuracy of the data analysis. Study concept and design: L.S.G. Acquisition of data: M.D.K. Statistical analysis: J.C.S. Analysis and interpretation: J.C.S. and L.S.G. Drafting of the manuscript: L.S.G., J.C.S., M.D.K. A critical review of the manuscript for important intellectual properties: All the authors.

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Conflicts of Interest

There are no conflicts of interest to disclose for all named authors. The study protocol was approved by the Institutional Review Boards at the universities where the data was collected and analyzed, respectively.

Ethical Considerations

The manuscript, along with its related data, figures, and tables, has not been published before, and it is not being reviewed by any other source.

Data Availability

IBD Partners and SPARC IBD data can be made available, upon request, by contacting the IBD Plexus program at the Crohn's & Colitis Foundation. https://www.crohnscolitisfoundation.org/research/grants-fellowships/ibd-plexus.

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