Physiological Reactivity and Psychosocial Functioning in Pediatric Patients with Gastrointestinal Disease

NCT05202418

Date: April 21, 2023
IRB00085974

1. Title Page:
    - Full study title: Physiological Reactivity and Psychosocial Functioning in Pediatric Patients with Gastrointestinal Disease
    - Short study title: Stress in IBD
    - Name, Title(s), and Department of Principal Investigator
        - Bonney Reed, PhD, Associate Professor of Pediatrics
    - Sponsor(s): Children's Healthcare of Atlanta and NIH, NIDDK, EPEX 52353, EPEX 70844
    - Protocol version number and version date
        - Version 13
        - April 21, 2023

2. External (non-Emory) Collaborators (if applicable):
   - GI Care for Kids and Children's Healthcare of Atlanta. Letter of Support uploaded 1/26/2022. No other IRB review

3. Precis/Abstract: A brief (usually 400 words or fewer) description of the study objectives, population, design, and outcome measures

   Similar to other chronic stressors, diagnosis with a chronic illness places youth at risk for adverse psychosocial outcomes. Inflammatory bowel diseases (IBD), Crohn's disease, ulcerative colitis, and indeterminate colitis, are chronic, immune-mediated diseases of the gastrointestinal tract characterized by unpredictable remissions of disease activity followed by relapses of symptoms. Increased risk for developing anxiety disorders and depression has been documented in youth with IBD. Individual differences in physiological reactivity may affect patients' risk for developing psychosocial difficulties within the context of chronic stress. The aim of the current study is to test whether differences in psychophysiological reactivity serve as risk factors in the relationship between clinical disease activity in youth newly diagnosed with IBD and psychosocial adjustment problems.

   Up to 56 additional youth with IBD will be enrolled in a coping skills treatment to test the effectiveness of a cognitive behavioral intervention including biofeedback to reduce anxiety and depression and disease symptoms.

4. Introduction and Background: A summary of the primary hypothesis, purpose, scholarly rationale, and prior literature.

Similar to other chronic stressors, diagnosis with a chronic illness places youth at risk for adverse psychosocial outcomes. Inflammatory bowel diseases (IBD), Crohn's disease, ulcerative colitis, and indeterminate colitis, are chronic, immune-mediated diseases of the gastrointestinal tract characterized by unpredictable remissions of disease activity followed by relapses of symptoms including abdominal pain, diarrhea, rectal bleeding, weight loss, growth and pubertal delay, fever, fatigue, and arthritis (Mackner, Sisson, & Crandall, 2004). Approximately 25 to 30% of patients have onset of symptoms before the age of 18 years, making IBD one of the most prevalent childhood chronic illnesses (Malaty, Fan, Opekun, Thibodeaux, & Ferry, 2010).

Increased risk for developing anxiety disorders and depression has been documented in youth with Crohn's disease (Loftus et al., 2011). Compared to parents of healthy adolescents, parents of adolescents with IBD rated their adolescents as experiencing greater difficulties with anxiety and/or depression on the Child Behavior Checklist (Mackner et al., 2013). An early study, limited by a small sample size of 20 youth with IBD, found higher rates of self-reported depressive and parent-reported internalizing symptoms for youth with IBD compared to a healthy control group (Engstrom, 1999). In a recent meta-analytic review of psychosocial adjustment, youth with IBD were found to experience higher rates of depressive disorders as measured via diagnostic interview when compared to youth with other chronic illnesses (odds ratio = 5.80) (Greenley et al., 2010).

Although some research has found higher levels of disease activity to relate to greater depressive symptoms, the overall relationship between disease activity and emotional functioning has been mixed, suggesting that additional individual differences need to be considered in addition to illness related factors when predicting emotional outcomes (Mackner & Crandall, 2007). Maternal depression, stressful life events, family dysfunction, and steroid usage have been shown to relate to higher rates of depressive symptoms (Burke, Neigut, Kocoshis, Sauer, & Chandra, 1994; Mrakotsky et al., 2005). Additional risk factors for the development of psychosocial difficulties need to be identified to identify moderators of outcome above and beyond disease activity. Individual differences in physiological reactivity may affect patients' risk for developing psychosocial difficulties within the context of chronic stress. Physiological reactivity, which broadly refers to bodily reactions in response to a stressor, varies with regards to intensity and threshold for activation between individuals. When presented with a stressor, activity in the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal axis (HPA) increases in preparation for managing the stressor (Chida & Hamer, 2008). Bodily tissues including the heart, vasculature, and adrenal medulla are activated by the SNS, resulting in consistent physiological responses that can be measured to quantify physiological reactivity. In humans, stress processing can be measured through complementary modes including heart rate variability (HRV) and skin conductance (SC). HRV and SC are non-invasive, easy to administer measures of the ANS suitable for pediatrics. HRV refers to fluctuation in the interval between consecutive heartbeats and is a product of the activating SNS and the inhibitory parasympathetic nervous system. Low HRV reflects reduced parasympathetic cardiac activity and is indicative of ANS rigidity and increased emotional reactivity to stress. High HRV is more adaptive, reflecting flexibility within the ANS and emotional responsivity(Walker et al., 2017). SC is the electrodermal activity (electrical impulses on the surface of the skin) produced by sweat glands that are stimulated by the SNS (Cummings, El-Sheikh, Kouros, & Keller, 2007). Skin conductance during periods of physical, cognitive, or emotional stress can be compared to baseline periods to obtain skin conductance level reactivity (SCLR), which has been shown to be a stable construct within individual across time and situation(El-Sheikh, 2007). SCLR is related to emotional and behavioral functioning, with higher reactivity most typically related to internalizing problems, and lower reactivity related to externalizing problems(Raine, Venables, & Williams, 1990).

In youth affected by non-medical chronic stress (e.g., family conflict, trauma history), measures of autonomic dysfunction have been used to explain why some individuals have worse psychological and physical outcomes compared to others exposed to similar levels of chronic stress(Cummings et al., 2007; El-Sheikh, 2005). Results support autonomic dysfunction as a vulnerability factor for adjustment problems within the context of chronic environmental stress.

In addition to the observational study, we will conduct a pilot intervention targeting autonomic dysfunction through a biofeedback enhanced coping skills treatment delivered virtually over 6-sessions.

5. Objectives: The primary and secondary aims and outcome measures.

Wave 1. Used to refer to originally approved protocol that has been ongoing.:
The aim of the current study is to test whether greater skin conductance reactivity or SCLR will serve as a risk factor in the relationship between clinical disease activity in youth newly diagnosed with IBD and psychosocial adjustment problems. Findings will extend previous research that has identified SCLR as a vulnerability factor for children's adjustment problems within the context of family stress to youth with chronic illness.
Additional outcome measures will include self-report measures of anxiety and depression and psychological functioning.

Wave 2:
Objective of Wave 2 data collection is to evaluate associations between psychophysiological reactivity (skin conductance reactivity and heart rate variability) and systemic inflammation (C-reactive protein levels) with levels of anxiety, depressive, and disease symptoms in youth with IBD. Patients with IBD will then be followed longitudinally for a total of six data collection points across 24-months.

Intervention:
Procedures. We will enroll participants with IBD (n=56 total) in a biofeedback enhanced cognitive behaviorally based coping skills treatment. Participants will be randomized to biofeedback enhanced treatment (n=28 for IBD) or wait-list control (n=28 for IBD). Autonomic reactivity in response to stress induction and coping strategies will be measured at time of random assignment, at treatment end, and at 2-months follow-up to compare to wait-list control participants completing assessment only (n=28 for IBD). Treatment will consist of a 6-visit group intervention conducted online, via Emory zoom. Groups will include 5-8 patients. Groups will meet approximately each week for 6 weeks. I will train advanced PhD students in clinical psychology to assist me in delivering the treatment protocol. Trained research assistants who are not delivering the treatment will conduct all assessments. Sessions will include brief, daily homework to facilitate mastery that is developmentally tailored to youth (e.g., practice skills with support from phone or tablet apps). We anticipate that following treatment, participants will demonstrate statistically significant decreases in autonomic reactivity compared to wait-list control participants. Wait-list Control: Participants randomized to the wait-list control group will complete the same measures of lifetime stress, autonomic reactivity, depression, anxiety. The identical treatment will be offered to control participants after the 6-week time point.

Content of treatment will include:

Biofeedback Enhanced Coping Skills Treatment Protocol					
		Treatment Targets			
Session Content		Coping with illness	Anxiety Symptoms	Depressive Symptoms	Autonomic Dysfunction
1	Disease education; Goal Setting	X			
2	Deep breathing; Guided imagery; Progressive muscle relaxation	X	X		X
3	Biofeedback		X	X	X
4	Mindfulness-based exposure to negative emotions; Biofeedback		X	X	X
5	Pleasant activity scheduling; Biofeedback practice	X		X	
6	Biofeedback Maintenance Plan		X	X	X

6. Study design and methods:

Waves 1 and 2 of Recruitment:

Patients will be recruited to participate within 30 to 45 days of diagnosis with IBD. Patients will be recruited through GI Care for Kids, with potential participants identified through upcoming scheduled visits, new diagnoses of IBD based on colonoscopy, as well as generated lists of newly diagnosed IBD patients generated for ongoing quality improvement and research initiatives. GI Care for Kids is a private, pediatric gastroenterology practice; all physicians employed through GI Care for Kids are affiliated with Children's Healthcare of Atlanta.

Primary site of recruitment will remain GI Care for Kids. Recruitment will also occur through Egleston Children's Center IBD Clinic, where the PI serves as psychologist as well. PI is credentialed through Children's Healthcare of Atlanta and is fully integrated into this clinic.

Initial recruitment will occur via telephone, and patients will be given the choice of coming in separately for a research appointment or participating on the same day as an upcoming medical appointment if it is within the 30 to 45-day time window. At T1, informed consent and assent will be obtained.

In response to social distancing measures put in place due to Covid19, both primary sites of recruitment are increasingly offering telemedicine appointments, reducing the frequency with which potential participants come into the medical office for an appointment. To address these changes, we will offer electronic data capture for child and parent-report measures that can be completed via RedCap remotely (from home). Separate links for parent and child self-report measures on RedCap will be emailed to subjects following informed consent. Consent and assent will also be captured electronically via RedCap.

For in-person study visits, participants will complete assessments of physiological reactivity, followed by child- and parent-report of child stress, adjustment, and contextual risk. At the time of enrollment, a blood draw of approximately 12 ml of blood will be collected. The blood obtained will be used to collect serum CRP. In the

event the patient is scheduled by their physician to have serum CRP measured at the same visit, this standard of care blood draw result will be used for purposes of this study. In addition, at the T1 visit, we will obtain saliva samples to analyze DNA.

Original Wave 1 Recruitment (IRB approved recruitment that has been ongoing):

Original Wave 1 recruitment was approved for goal of 60 patients with IBD to be recruited at baseline and then Time 2 (six months after T1) and T3 (12 months after T1). We aim to complete assessment as previously approved for participants already enrolled in Wave 1.

At T2 (six months after T1) and T3 (12 months after T1) child stress, child adjustment, and contextual risk will be re-assessed. Questionnaires will be completed either via secure weblink on RedCap or during scheduled research visit for T2 and T3. Clinical disease activity indices will be assessed at all data collection points within 3 days of questionnaire completion via stool tests. Participants will be compensated for their time with $25 gift cards at T1 and $25 gift cards at T2 and T3 following completion of questionnaires. Participants will be compensated with an additional $25 gift card for completion of stool tests within 1 week of study questionnaire completion, to be mailed.

Measures collected as part of Wave 1 recruitment include:
Patient Report.
Depression. Children's Depression Inventory 2 (CDI-2) (Kovacs, 2011). The CDI 2 is a child-report measure of physiological, behavioral, and emotional symptoms of depression. This is the most widely used measure of depressive symptoms in pediatric IBD research and will serve for comparative analyses.
Anxiety. The Screen for Child Anxiety Related Disorders (SCARED) (Birmaher et al., 1999). The SCARED is a 41-item inventory rated on a 3-point Likert-type scale used to screen for anxiety disorders. The SCARED offers a Total score as well as five symptom domains: panic/somatic, separation anxiety, generalized anxiety, social anxiety, and school phobia. The SCARED is a screening measure and not diagnostic of anxiety disorders. That being said, the authors provide cut scores for each score domain that may be indicative of an anxiety disorder. A total score of ≥ 25 may indicate an anxiety disorder, and for each of the subscales, a score of 7 may indicate Panic Disorder, a score of 9 may indicate Generalized anxiety, a score of 8 may indicate Social Phobia, and a score of 3 may indicate significant school avoidance.
Child Stress. *PROMIS Pediatric Stress.* (Ader, 2007). The Patient-Reported Outcomes Measurement Information System (PROMIS) is the outcome of an NIH initiative aimed at developing patient-report of domains important for clinical research. The Pediatric Stress set consists of 8-items measuring physiological experience of stress (e.g., tight muscles, heart beating fast), and 8-items measuring psychological experience of stress (e.g., feeling overwhelmed). Child stress symptoms will be measured at T1.

Lifetime Stress and Contextual Risk. To further assess patients' contextual risk beyond disease activity, lifetime exposure to traumatic events will be assessed. *The Lifetime Incidence of Traumatic Events – Student/Parent Forms* (Greenwald & Rubin, 1999) is a 16-item measure of potential trauma and loss events and asks parent and child respondents to first indicate if the child has ever experienced the event and if so, to rate the emotional impact at the time and at present. This measure will be completed by patients and parents at T1. Parents will also complete a 10-item measure of children's emotional reactivity, *Parent Report of Children's Reactivity,* at T1.

Child Pain. *PROMIS Pediatric Pain Interference*. The Pain Interference set consists of 13-items measuring the extent to which pain interfered with ability to engage in preferred or normative activities. Child Pain Interference will be measured at T1, T2, and T3.

Self-report of disease activity using the *PedsQL GI Module,* a gastrointestinal specific symptom assessment for use across gastrointestinal disorders (Varni et al., 2014) will be collected.

Parent Report. *Behavior Assessment System for Children-2nd Edition (BASC-2), Parent Form (Reynolds & Kamphaus, 2004)*. The BASC-2: PRS is a behavior assessment questionnaire to assess problem behaviors including internalizing and externalizing behaviors as well as adaptive behaviors. Parents rate how frequently behaviors occur from "Never" to "Almost Always." *T*-scores are used to compare respondents' answers to norms for same gender and aged children. *T*-Scores between 41 and 59 fall in the average range, with successive 10 point increments representing "at risk" and "clinically significant" ranges. The parallel child or adolescent self-report form will also be utilized.

Demographics. A demographics questionnaire will assess participant's age, gender, ethnicity, family income, IBD subtype, date of diagnosis, and parental highest education level. Medical chart review will be conducted to obtain indices of disease activity, IBD-related surgery history, and currently prescribed medication regimen.

PsychoPhysiology. Pediatric patients will participate in a psychophysiological session to measure skin conductance at Baseline, 12-months, and 24-months. Skin conductance level (SCL) and skin conductance response (SCR) data will be acquired at a sampling rate of 10 Hz using the eSense system connected to an iPad. Two 5 mm Ag/AgCl electrodes filled with isotonic paste will be attached to middle phalanges of the second and third finger of the non-dominant hand during an approximately 10-minute period while conversing with the research assistant and parent to allow for acclimation. Then parents will be asked to leave the room, and patients will have an additional 2-minute adaptation period. A 3-minute Baseline Assessment will occur first followed by two 3-minute stress trials. In one stress trial, youth will be asked to describe their most embarrassing or challenging experience since being diagnosed with IBD to the research assistant. In the second trial, youth will complete a star tracing task in which they trace an image of a star using only an inverted image through a mirror as a guide. This task will be audio recorded to insure and measure

study fidelity and to assess subjective level of stress when youth describe their most embarrassing or challenging time since being diagnosed with IBD. Order of stress trials will be counterbalanced.

***Clinical Disease Activity*.** At all measurement points, participants' treating pediatric gastroenterologist will complete measures of clinical disease activity including either the abbreviated *Pediatric Crohn's Disease Activity Index* (abbPCDAI) or the *Pediatric Ulcerative Colitis Activity Index* (PUCAI). Results of IBD diagnostic procedures (e.g., colonoscopy, MRI, video capsule endoscopy) and lab tests (e.g., hematocrit, platelet count, ESR, CRP, and albumin) ordered as part of standard medical care will be collected to characterize disease activity and severity.

Fecal calprotectin (FCAL). Stool samples will be collected at frequency outlined in measurement table to evaluate inflammatory disease activity in the gut through fecal calprotectin tests. For patients with a Children's Healthcare of Atlanta medical record, results from this test will be entered into their medical record, as well as copies of signed consent.

Inflammatory Markers/Laboratory Values.

CRP. Blood samples will be collected at T1 to assess for inflammatory markers in the peripheral blood. A blood draw of approximately 12 ml of blood will be collected.

DNA. Saliva samples will be collected at T1 to assess for genes related to emotional and behavioral difficulties in youth shortly after diagnosis. Saliva will be collected in Oragene Discover collection kits for collection of human DNA, OGR-500.

<u>Wave 2 Recruitment added to Protocol version 6</u>

Wave 2 recruitment will recruit the same patient population, at the same recruitment sites as Wave 1. Frequency of follow-up will be adjusted as described in Table 1.

Patient recruitment: 60 patients will be recruited to participate within 30 to 45 days of diagnosis with IBD.

Table 1. Timeline for Data Collection Aim 1 (n = 120; 60 IBD and 40 control at baseline; IBD patients followed over 24 months)

		Month of Follow-up (IBD only)				
Scheduled Assessments	Baseline (IBD and Control)	4	8	12	18	24
Patient Report						
Depression: CDI-2	X	X	X	X	X	X
Anxiety: MASC	X	X	X	X	X	X
Stress: PROMIS	X	X	X	X	X	X
Lifetime stress: LITE	X	X	X	X	X	X
Disease symptoms: PedsQL GI Module	X	X	X	X	X	X
Pain Interference						
Parent Report						
Parent Report of Children's Reactivity.	X					
BASC-2						
Psychophysiology						

Skin conductance	X			X		X
Heart rate variability	X			X		X
Inflammatory markers						
CRP	X	X	X	X		X
Fecal calprotectin	X	X	X	X		X
Physical Assessment/Chart Review						
BMI; Height; growth velocity	X	X	X	X	X	X
PUCAI/PCDAI (IBD pts)	X	X	X	X	X	X
Clostridium difficile diagnosis history	X	X	X	X	X	X

Measures.

Patient Report.

Depression. Children's Depression Inventory 2 (CDI-2) (Kovacs, 2011). The CDI 2 is a child-report measure of physiological, behavioral, and emotional symptoms of depression. This is the most widely used measure of depressive symptoms in pediatric IBD research and will serve for comparative analyses.

Anxiety. The Screen for Child Anxiety Related Disorders (SCARED) (Birmaher et al., 1999). The SCARED is a 41-item inventory rated on a 3-point Likert-type scale used to screen for anxiety disorders. The SCARED offers a Total score as well as five symptom domains: panic/somatic, separation anxiety, generalized anxiety, social anxiety, and school phobia. The SCARED is a screening measure and not diagnostic of anxiety disorders. That being said, the authors provide cut scores for each score domain that may be indicative of an anxiety disorder. A total score of ≥ 25 may indicate an anxiety disorder, and for each of the subscales, a score of 7 may indicate Panic Disorder, a score of 9 may indicate Generalized anxiety, a score of 8 may indicate Social Phobia, and a score of 3 may indicate significant school avoidance.

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Lifetime Stress and Contextual Risk. To further assess patients' contextual risk beyond disease activity, lifetime exposure to traumatic events will be assessed. *The Lifetime Incidence of Traumatic Events – Student/Parent Forms* (Greenwald & Rubin, 1999) is a 16-item measure of potential trauma and loss events and asks parent and child respondents to first indicate if the child has ever experienced the event and if so, to rate the emotional impact at the time and at present. This measure will be completed by patients and parents at T1. Parents will also complete a 10-item measure of children's emotional reactivity, *Parent Report of Children's Reactivity,* at T1.

Child Pain. *PROMIS Pediatric Pain Interference*. The Pain Interference set consists of 13-items measuring the extent to which pain interfered with ability to engage in preferred or normative activities. Child Pain Interference will be measured at T1, T2, and T3.

Self-report of disease activity using the *PedsQL GI Module,* a gastrointestinal specific symptom assessment for use across gastrointestinal disorders (Varni et al., 2014) will be collected.

Child Self-Regulation. *Adolescent Self-Regulation Inventory (Moilanen, 2006), Regulation of Emotions Questionnaire (Phillips & Power, 2007)*. These questionnaires assess child self-regulatory capabilities.
Covid-19 Exposure and Family Impact Survey (CEFIS). This is a measure developed in late March/early April 2020 to assess adolescent and parent report of exposure to Covid-19 and impact on the family related to exposure and impact due to social distancing.

Parent Report. *Behavior Assessment System for Children-2nd Edition (BASC-2), Parent Form (Reynolds & Kamphaus, 2004)*. The BASC-2: PRS is a behavior assessment questionnaire to assess problem behaviors including internalizing and externalizing behaviors as well as adaptive behaviors. Parents rate how frequently behaviors occur from "Never" to "Almost Always." *T*-scores are used to compare respondents' answers to norms for same gender and aged children. *T*-Scores between 41 and 59 fall in the average range, with successive 10 point increments representing "at risk" and "clinically significant" ranges. The parallel child or adolescent self-report form will also be utilized.
Demographics. A demographics questionnaire will assess participant's age, gender, ethnicity, family income, IBD subtype, date of diagnosis, and parental highest education level. Medical chart review will be conducted to obtain indices of disease activity, IBD-related surgery history, and currently prescribed medication regimen.

PsychoPhysiology. Pediatric patients will participate in a psychophysiological session to measure skin conductance level via electrodermal activity and heart rate variability at Baseline, 12-months, and 24-months. Skin conductance will be measured using two Velcro electrodes attached to the index-and middle fingers. Active measurement involves applying a very low, unnoticeable, painless voltage to the fingers. Skin conductance increases when a person is physiologically aroused. Heart rate variability refers to the variation between individual heart beats in milliseconds. Heart rate variability will be assessed using electrocardiogram with 3-electrodes attached to the child's chest. Assessment of heart rate variability is painless, and no stimulation is given through the electrodes; only data are collected.

Electrodes will be attached to the child during a 10-minute warm-up period in which research assistants converse with the child. The child will then be asked to participate in a 3-minute "stress trial" where they describe their most embarrassing or challenging experience since being diagnosed with IBD to the research assistant. In a second 3-minute trial, youth will complete a star tracing task in which they trace an image of a star using only an inverted image through a mirror as a guide. Skin conductance and heart rate variability will be assessed during these tasks. Participants will be connected to the electrodes for about 20 minutes total.

Physiological data (skin conductance and heart rate variability data) will be collected using the Mindware Mobile device using Biolab software (https://mindwaretech.com/mindware-mobile/)

***Clinical Disease Activity*.** At all measurement points, participants' treating pediatric gastroenterologist will complete measures of clinical disease activity including either the abbreviated *Pediatric Crohn's Disease Activity Index* (abbPCDAI) or the *Pediatric Ulcerative Colitis Activity Index* (PUCAI). Results of IBD diagnostic procedures (e.g., colonoscopy, MRI, video capsule endoscopy) and lab tests (e.g., hematocrit, platelet count, ESR, CRP, and albumin) ordered as part of standard medical care will be collected to characterize disease activity and severity.

Fecal calprotectin (FCAL). Stool samples will be collected at frequency outlined in measurement table to evaluate inflammatory disease activity in the gut through fecal calprotectin tests. For patients with a Children's Healthcare of Atlanta medical record, results from this test will be entered into their medical record, as well as copies of signed consent. Participants will be provided with supplies necessary to collect the stool sample at home and a pre-labeled FedEx box to ship the sample back to the Kugathasan lab at Emory for processing and storage in the -80 degrees freezer.

Inflammatory Markers/Laboratory Values.
CRP. Blood samples will be collected at T1 to assess for inflammatory markers in the peripheral blood. A blood draw of approximately 12 ml of blood will be collected.

DNA. Saliva samples will be collected at T1 to assess for genes related to emotional and behavioral difficulties in youth shortly after diagnosis. Saliva will be collected in Oragene Discover collection kits for collection of human DNA, OGR-500.

Compensation. A total of 60 participants diagnosed with IBD will be recruited at baseline and receive up to $60 total for participation in baseline measures. Participants will receive a $40 gift card after completing patient and parent-report questionnaires and an additional $20 gift card for providing stool, blood, and DNA samples. The 60 diagnosed with IBD will be enrolled in the longitudinal assessment component of the research plan with 5 subsequent visits at $45 compensation for each subsequent participation. Participants will receive a $25 gift card after completing patient and parent-report questionnaires and an additional $20 gift card for providing stool, blood, and DNA samples.

- Risks/discomforts: The most common risks and discomforts expected in this study are: Time spent completing the questionnaire (approximately 30 minutes expected), and discomfort with discussing sensitive information during the interview.
- Taking blood may cause some pain, bleeding, bruising at the site of vein puncture, or inflammation of the vein. Rarely patients may experience fainting or develop an infection at the site of vein puncture. Care will be taken to avoid these complications. Venipuncture will be performed by medical and nursing staff with expertise in performing these procedures in children.

- The less common risks and discomforts expected in this study are: Emotional distress resulting from completing questionnaires of emotional and behavioral functioning.
- There is a slight risk participants could be identified. Every effort will be made to protect identity.
- Potential benefits: Patient participants will have tests of disease activity completed at each study visit through stool samples. If these were not already ordered as part of standard medical care, these tests will not be charged to participants but will be available for medical care. The study is not designed to benefit participants directly, however. Results may help others with IBD in the future.

Intervention: As a follow-up to our observational studies described above, we have developed a biofeedback enhanced cognitive behavioral therapy to address symptoms of psychophysiological reactivity and anxiety and depression. We plan to enroll up to 56 patients with IBD in this intervention. Participants will be randomized to biofeedback enhanced treatment (n=28 patients with IBD) or wait-list control (n=28 patients with IBD). Autonomic reactivity in response to stress induction, symptoms of anxiety and depression, and coping strategies will be measured at time of random assignment, at treatment end, and at 2-months follow-up to compare to wait-list control participants completing assessment only (n=28 patients with IBD). Patients will also rate their disease symptoms and measures of clinical disease activity will be collected via chart review.

Potential participants will be recruited based on patients with IBD for psychological intervention and advertising through patient email listserves.

Treatment will consist of a 6-visit group intervention conducted via Emory zoom. Groups will include 5-8 patients each. I will train advanced PhD students in clinical psychology to assist me in delivering the treatment protocol. Trained research assistants who are not delivering the treatment will conduct all assessments. Sessions will include brief, daily homework to facilitate mastery that is developmentally tailored to youth (e.g., practice skills with support from phone or tablet apps). We anticipate that following treatment, participants will demonstrate statistically significant decreases in autonomic reactivity compared to wait-list control participants. Wait-list Control: Participants randomized to the wait-list control group will complete the same measures of lifetime stress, autonomic reactivity, depression, anxiety. The identical treatment will be offered to control participants after the 6-week time period.

7. If applicable: if data/samples collected for this study will be saved/banked/archived for future use, describe plans, who may use the material, and for what purposes (may require a separate repository-specific IRB submission).

Wave 1 and 2 observational research:

Stool samples collected to run fecal calprotectin tests to measure disease activity will be stored after FCAL tests are run. Samples will be stored in laboratory grade, minus 80-degree freezer in lab of Dr. Subra Kugathasan). Purpose will be for future research on relationship between microbiome/stool constituents and IBD outcomes in youth with IBD.

Saliva samples collected to run DNA testing will be stored in the research laboratory space of Dr. Vas Michopoulos, of the Emory University School of Medicine Department of Psychiatry. Samples will be stored after DNA tests are run. Purpose will be for future research on potential genes related to emotional and behavioral functioning after a recent chronic illness diagnosis.

8. Participant selection:
    - Waves 1 and 2 of Observational Research:
    - Youth ages 8 to 17 years diagnosed with Crohn's disease, ulcerative colitis, or indeterminate colitis within the last 30 days. One parent or primary caregiver will be recruited along with each child. Inclusion criteria will include (1) biopsy confirmed diagnosis of IBD within last 30 days and (2) English fluency for parent and child participants. Exclusion criteria will include (1) documented history or parent report of developmental delay or intellectual disability (2) parent unwilling to participate. Emory University IRB approval will be obtained for all study procedures prior to start of data collection.
    - Requested sample size for Wave 1: 60 youth; 10% refusal rate and 10% withdrawal rate expected based on previous research with this sample
    - Requested sample size for Wave 2: 60 youth diagnosed with IBD; 10% refusal rate and 10% withdrawal rate expected based on previous research with this sample
    - Screening for eligibility of IBD patients will occur through medical records review and in collaboration with doctors/nurses at GI Care for Kids and Egleston Children's Center based on newly diagnosed IBD patients.
    - **Inclusion Criteria.** To participate, patients must be (a) Diagnosed with biopsy-confirmed IBD within the last 30 days, (b) ages 8 through 17 years inclusive, (c) speak English, (d) accompanied by at least 1 parent/guardian who is willing to participate. Control participants must meet all inclusion criteria excluding diagnosis with IBD or other chronic health condition. **Exclusion Criteria.** Patients meeting any of the following criteria will be excluded from participation: (a) Previous diagnosis of intellectual disability, (b) autism spectrum disorder.
    - If a subject withdraws, their previously collected data will be destroyed if requested. Otherwise, previously collected data will remain part of data collected but no further attempts to contact this participant will be made.
    - **Intervention**: **Inclusion Criteria.** To participate, patients must be (a) Diagnosed with biopsy-confirmed IBD, (b) ages 13 through 18 years, (c) speak English, (d) accompanied by at least 1 parent/guardian who is willing to participate, (e) positive depression or anxiety symptom screen using the PHQ-9 or PROMIS Pediatric Anxiety measures. **Exclusion Criteria.** Patients

meeting any of the following criteria will be excluded from participation: (a) Previous diagnosis of intellectual disability, (b) autism spectrum disorder.

9. Informed Consent Process:
    - Primary method for obtaining informed consent will be through use of electronic signature (e-signature) through Redcap. The signature area will be the same as the normal ICF/HIPAA template, but participants will be able to sign via a touch-screen-enabled device (iPad) following in-person consent. A copy of the signed and dated consent will be sent to participants via encrypted email following IC discussion.
    - For instances in which in-person informed consent is not feasible or convenient for families based on clinic schedules or Covid19 social distancing precautions, the informed consent discussion will occur via telephone. At the beginning of the IC discussion, participants will be emailed a RedCap link to take them to the IC document. The research assistant leading the IC discussion will confirm that the participant can read all pages of the IC document. Subjects will then be able to sign electronically. A copy of the signed consent will be emailed to subjects via encrypted email for their records
    - A copy of all signed consent documents will be stored on Redcap, allowing for electronic audit if necessary. All subjects' identify will be verified prior to signing the IC based on government issued ID (driver's license) which is required of all guardians at the time of check-in at the medical clinic, the site of research participation.
    - Child assent will also be obtained via e-signature
    - As a back-up option, wet signature signed consent will be obtained in person from patients' parent or legal guardian.
    - Consent will be obtained in private exam rooms from individuals who do not already have a relationship with the subject to minimize undue influence.
    - To ensure comprehension of the informed consent information, study personnel will allow time for questions, will verbally summarize the material to the subject and child participants, and will answer all questions.
    - Informed consent conversation will take place in private exam room, led by study personnel including study coordinator, principal investigator, or trained research assistant.

10. Compensation for time and effort:

    Wave 1: Participants will be compensated for their time with $25 gift cards at T1 and $25 gift cards at T2 and T3 for completion of study questionnaires. Participants will be compensated with an additional $25 gift card for completion of stool tests within 1 week of study questionnaire completion, to be mailed. Total possible compensation for each subject is $150 across all 3 time points of the study.

Wave 2: A total of 60 participants (diagnosed with IBD) will be recruited at baseline and receive up to $60 total for participation in baseline measures. Participants will receive a $40 gift card after completing patient and parent-report questionnaires and an additional $20 gift card for providing stool, blood, and DNA samples. The 60 diagnosed with IBD will be enrolled in the longitudinal assessment component of the research plan with 5 subsequent visits at $45 compensation for each subsequent participation. Participants will receive a $25 gift card after completing patient and parent-report questionnaires and an additional $20 gift card for providing stool, blood, and DNA samples. Total possible compensation for each subject with IBD is $285 across baseline and 5 subsequent assessment points.

Intervention: Participating patients will receive a $50 gift card for enrolling in the biofeedback enhanced coping skills group treatment. Each participant will earn an additional $15 in gift cards for attending each of the 6 group treatments. Finally, each participant will earn an additional $30 for completing post-assessment and follow-up measures, for a total possible compensation of $200.

11. Statistical analysis: Multi-level modeling will be utilized to estimate children's adjustment at follow-up points after controlling for adjustment at T1. The linear (main) effects of disease activity and physiological reactivity on children's adjustment will be examined as will the interaction between physiological reactivity and disease activity. Contextual risk and perception of stress will be explored as additional moderators in the model.

    In the cross-sectional comparison of IBD patients with age-sex-matched controls, measures of psychophysiological and immune functioning and levels of anxiety, depressive, and disease symptoms will be summarized using standard descriptive statistics. Differences between groups (IBD vs. control) will be made using paired t-test or Wilcoxon signed rank tests to account for paired samples. Linear models will be used to examine the relationship between ANS and neuroimmune function with levels of anxiety, depression and disease symptoms. Specifically, models will include the main effect of group, the main effect of predictor (e.g., physiological reactivity or CRP), and the interaction between group and predictor. The interaction serves as the statistical test to determine if the correlation between predictor and outcome (e.g., anxiety, depression, etc.) differs between IBD patients and controls.

    Intervention: Primary goals of the intervention are to establish the feasibility and acceptability of a RCT of enhanced biofeedback to improve autonomic reactivity and reduce levels of depression, anxiety and clinical symptoms in pediatric patients with IBD. Feasibility measures including consent rates, completion/retention rates, and treatment satisfaction ratings will be summarized using counts and percentages or means and standard deviations, as appropriate. Changes in clinical scores (anxiety, depression, and clinical symptoms) and autonomic reactivity from baseline, to end of treatment, and 2 months post treatment will be summarized within groups at each study time-point. The changes in the measures *within* and *across* groups will be analyzed using a two-factor repeated measures analysis of variance model

(rmANOVA). Models will include the main effect of group, the effect of time and the group X time interaction term. Other baseline covariates including age, disease severity, and other clinical characteristics may be included in the models. Data will be modeled using the *MIXED* procedure in SAS which allows for use of all outcome data, even in the presence of missing data. Differences in group means will be calculated and presented along with 95% confidence intervals. Effect sizes will also be calculated to further describe the degree of difference between groups. Appropriate modeling assumptions will be verified prior to analysis and analysis will follow the intention to treat principal. In exploratory analyses, we will determine whether reductions in anxiety, depression and stress are mediated by changes in autonomic reactivity and coping strategies by exploring the direct and indirect effects of autonomic reactivity and coping strategies on perceived stress, anxiety and depression. For each outcome of interest (e.g., depression), an estimation of the mediation effect will be calculated using the difference in the regression coefficients (β1-β2) obtained from the two linear regression models with and without the mediator (i.e., skin conduction measure or HRV). Bootstrapping (5000 samples) will be used to obtain the empirical distribution of the mediation effect and test the null hypothesis that the difference-in-coefficients (β1-β2) is zero. This method has superior statistical power for relatively small sample sizes and does not require a large effect size.

12. Data and Safety Monitoring and Reporting: The IRB will be notified of any unexpected, adverse events. As this study is low risk, no such events are anticipated. Any adverse events associated with venipuncture will be monitored by the PI and reported to site medical doctors, Drs. Kugathasan and patients' primary physician at GI Care for Kids, as well as Emory IRB.

13. Confidentiality:
    - Privacy will be protected by handling all in-person conversation and study procedures in private exam rooms.
    - Confidentiality will be established and maintained by using numerical codes to identify all participants' samples and responses, with only the principal investigator having access to the key linking codes to participant names. This key will be kept on a password protected Emory OneDrive. Key will be destroyed once all data collection is complete, analyses conducted, and study IRB closed. Audio recordings of stress tasks will be stored electronically on a password protected Emory OneDrive.

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