Perceived Stress, Its Physiological Correlates, and Quality of Life in Patients With Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is a chronic, common disorder of the gastrointestinal tract associated with high psychological comorbidity and diminished quality of life. Patients with IBS display a heightened sensitivity to stress, although the literature is inconsistent as to whether they have a dysregulated stress response. The purpose of the present investigation, a substudy of a larger research effort, was to examine physiological correlates of perceived stress in patients with IBS (cortisol and adrenocorticotrophic hormone) and to explore associations between perceived stress and quality of life. A total of 101 participants (35 with IBS [predominant subtypes IBS-constipation and IBS-diarrhea] and 66 healthy controls [HCs]) completed self-report inventories regarding perceived stress and quality of life, and fasting peripheral blood was drawn. Participants with IBS did not differ from the HC in demographic or physiological measures but did differ in psychological measures, reporting significantly higher levels of perceived stress and lower levels of quality of life. Perceived stress and quality of life were not significantly associated in IBS participants. However, differential findings of the stress response were found within IBS participants by sex, race, and subtype. These findings illustrate the heterogeneity of the IBS patient population, underscore the necessity of evaluating larger sample sizes and increasing the diversity of such samples to include males and ethnic minorities, and demonstrate the importance of taking an individualized approach to evaluation and treatment in the IBS patient population.

Keywords

irritable bowel syndrome, perceived stress, quality of life, HPA axis, sex differences

Irritable bowel syndrome (IBS) is a chronic, common disorder of the gastrointestinal (GI) tract associated with high psychological and medical comorbidity, increased health-care utilization, decreased work productivity, and diminished quality of life (Ballou, Bedell, & Keefer, 2015). IBS is diagnosed according to a system-based classification system, the Rome Criteria, and is characterized by abdominal pain and disordered bowel habits (Lacy et al., 2016). It is classified into four subtypes based upon patients' predominant stool pattern: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), or if unable to be accurately characterized, IBS-unclassified. The cause of IBS is acknowledged as multifactorial in nature, with proposed contributors including gut dysbiosis, bowel motility dysfunction, altered visceral sensitivity, immune activation, and genomic associations (Enck et al., 2016). Alterations in the hypothalamic-pituitary-adrenal (HPA) axis, a component of the central stress response, have also been implicated in IBS, although often with inconclusive evidence (Vidlock et al., 2009). Given the heightened stress sensitivity that patients with IBS characteristically display as well as the adverse consequences of IBS for

patients' quality of life, the purpose of this investigation was to examine physiological correlates of perceived stress in patients with IBS and to explore associations between perceived stress and quality of life in this patient population.

Research investigations of the stress response often include two markers of the HPA axis, cortisol, and adrenocorticotrophic hormone (ACTH). Findings have been discordant, however, in patients with IBS. Research has found that women with IBS display lower baseline levels of ACTH in comparison to healthy controls (HCs) and tend to display higher levels of

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cortisol both at baseline and in response to a physical stressor (Chang et al., 2009). In response to the Trier Social Stress Test (TSST), a psychosocial stressor, women with IBS (without psychopathology) displayed diminished cortisol reactivity compared with HC and scored higher on psychometric measures of stress (Suarez-Hitz et al., 2012). In another investigation employing the TSST, researchers found that female patients with IBS experienced a sustained HPA axis response of cortisol output in comparison to HC (Kennedy, Cryan, Quigley, Dinan, & Clark, 2014). Authors have reported a blunting of the stress response in patients with IBS, in that these patients experience diminished levels of ACTH and cortisol following an acute physical stressor in comparison with HC (FitzGerald, Kehoe, & Sinha, 2009). In another study, however, researchers observed no differences in cortisol levels between patients with IBS and HC, either at baseline or after a conditioned pain modulation experiment, although patients with IBS did report higher levels of daily stress (Jarrett et al., 2014). Lastly, research has shown that the stress response of patients with IBS differs based upon sex, in that males with IBS exhibit an increased cortisol response after ACTH administration when compared with male HC, whereas females with IBS exhibit a decreased response when compared with female HC (Videllöck et al., 2016).

Inconsistencies in the literature regarding the stress response of patients with IBS, however, need to be viewed in light of the heterogeneity of such research investigations. The timing of measurements (baseline vs. after a stressor), the type of stressor (physical vs. psychosocial), the type of specimen (saliva vs. peripheral blood), and the type of subject (male vs. female) all potentially influence the noted variability of the stress response in patients with IBS. Although the aforementioned investigations varied in design and methodology, their findings do suggest that patients with IBS experience an altered stress response, as evaluated through markers of the HPA axis and through patient self-report, when compared with HC. Such findings are relevant to clinical interventions, for if an association, or conversely, a disassociation, is found between patients' subjective reports of stress and objective markers of that physiological state, treatments can be tailored accordingly to optimize patient outcomes.

Poor treatment response and greater impairments in quality of life have been associated with comorbid psychopathology; importantly, research has shown that patients with IBS experience comorbid psychological disorders at rates of 40–60% or higher in centers of tertiary care (Dekel, Drossman, & Sperber, 2013). Psychological factors, such as somatization and catastrophizing, have been associated with IBS symptom severity (van Tilburg, Palsson, & Whitehead, 2013). Moreover, catastrophizing and specific illness representations have been associated with impairments in health-related quality of life (Sherwin, Leary, & Henderson, 2016). Notably, one investigation found that representations that patients with IBS hold about their illness (both cognitive and emotional) mediate the connection between bowel symptom severity and quality of life (De Gucht, 2015).

IBS symptom severity has been associated not only with self-ratings of health from patients with IBS but also with social, psychological, and extraintestinal somatic factors (Lackner et al., 2014). Furthermore, researchers have shown that body weight is related to abdominal pain severity in patients with IBS (Fourie et al., 2016), although a clear association between obesity and IBS has not yet been elucidated (Pickett-Blakely, 2014). Therefore, given the relevance of patient perceptions and representations for symptomatology and measures of quality of life as well as the diversity of findings regarding the stress response of patients with IBS, we set forth the following aims for the current investigation: (1) to examine the physiological correlates of perceived stress, (2) to explore associations between IBS patients' perceptions of stress with quality of life, and (3) to examine the influences of demographics, socioeconomic factors, and body mass index (BMI) upon IBS patients' perceptions of stress, quality of life, and objective physiological markers of the stress response.

Method

Recruitment and Study Participants

Males and females between 13 and 45 years of age were recruited to an ongoing natural history protocol at the National Institutes of Health (NIH) in Bethesda, MD (ClinicalTrials.gov Identifier NCT00824941). The objective of this parent protocol is to evaluate the pathophysiology and GI symptoms of chronic abdominal pain (CAP) at the molecular level and to assess the relationship between intestinal inflammation and CAP. The hypothesis of the parent investigation is that an inflammatory mechanism underlies CAP of unknown etiology, and it therefore tests this relationship in both normal—and overweight participants with CAP and in both normal—and overweight HC. Recruitment efforts included the use of flyers, protocol listing on clinicaltrials.gov, referral from health-care providers, mass-media strategies (including radio announcements, local newspaper ads, bulletin-board postings, and social media) in addition to the Patient Recruitment and Referral Center of the NIH. Upon initial participant inquiry, researchers provided a study explanation and performed an initial screening interview via telephone to cover inclusion/exclusion criteria. Participants with CAP were required to have a history of abdominal pain for greater than 6 months prior to study enrollment, and all females were required to have had onset of menses at least 2 years prior to study participation and have regular monthly cycles.

Participants were excluded if they had evidence of organic GI disease (including biliary disease, inflammatory bowel disease, etc.); prior GI surgery; evidence of pulmonary, renal, endocrine, cardiac, neurologic, or gynecological pathology; or if they had been diagnosed with a severe psychiatric or comorbid pain condition. Exclusion criteria also included taking daily medications for GI symptoms or medications that act on the serotonergic, catecholaminergic, or cortisol systems. Participants were also excluded if they consumed greater than 300 mg of caffeine in the evening or afternoon, consumed

greater than two alcoholic beverages a day, or engaged in shift work (working during the night or late evening).

Procedures

Participants deemed eligible for study inclusion (both participants with CAP and participants to serve as HC) were scheduled for a first visit to the Clinical Research Center between 8 a.m. and 11 a.m. and instructed to have fasted for the previous 12 hr. The morning appointment was timed for all participants out of consideration for the circadian rhythms of certain biomarkers (e.g., cortisol, ACTH), and the visit was performed between Days 3 and 10 of female participants' menstrual cycles. This scheduling was an attempt to minimize the potential for fluctuating hormone levels to influence female symptomatology. Research staff obtained written consent for study participation including the storage and use of biological samples for research purposes. For participants between the ages of 13 and 17 years, the participant provided assent, and their parents/guardians provided written consent. Phlebotomy technicians drew fasting, peripheral whole blood via venipuncture, and staff at the Department of Laboratory Medicine at the NIH analyzed the samples for cortisol and ACTH levels. Trained personnel assessed participant height and weight in order to calculate BMI (in kg/m²). Clinical practitioners (physician or nurse practitioner) performed a history and physical examination upon all participants and evaluated CAP participants for IBS per Rome III criteria. The present investigation included data only on those CAP participants who met criteria for IBS, in addition to HC. All participants underwent a second study visit a few days after the first to complete the collection of psychological and physiological data.

Study Measures

Participants completed self-report inventories through <http://braingutstudy.ninr.nih.gov/>, with questionnaires and website monitored by the Clinical Trials Database. This database houses protocol data, is protected by two firewalls, and may only be accessed by preauthorized users. Study measures included a standard sociodemographic questionnaire to report age, sex, race, years of formal education, total annual household income, and whether income met one's needs. Parents or guardians with whom participants lived, if present, were able to provide assistance in answering questions relating to household income. Among the inventories completed per study protocol were the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) and the IBS quality of life (IBS-QOL) measure (Patrick, Drossman, Frederick, DiCesare, & Puder, 1998).

PSS. The PSS evaluates the degree to which the respondent appraises situations in her or his life, within the past month, to be stressful. The PSS was designed for use in community samples and may be used to evaluate the role of stress in behavioral disorders and disease etiology. The original measure consists of 14 items, with subsequent versions consisting of 4

and 10 items. Each item is scored from 0 (*never*) to 4 (*very often*), with total PSS score calculated by tallying scores across the negative items and adding the reverse scores of the positive items. Psychometric evaluation of the tool has found it to be reliable (estimates across two samples of college students and one sample of a smoking-cessation group: Cronbach's $\alpha = .84-.86$; Cohen et al., 1983), and there is evidence of concurrent and predictive validity. A study assessing social relationships and IBS outcomes employed the 4-item PSS (Lackner et al., 2013), while investigators have successfully used the 10-item PSS, which we used in the present study, in related investigations of stress (Liston, McEwen, & Casey, 2009).

IBS-QOL measure. The IBS-QOL assesses specific concerns of IBS patients that are omitted in standard quality-of-life inventories. The IBS-QOL consists of 34 items in which respondents rate how much a statement describes their feelings within the past month. Responses are scored along a 5-point Likert-type scale and then transformed to a 0–100 scale. Psychometric evaluation of the tool confirmed internal consistency/reliability (Cronbach's $\alpha = .95$), reproducibility (intraclass correlation = .86), and convergent and discriminant validity, and a factor analysis revealed a substructure of eight factors: social reaction, food avoidance, dysphoria, body image, relationships, interference with activity, sexual and health worry (Patrick et al., 1998). Subsequent study provided longitudinal construct validity of the IBS-QOL (Drossman et al., 2000).

Statistical Analysis

We performed statistical analysis of the data using SPSS Version 24 (IBM Corp., released 2015, Armonk, NY), with level of significance set a priori as $p < .05$ for primary analyses. Preliminary data analysis was performed to determine distributions of normality prior to further analyses. Nonparametric techniques (Mann–Whitney *U*, Kruskal–Wallis, Spearman's ρ) were employed for nonnormally distributed data and subgroup analysis of small samples ($n < 30$), and significance level for post hoc tests was adjusted for multiple comparisons. Independent-groups *t* tests were used to assess for differences between groups (IBS and HC) in demographic, psychological, and physiological data points. To address the study's aim of investigating physiological correlates of perceived stress, we created a multivariate linear regression model with cortisol, ACTH, and IBS diagnosis as independent variables and with PSS scores as the dependent variable. In addition, we created a logistic regression model with IBS grouping as the dependent variable and with cortisol, ACTH, and PSS scores as independent variables. We examined regression diagnostics for both models to assess for unusual data, influential data, and model fit (including the use of scatterplots and P–P plots of regression standardized residuals). To address the study's aim of examining associations between participants' perceived stress and quality of life, we performed Pearson's correlation coefficient between PSS scores and IBS-QOL scores. We did not include inventories in the statistical analysis if participant responses

Table 1. Demographic and Clinical Characteristics of Study Participants.

Variable	Total N = 101	HC n = 66	IBS n = 35	p
Age (years), mean $\pm$ SD	27.83 $\pm$ 7.74	28.06 $\pm$ 7.88	27.40 $\pm$ 7.57	.685
Sex, male, n (%)	48 (47.5)	34 (51.5)	14 (40.0)	.301
Race, n (%)				.737
Asian	16 (15.8)	11 (16.7)	5 (14.3)	
African American	28 (27.7)	20 (30.3)	8 (22.9)	
Caucasian	47 (46.5)	28 (42.4)	19 (54.3)	
Mixed/other	10 (9.9)	7 (10.6)	3 (8.6)	
Years of formal education, ^a mean $\pm$ SD	15.66 $\pm$ 3.74	15.75 $\pm$ 3.50	15.48 $\pm$ 4.19	.745
Total annual income, ^a n (SD)				.436
$\leq$ US\$10,000	7 (8.8)	4 (7.8)	3 (10.3)	
US\$10,000–US\$13,000	5 (6.3)	2 (3.9)	3 (10.3)	
US\$13,000–US\$20,000	5 (6.3)	5 (9.8)	0 (0.0)	
US\$20,000–US\$30,000	12 (15.0)	9 (17.6)	3 (10.3)	
US\$30,000–US\$50,000	20 (25.0)	12 (23.5)	8 (27.6)	
$\geq$ US \$50,000	31 (38.8)	19 (37.3)	12 (41.4)	
Income meeting basic needs, ^a yes, n (%)	72 (81.8)	48 (84.2)	24 (77.4)	.564
IBS subtype, n (%)				
IBS-C	17 (16.8)	n/a	17 (48.6)	
IBS-D	13 (12.9)	n/a	13 (37.1)	
IBS-M	1 (1.0)	n/a	1 (2.9)	
IBS-U	4 (4.0)	n/a	4 (11.4)	
BMI (kg/m ²), mean $\pm$ SD	26.39 $\pm$ 5.64	26.60 $\pm$ 5.77	26.00 $\pm$ 5.44	.615
Cortisol (mcg/dl), mean $\pm$ SD	10.29 $\pm$ 4.23	10.26 $\pm$ 4.03	10.36 $\pm$ 4.63	.906
ACTH (pg/ml), ^a mean $\pm$ SD	18.79 $\pm$ 11.47	18.68 $\pm$ 11.50	18.99 $\pm$ 11.58	.897
PSS, mean $\pm$ SD	12.36 $\pm$ 6.67	11.05 $\pm$ 6.28	14.83 $\pm$ 6.75	.006
IBS-QOL, ^a mean $\pm$ SD	92.19 $\pm$ 13.77	99.05 $\pm$ 2.09	79.46 $\pm$ 16.94	.001

Note. Bold face values denote the significant values. ACTH = adrenocorticotropic hormone; BMI = body mass index; HC = healthy controls; IBS = irritable bowel syndrome; IBS-C = constipation predominant; IBS-D = diarrhea predominant; IBS-M = IBS mixed; IBS-QOL = IBS quality of life; IBS-U = IBS unclassified; PSS = Perceived Stress Scale. ^aYears of formal education, $n = 93$; total annual income, $n = 80$; income meeting basic needs, $n = 88$; ACTH, $n = 100$; IBS-QOL, $n = 100$.

were missing on three or more questions ($n = 1$); for those inventories with up to two missing data points, we mean imputed responses ($n = 3$). To determine the effects that would be detected from this pilot investigation, we performed a power analysis a priori using G*Power (Version 3.1.9.2, www.gpower.hhu.de/en.html). For a sample size of 60 participants (30 IBS and 30 HC), using α of .05 and power ($1 - \beta$) of .80, we would be able to detect the following effect sizes representing medium-to-large effects as defined by Cohen (1988): independent groups t test, effect size $d = .736$; regression model, effect size $f^2 = .237$; and correlation, effect size $r = .352$.

Results

We included data from 101 participants in the study analysis (see Table 1). The sample consisted of 48 males and 53 females, average age 27.8 ± 7.7 years, with 35 participants diagnosed with IBS (60% female) and 66 participants serving as HC (48.5% female). Participants with IBS did not differ from HC in demographic measures of age, race, years of education, total annual household income, or income meeting one's basic needs. Participants with IBS also did not differ from HC in physiological measures of BMI, cortisol, or ACTH. Participants with IBS, however, did differ from HC in scores on the PSS ($p = .006$) and IBS-QOL ($p = .001$), with IBS

Table 2. Scores (Mean $\pm$ SD) on Inventories by Study Group.

Inventory	HC n = 66	IBS n = 35	P
PSS			
Male	10.26 $\pm$ 6.47	15.50 $\pm$ 7.58	.023
Female	11.88 $\pm$ 6.07	14.38 $\pm$ 6.30	.153
IBS-QOL			
Male	99.33 $\pm$ 1.80	81.00 $\pm$ 18.03	.001
Female	98.75 $\pm$ 2.34	78.43 $\pm$ 16.54	.001
PSS			
Asian	11.18 $\pm$ 6.45	16.80 $\pm$ 8.41	.145
African American	11.40 $\pm$ 6.15	16.25 $\pm$ 7.25	.089
Caucasian	10.07 $\pm$ 6.23	13.89 $\pm$ 6.55	.044
Mixed/other	13.71 $\pm$ 6.82	13.67 $\pm$ 6.03	.833
IBS-QOL			
Asian	99.00 $\pm$ 1.67	81.40 $\pm$ 6.73	.001
African American	99.25 $\pm$ 1.25	78.13 $\pm$ 16.84	.008
Caucasian	98.85 $\pm$ 2.88	77.21 $\pm$ 19.21	.001
Mixed/other	99.29 $\pm$ 0.76	94.00 $\pm$ 9.54	.667

Note. Bold face values denote the significant values. Group differences assessed with Mann-Whitney U test. HC = healthy controls; IBS = irritable bowel syndrome; IBS-QOL = IBS quality of life; PSS = Perceived Stress Scale.

participants reporting significantly higher levels of perceived stress and lower levels of quality of life in comparison to HC (see Tables 1 and 2).

Table 3. Comparisons of Study Measures (Mean $\pm$ SD) Within IBS Participants.

Variable	ACTH	BMI	Cortisol	PSS	IBS-QOL
Sex					
Male	22.99 $\pm$ 14.34	26.19 $\pm$ 5.41	8.83 $\pm$ 3.35	15.50 $\pm$ 7.58	81.00 $\pm$ 18.03
Female	16.32 $\pm$ 8.71	25.88 $\pm$ 5.59	11.39 $\pm$ 5.14	14.38 $\pm$ 6.30	78.43 $\pm$ 16.54
Race					
Asian	13.84 $\pm$ 7.89	24.48 $\pm$ 5.19	9.44 $\pm$ 4.93	16.80 $\pm$ 8.41	81.40 $\pm$ 6.73
African American	18.91 $\pm$ 9.56	30.00 $\pm$ 4.73*	7.38 $\pm$ 2.46	16.25 $\pm$ 7.25	78.13 $\pm$ 16.84
Caucasian	19.31 $\pm$ 13.53	24.05 $\pm$ 4.00*	12.23 $\pm$ 4.57	13.89 $\pm$ 6.55	77.21 $\pm$ 19.21
Mixed/other	25.77 $\pm$ 7.27	30.23 $\pm$ 9.69	8.07 $\pm$ 5.32	13.67 $\pm$ 6.03	94.00 $\pm$ 9.54
Subtype					
IBS-C	19.50 $\pm$ 7.03 [†]	25.88 $\pm$ 5.27	10.74 $\pm$ 4.47	15.53 $\pm$ 7.81	77.00 $\pm$ 19.82
IBS-D	17.47 $\pm$ 16.33 [†]	26.52 $\pm$ 6.05	11.02 $\pm$ 5.21	12.92 $\pm$ 4.72	80.69 $\pm$ 15.20

Note. $N = 35$. ACTH = adrenocorticotrophic hormone; BMI = body mass index; IBS = irritable bowel syndrome; IBS-QOL = IBS quality of life; PSS = Perceived Stress Scale; IBS-C = constipation predominant; IBS-D = diarrhea predominant.

[†]Significant difference ($p = .047$) between IBS-C and IBS-D subtypes in ACTH—Mann-Whitney U test. *Significant difference ($p = .038$) between African American and Caucasian IBS participants in BMI—Kruskal-Wallis test, adjusted for multiple comparisons.

Further analysis of differences between participants with IBS and HC revealed sex and race effects. When we stratified participant responses by sex, males with IBS reported significantly higher levels of perceived stress compared with male HC ($p = .023$), whereas females with IBS did not differ significantly from their HC counterparts on levels of perceived stress ($p = .153$). On the other hand, significant differences were maintained between IBS participants and HC, regardless of sex, on the IBS-QOL (males, $p = .001$; females, $p = .001$). Exploring inventory differences by race revealed that only Caucasian participants with IBS significantly differed from HC participants matched on race on the PSS ($p = .044$), whereas Asian, African American, and Caucasian participants with IBS significantly differed from their race-matched HC counterparts on the IBS-QOL (mixed/other race grouping did not show a significant difference). Recognition of such differences prompted exploration of study variables within IBS participants, with differences noted by race and IBS subtype. Our analysis was focused upon subtypes IBS-C and IBS-D, given their prevalence within the cohort (see Table 3).

To address the first study aim of examining physiological correlates of perceived stress, we created a multivariate linear regression model with cortisol, ACTH, and IBS diagnosis as independent variables and PSS score as the dependent variable (see Table 4). Cortisol and ACTH were not significantly correlated ($r = -.010$, $p = .92$); therefore, we included both in the model. Cortisol, ACTH, and IBS diagnosis accounted for 13.4% of the total variance in PSS scores, with cortisol and IBS diagnosis as the significant predictors ($p = .015$ and $p = .005$, respectively). IBS diagnosis was associated with higher levels of perceived stress, whereas cortisol level was negatively associated with perceived stress. We performed logistic regression to explore which variables predicted IBS diagnosis, with cortisol, ACTH, and PSS included in the model (see Table 5). The model correctly classified IBS diagnosis 67% of the time, with the probability of IBS diagnosis increasing as PSS scores increased.

Table 4. Physiological Correlates of Perceived Stress—Linear Regression Model.

Model	B	SE (B)	β	t	p
Intercept	15.681	2.027		7.737	<.001
Cortisol	−0.370	0.150	−.235	−2.468	.015
ACTH	−0.044	0.055	−.076	−0.795	.428
IBS diagnosis	3.823	1.328	.274	2.879	.005

Note. Bold face values denote the significant values. $R^2 = .13$; $p = .003$. ACTH = adrenocorticotrophic hormone; IBS = irritable bowel syndrome.

Table 5. Predictors of IBS Diagnosis—Logistic Regression Model.

Predictor	β	SE	OR	p	95% CI (OR)
Cortisol	.043	.054	1.044	.423	[0.940, 1.160]
ACTH	.008	.019	1.008	.690	[0.971, 1.045]
PSS	.098	.036	1.103	.007	[1.028, 1.184]

Note. Bold face values denote the significant values. ACTH = adrenocorticotrophic hormone; IBS = irritable bowel syndrome; PSS = Perceived Stress Scale.

To address the second study aim of exploring associations between participants' perceived stress and quality of life, we calculated Pearson's correlation coefficient between PSS and IBS-QOL scores. Overall, we found a significant, negative association between participants' reports of levels of perceived stress and quality of life ($r = -.23$, $p = .025$). When we explored associations by IBS diagnosis, however, the association was no longer significant for either HC ($r = -.06$, $p = .626$) or participants with IBS ($r = -.07$, $p = .683$). We used Spearman's ρ to explore associations within IBS participants by sex, race, and IBS subtype, but it did not reveal any significant associations between perceived stress and quality of life.

The third study aim was to examine associations of participant BMI with markers of the stress response. BMI was not significantly associated with level of ACTH, but we did note a

significant association between BMI and cortisol ($r = -.38$, $p = .001$). This association was significant in both HC and participants with IBS ($r = -.26$, $p = .038$ and $r = -.60$, $p = .001$, respectively). We did not find a significant association between BMI and IBS-QOL scores, although we detected a near significant association between BMI and PSS scores ($r = .19$, $p = .052$). Stratifying by IBS diagnosis, this association was no longer near significant in HC participants but was significant in IBS participants ($r = .37$, $p = .027$). Evaluating within IBS participants using Spearman's ρ , we found that the association proved significant in males with IBS ($r = .65$, $p = .012$) but not in females with IBS. When evaluating by race, we found that Asian ($r = .90$, $p = .037$), African American ($r = .72$, $p = .045$), and Caucasian ($r = .50$, $p = .030$) participants with IBS had significant associations between BMI and PSS scores, whereas their HC counterparts did not. Lastly, in evaluating by IBS subtype, we found a significant association between BMI and PSS scores in IBS-C participants ($r = .52$, $p = .031$) but not in IBS-D participants.

Discussion

In the present investigation, we aimed to explore physiological correlates of perceived stress in participants with IBS and to examine associations between perceived stress and quality of life. The main findings of this study can be summarized as follows: We noted differences between participants based upon disease state (IBS vs. HC), sex (male vs. female), subtype (IBS-C vs. IBS-D), and race (African American, Asian, and Caucasian), although all findings warrant further discussion.

Participants with IBS and HC did not differ overall in demographic, socioeconomic, or physiological variables, although we did observe differences in psychological variables. This lack of difference between groups in physiological variables is both in concert with and divergent from prior investigations of the stress response in patients with IBS. The current investigation assessed markers of the stress response at participants' baseline state—in other words, we did not obtain measurements after a physical or psychosocial stressor—and findings must be evaluated within this context. The results should also be viewed in the context of the method of cortisol/ACTH collection (peripheral needle stick vs. indwelling catheter) as well as the timing of specimen collection. Although we attempted to control for diurnal fluctuations in measures through the timing of morning appointments, we did not admit participants to the hospital overnight. Therefore, our results reflect markers of the stress response after participants traveled to the Clinical Research Center, as opposed to upon a waking state.

Participants with IBS differed from HC in the psychological variables under investigation, scoring significantly higher on levels of perceived stress (PSS scores) and lower on levels of quality of life (IBS-QOL scores). Closer examination of the PSS scores in participants with IBS, however, revealed a sex effect: Males with IBS reported significantly higher levels of perceived stress than their HC counterparts, whereas females with IBS did not. Also of note, Caucasian participants with IBS

differed significantly from their HC counterparts on PSS scores, whereas Asian, African American, and mixed/other participants with IBS did not. As participants with IBS did not differ significantly on PSS scores by race, this finding may reflect differences in levels of perceived stress of HC or be a function of sample size.

As prevalence rates of IBS are higher in females than males (Sperber et al., 2016), many investigations naturally focus upon female subjects when studying the disorder. Researchers have reported differences between males and females with IBS, however, including in studies that focus upon psychosocial factors. Thakur, Gurtman, Keefer, Brenner, and Lackner (2015) found males with IBS to report more interpersonal difficulties and less social support than females with IBS, and these relationship problems correlated with IBS symptom severity. Other researchers have found that patients with IBS report internalized and perceived stigma secondary to their illness and perceive greater stigma from their personal relations than from their health-care providers (Taft, Riehl, Dowjotas, & Keefer, 2014). Furthermore, Lackner and colleagues (2013) reported that the negative aspects of interpersonal relationships were more salient to the illness burden of patients living with IBS than the influence of supportive relationships. Therefore, psychosocial factors may account for the sex effect we observed in IBS participants' levels of perceived stress when compared with HC. Perhaps in the present cohort, males with IBS experienced greater illness stigmatization or possessed fewer supportive, interpersonal relationships than females with IBS, and this is reflected by greater levels of perceived stress.

Psychological factors and intestinal symptoms have been found to differentially affect quality of life in males and females with IBS (Zhu et al., 2015). Zhu and colleagues found overall quality of life to be similar between males and females with IBS-D but also found food avoidance and social reaction to have a greater impact upon the quality of life of female patients with IBS-D. These researchers assessed different aspects of quality of life using the IBS-QOL, the same measure we utilized in the current investigation, in which we found that both male and female participants with IBS scored significantly lower than HC on overall quality of life. The use of this inventory, however, warrants further examination. A strength of the IBS-QOL is that it addresses factors relevant to patients with IBS that are not typically included in other more generic quality-of-life inventories. A limitation of this investigation, however, is that, in employing the IBS-QOL as our only measure of quality of life, we may not have elicited or accounted for certain factors relevant to quality of life in non-IBS participants, thus leading to a ceiling effect in HC. Total scores on the IBS-QOL did not significantly differ between IBS participants based upon sex, race, or subtype; however, we did not explore potential differences in the eight factors composing the measure.

Our findings regarding quality of life in IBS participants are once again both in concert with and divergent from findings of other research investigations of IBS. In line with our results regarding race, Gralnek, Hays, Kilbourne, Chang, and Mayer

(2004) found non-White IBS patients to report overall health-related quality of life impairments that were comparable to those that White IBS patients reported. Contrary to our findings regarding subtype, however, Singh et al. (2015) reported patients with IBS-D and IBS-M to have lower overall quality of life than patients with IBS-C. This investigation also utilized the IBS-QOL but in a significantly larger number of IBS patients; therefore, differences between subtypes in quality of life may exist that our study was not powered to detect. Roohafza et al. (2017) also reported subtype differences in a large study of IBS patients, finding that patients with IBS-M experienced more depression, anxiety, and distress than patients with the other IBS subtypes. In an earlier investigation, researchers found patients with IBS-C and IBS-A (alternating subtype according to Rome II criteria) to experience more anxiety, depression, and lower quality of life than IBS-D patients (Eriksson, Andren, Eriksson, & Kurlberg, 2008). These investigators also evaluated cortisol levels but did not detect significant differences between IBS patients and HC.

In the current investigation, we also did not detect significant differences between IBS participants and HC in levels of cortisol or ACTH; however, we did find differences in levels of ACTH between IBS subtypes, in that IBS-C participants exhibited higher levels of ACTH than IBS-D participants. Videlock et al. (2016) similarly found IBS-C participants to differ from other subtypes on markers of the HPA axis, exhibiting a blunted response in ACTH-stimulated cortisol and corticotropin-releasing factor–stimulated ACTH and higher baseline levels of morning cortisol. Suarez-Hitz et al. (2012) did not find that patients differed by IBS subtype in levels of cortisol or ACTH in response to a psychosocial stressor, the TSST, although they did find that IBS-D participants had a significantly lower rise in salivary morning cortisol compared with HC. Lastly, Chang et al. (2009) did not find significant differences between bowel-habit subgroups in cortisol or ACTH levels but noted that further examination was warranted with a larger sample size. In an earlier investigation looking at differences in autonomic nervous system (ANS) abnormalities between IBS subtypes, Aggarwal et al. (1994) reported IBS-C patients to have vagal cholinergic dysfunction, whereas IBS-D patients had sympathetic adrenergic dysfunction. Therefore, investigations that incorporate both components of the stress response (HPA axis and ANS) may shed additional light upon differences in the stress response between IBS subtypes.

The first aim of this investigation was to evaluate physiological correlates of perceived stress using a multivariate linear regression model. We found cortisol and IBS diagnosis to be significant predictors of perceived stress, albeit accounting for a small percentage of the variation. We also explored which variables could predict IBS diagnosis, finding PSS scores to increase the odds of IBS diagnosis, although admittedly, once again, in small amounts. Such findings are not surprising, given the relevance of perceived stress or psychological factors, as opposed to physiological ones, that distinguished the IBS cohort of this investigation from HC.

The second aim of this investigation was to explore associations between perceived stress and quality of life. It would be meaningful from a clinical perspective to determine whether perceptions of stress influence participants' quality of life, regardless of whether physiological correlates of perceived stress were detected. Psychotherapy has proven efficacious in improving daily functioning and mental health of IBS patients (Laird, Tanner-Smith, Russell, Hollon, & Walker, 2017), and such strategies could be implemented if perceived stress was found to negatively impact participants' quality of life. As we previously noted, the significant association between PSS and IBS-QOL scores disappeared when we evaluated participants by IBS diagnosis. This finding is unexpected, in that IBS participants' higher levels of perceived stress were not associated with poorer quality of life and may reflect inadequate power for these subgroup analyses. Given the efficacy of psychological therapies in treating IBS (Ford et al., 2014), such interventions should be encouraged in the IBS patient population despite this finding.

In the current investigation, we also evaluated the association between BMI and markers of the stress response. We noted a significant negative association across participants between BMI and cortisol, which was maintained when we evaluated participants by IBS diagnosis. This finding is similar to those of Schorr, Lawson, Dichtel, Klibanski, and Miller (2015), who, in a study assessing cortisol across the weight spectrum, reported that overweight women demonstrated the lowest measures of cortisol; however, these authors noted that the relationship between cortisol and BMI is actually U-shaped, with increasing levels of cortisol at BMI extremes. We also detected a positive association between BMI and our psychological measure of stress, the PSS, but it was only significant in IBS participants. Furthermore, the association between BMI and PSS was significant across groups of Asian, African American, and Caucasian participants with IBS. This finding in participants with IBS, a disorder characterized by heightened stress sensitivity, is similar to that of Olstad et al. (2016), who found that women from a socioeconomically disadvantaged neighborhood had a positive association between scores on the PSS and BMI.

Within IBS participants, we found additional differences by sex and subtype for the association between BMI and PSS. Males with IBS displayed a significant, positive association, whereas females with IBS did not. This finding relates to the prior description of males with IBS having significant differences on the PSS from HC, whereas females with IBS did not. Lastly, we found IBS-C participants to display a significant association between BMI and PSS scores, whereas participants with IBS-D did not. As we noted differences between these groups in physiological markers of the stress response as well, further investigation of subtype differences is warranted with larger sample sizes.

Conclusions

IBS is a multifactorial, stress-related disorder that negatively impacts patients' quality of life and is without efficacious

clinical interventions. Although we did not find strong physiological correlates of perceived stress in patients with IBS in the present study, findings contribute to the field by highlighting the relevance of psychological stress in patients with IBS in comparison to HC. Furthermore, this investigation adds to the literature by reporting differential findings of the stress response within IBS participants by sex, race, and subtype. These findings illustrate the heterogeneity of the IBS patient population, underscore the necessity of evaluating larger sample sizes and increasing the diversity of such samples to include males and ethnic minorities, and demonstrate the importance of taking an individualized approach to evaluation and treatment in this patient population. Such findings are most relevant to the practice of nursing, for enhanced understanding of a disorder translates into improved care of those afflicted. A personalized approach to patients with IBS may identify etiological and perpetuating mechanisms behind symptom exacerbation and help to direct medicinal, nutritional, psychological, and/or physical interventions with which to optimize patient care.

Authors' Note

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Author Contribution

Kristen R. Weaver contributed to conception, design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Gail D'Eramo Melkus contributed to conception, design, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Jason Fletcher contributed to conception, design, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Wendy A. Henderson contributed to conception, design, acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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