Targeting chronic stress for reducing risk factors for colorectal cancer: a pilot feasibility study among vulnerable at-risk Black females

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LIST OF ABBREVIATIONS

AR	Adrenergic Receptor
B-AR	Beta Adrenergic Receptor
BMI	Body Mass Index
CORT	Cortisol
CRC	Colorectal Cancer
EPI	Epinephrine
U.S.	United States
Hs-CRP	High Sensitivity-C Reactive Protein
GMBA	Gut-Microbiota-Brain Axis
MBSR	Mindfulness Based Stress Reduction
HPA	Hypothalamic-Pituitary-Adrenal
SNS	Sympathetic Nervous System
NE	Norepinephrine
NHW	Non-Hispanic White
UIC	University Of Illinois Chicago
PSS	Perceived Stress Score

1.0 **Project Summary/Abstract.**

Chronic stress can directly and indirectly promote carcinogenesis through immune, metabolic, and microbial pathways. Our overarching hypothesis is that reducing chronic stress will have important implications for CRC risk reduction among vulnerable and high-risk populations. A promising approach for reducing chronic stress is mindfulness-based stress reduction (MBSR). Mindfulness is a meditation-based technique to achieve a state of mind that is used to experience higher awareness or consciousness. Existing small studies suggest Mindfulness may positively regulate stress response in a way that translates to anti-cancer effects including reduced inflammation. We propose here to test an 8-week Mindfulness intervention delivered in a hybrid format (synchronous and asynchronous sessions) among 40 Black females at elevated risk of CRC, who reside in vulnerable communities and who report moderate to high perceived stress. This is a single-arm trial. At baseline and post-intervention, participants will provide blood, hair and stool and undergo body composition analysis and complete mood and lifestyle related surveys. The specific aims are to test the feasibility and acceptability of the intervention and explore changes (baseline to post-intervention) on stress, weight, fasting glucose, inflammation markers, and the gut microbiota – risk markers and risk pathways associated with CRC. While relieving social stressors is the paramount goal, addressing chronic stress at the individual level is achievable now, with implications for CRC risk reduction. Data generated will be leveraged toward the development of a fully powered trial to test if Mindfulness is efficacious for CRC risk reduction among high-risk vulnerable populations in Chicago.

2.0 Background/Scientific Rationale

CRC health inequities among Black Americans. Black Americans have among the highest CRC incidence and mortality for reasons that are not fully elucidated but are known to exceed the impact of screening and early detection differences.[1] Both biological and environmental exposures play a significant role in colorectal carcinogenesis, which develops through a multistep mutational process.[2] Socio-environmental stressors are widely regarded as important drivers of cancer health inequities. Compared to other racial-ethnic groups, Black Americans are more likely to live in urban areas that are affected by violent crime and socioeconomic deprivation. Chronic exposure to violence and fear of violence, together with socioeconomic stressors, can elicit a sustained stress response with downstream effects linked to carcinogenesis.[3] Specifically, chronic stress can dysregulate the SNS and HPA axis in a manner that promotes cancer through hormonal,[4] immune,[5, 6] metabolic,[7] and microbial[8, 9] pathways. Supported by our preliminary data, this ChicagoCHEC full project will be the first step in a line of inquiry to determine if mitigating chronic stress is a formidable target for CRC risk reduction among a vulnerable population of high-risk Black adults in Chicago.

Chronic stress and carcinogenesis. Anecdotal evidence linking chronic stress to cancer goes back almost two millennia with early reports describing that cancer was less likely to occur in persons with better mental well-being.[10] Chronic stress dysregulates and augments the release of mediators of the neuroendocrine stress response system including SNS-related catecholamines, EPI and NE, and HPA-axis-related hormones including CORT.[4, 10] Animal studies have connected stress-related increases in EPI, NE, and CORT to cancer initiation.[10, 11] CORT can affect cell cycle control and reduce DNA repair processes to promote carcinogenesis.[10] In response to stress, NE and EPI potentiate their effect on adrenergic receptors (ARs). Chronic activation of β-ARs specifically has been implicated in carcinogenesis with their activation affecting established "hallmarks of cancer" including inflammation, proliferative signaling, genome instability, and immune evasion.[10, 12-14] Colon cancer cells express β-ARs, and their activation has been linked to cancer initiation and tumor progression.[12] In a human colon cancer cell line, β-AR antagonist drugs used to treat cardiovascular disease in humans significantly reduced cell proliferation in treated cells in the presence of an AR agonist.[12] Epidemiological and clinical evidence also links β-AR antagonist drug use to reduced cancer risk, including CRC, and lower cancer mortality.[15, 16] These studies provide strong evidence of the molecular mechanisms at the intersection between chronic stress and cancer. However, the epidemiological evidence directly linking chronic stress to cancer is mixed and fraught with limitations including failure to assess objective markers of stress with investigators relying largely on self-report measures. Moreover, the existing literature has focused largely on White and higher income individuals instead of the most vulnerable populations as it relates to both chronic stress and cancer.[14] There is strong human data however regarding the deleterious indirect effects of chronic stress and overexpressed NE, EPI and CORT on glucose metabolism (impaired),[7] overall and central adiposity (increased),[17] inflammation (increased),[18] and the gut microbiome (dysbiosis)[19] – known drivers of colorectal carcinogenesis.[20, 21] Given the totality of evidence, reducing chronic stress and augmenting chronic exposure to NE, EPI and CORT is a plausible approach to CRC risk reduction that remains grossly understudied**.**

Mindfulness for stress reduction. One promising approach to reducing chronic stress is Mindfulness. Mindfulness is a meditation-based technique to achieve a state of mind to experience higher awareness or consciousness and may include spirituality or religion.[22, 23] Importantly, studies indicate Mindfulness is desirable among Black populations and our team

has tailored Mindfulness interventions for Black adults in Chicago.[24-26] Several small studies suggest that short-term (~8 weeks) exposure to Mindfulness can lower perceived stress[27] CORT, and resting heart rate.[28-30] Existing evidence also suggests that short-term Mindfulness yields effects specific to body weight,[31] glucose metabolism[32] and inflammation which are known risk drivers of CRC.[33] Mindfulness's effect on the gut microbiota has not been reported, although there are a few ongoing studies that will undoubtedly add to this knowledge base. MBSR has been studied in the context of cancer care and among survivors with effects including lower perceived stress and decreased circulating CORT and pro-inflammatory cytokines.[34-37] However, **there is a gap in prospective trials exploring its use for cancer risk reduction**. To our knowledge, the proposed study will be the first to explore Mindfulness for CRC risk reduction in a vulnerable high-risk population in Chicago.

GMBA in the context of chronic stress – implications for CRC. The gut microbiota and brain are closely connected through a bidirectional pathway coined the GMBA such that dysfunction in one system can promote dysfunction in the other.[38] Chronic stress is associated with a shift in gut microbial ecology and microbial metabolic function that relates back to disruption of the SNS and HPA axis.[19] In animals and in a small number of human studies, chronic stress (self-reported in humans) is associated with decreased microbial community diversity and lower relative abundance of Lactobacillus that parallels an increase in systemic inflammation.[9, 39, 40] Thus, chronic stress can tip the microbial balance toward a pro-inflammatory colonic state conducive to carcinogenesis. We will explore if reducing chronic stress influences the gut microbiota and intestinal and systemic inflammation.

Chronic stress and colorectal neoplasia. We collected data (U54MD012523) to examine associations between chronic stress and colorectal adenoma among Black (n=27) and White (n=33) adults presenting for colonoscopy (no corticosteroid exposure in the previous 3 months). Overall, HCORT was significantly higher among the Blacks vs. Whites (mean (SD) 26.5 ± 38 pg/mg vs. 5.1 ± 9.1 pg/mg; $p < 0.0001$). A defining feature of the Black participants was their exposure to violent crime (e.g., homicide) compared to Whites that were living in both low and high disadvantaged areas ($p < 0.01$). This indicates exposure to violent crime as a potentially important social construct driving stress among Blacks in Chicago. When stratifying by race and colorectal adenoma, Blacks with colorectal neoplasia had the highest HCORT, suggesting chronic stress as a potential driver of neoplastic transformation. Black females also had the highest HCORT and BMI and poor diet quality (Healthy eating index (HEI)-2015)[68] (**Table 1**). The data supports our inquiry into mitigating chronic stress for CRC prevention and our initial focus on at-risk Black females in high crime areas.

Table 1. Hair cortisol concentration, BMI, and diet quality based on Healthy Eating Index-2015 by race and sex

	Age, years	HCORT pg/mg	BMI kg/m^2	HEI Score (0-100)
White males (n=17)	59.5 (56.5 - 62.63)	8.0 (0.7 – 15.3)	29.0 (26.6-31.4)	56.4 (49.4 – 63.3)
White females (n=16)	60.1 (57.0 - 63.2)	2.1 (-5.4 – 9.6)	27.2 (24.6 – 29.8)	58.3 (51.1 - 65.4)
Black males (n=5)	59.8 (54.2 - 65.4)	14.0 (0.6 – 27.5)	29.2 (23.4-35.0)	55.3 (40.9 – 69.9)
Black females (n=22)	59.7 (56.9 - 62.4)	**21. 7 (15.2 – 28.3)**	**34.5 (32.1 – 36.8)**	**47.1 (40.5 - 54.0)**

3.0 Objectives/Aims

Aim 1. Test the feasibility and acceptability of a Mindfulness intervention among Black females at elevated risk of CRC. Hypothesis: The study will be feasible (i.e., recruit ≥ 30% of those approached and retain ≥ 80% of the participants) and acceptable (i.e., participants in the intervention group will attend and engage with ≥ 80% of the intervention sessions and remote content and complete ≥ 80% of the planned assessments).

Aim 2. Explore changes (baseline to post-intervention) in perceived and objective measures of stress including heart rate, hair cortisol and circulating EPI, NE, and CORT.

Aim 3. Explore changes (baseline to post-intervention) in adiposity (% body fat and central adiposity) and immune and metabolic biomarkers.

Aim 4. Explore changes (baseline to post-intervention) in gut microbiota composition and colonic inflammation (fecal calprotectin).

4.0 Eligibility

This study will enroll 48 Black females, 45-65 years of age at elevated risk of CRC (fragment of colorectal adenoma or ≥ 1 colorectal adenoma past 36 months) who reside in a Chicago community area with high violent crime and report moderate to high perceived stress on the Perceived Stress Scale (PSS ≥ 14).

4.1 Inclusion Criteria

Inclusion: Female based on sex assigned at birth, identify as Black, 45-65 years old, have completed a colonoscopy in the past 36 months, classify as elevated risk of CRC (see above), own and use a smartphone, computer, or tablet with access to the Internet, score ≥ 14 on the PSS at screening and reside in a Chicago community with high violent crime (described above). Many patients at UIC live in stressed community areas and in our pilot, 90% of Black females scored ≥ 14 on the PSS.

4.2 Exclusion Criteria

Exclusion*:* 1) History of CRC, 2) Antibiotics (oral/IV) in the past 2 months; 3) Inflammatory bowel disease or genetic predisposition to CRC, 4) Cancer diagnosis or cancer treatment in the past 12 months, 5) > 50 grams of ethanol daily6) Bariatric surgery or bowel resection, 7) Immunodeficiency/autoimmune disease or uncontrolled diabetes (HbA1c > 9% based on EHR), 8) Fiber or pre-/probiotic supplements ≥ 3 days per week 9) Significant health conditions or take medications that impact participation or expected outcomes (e.g., β-blocker, Cushing's syndrome)

4.3 Excluded or Vulnerable Populations

This study will not involve children, pregnant women, or prisoners.

4.4 Sample Size Justification

Forty eight Black females will be recruited allowing for 20% dropout resulting in completed data collection on 40 individuals which supports the calculation of confidence intervals for feasibility and effect size components.[42] This feasibility-pilot study is not powered to detect statistically significant effects for improvement in chronic stress or the secondary/exploratory measures. The minimum detectable difference from baseline to post-intervention for these outcomes is 1 standard deviation with baseline and post-measurements that are correlated at r=0.5, alpha=0.05 and 80% power.

5.0 Subject Enrollment

Through an established clinical research infrastructure in the UIC GI Lab, we will recruit 48 Black females (anticipate 40 will complete the trial) at elevated risk of CRC defined as:

fragments of colorectal adenoma or ≥ 1 colorectal adenoma in the last 36 months,[43] who reside in a Chicago community with high levels of violent crime (>50th%tile based on data from the Chicago Health Atlas), and report moderate to high perceived stress on the Perceived Stress Scale (PSS) (score ≥14).[44] We will recruit in four waves of ~12 participants per wave. Electronic health records (EHR) will be screened (EPIC slicer dicer application) for eligibility among females scheduled for, or who have completed, a colonoscopy in the prior 36 months. In addition to screening the UI Health EHR, we will contact participants from past and ongoing studies 2020-1627 "Effects of Time-Restricted Eating Versus Daily Continuous Calorie Restriction on Body Weight and Colorectal Cancer Risk Markers Among Adults with Obesity" and 2022-0279 "Time restricted eating plus exercise for weight management" who indicated interest in future research on their consent forms. These individuals may have had a colonoscopy outside of UI Health and would still fit our eligibility criteria, We will also send our recruitment letter via UIC Listserv channels; UIC_SPH_NEWS, SPH_NEWS, SPH-STUDENTS, PACADEMY and, UICAP to reach individuals who may have had a colonoscopy outside of UI Health. We will also recruit through UI Health Research Registry (UIHRR) IRB 2018-1599 and "Be The New Normal Match" (TNN) granted exemption by IRB ChairB, which will help connect us with potentially interested participants not captured by the other methods listed above. As a way to engage the broader Chicago community, we will utilize targeted advertisements on Facebook and Instagram catered to individuals who may fit our recruitment criteria. Interested individuals will click a link which directs them to our REDCap survey to request future contact which will be conducted as outline below. Any participants who had a colonoscopy outside of UI Health will be required to bring a copy of their colonoscopy and pathology report to their first in person visit to confirm eligibility.

Potentially eligible females will be notified about opportunity to participate in this research via MyChart message, text message, phone or email to assess study interest. These messages will include a link to a video which explains what mindfulness is and what the study involves. Participants from ListServs, social media and previous studies will be contacted using the same methods and approved language as those identified through SlicerDicer. UI Health patients identify their willingness to be contacted for research when signing consent for clinical care at UIC and this is identified in their chart. We are looking for a very specific type of patient so prescreening using Slicer Dicer is necessary. Interested and eligible individuals will detail their willingness to be contacted by the study team to confirm interest and then invite to an in-person screen to confirm eligibility (measure weight and height and complete PSS) at the UIC Applied Health Sciences Building.

If the individual is eligible following the screen, the baseline visit will immediately follow. If the individual is a screen fail, $20 + transportation costs will be provided. The feasibility of our recruitment approach is supported by 1) our past success recruiting the target population;[45] and 2) The clinical volume of the UIC GI lab (approximately 4,000 colonoscopies annually). We anticipate 450 Black female patients will be eligible during the grant period based on our inclusion criteria (see below); 3) collaboration from gastroenterologist Naylor (Black male physician-scientist) as Co-I; 4) use of a historical patient list obtained from the UIC clinical data warehouse; and 5) use of patient portals in EPIC to facilitate recruitment.

6.0 Study Design and Procedures

This is a single arm feasibility/pilot study. This study will enroll 48 Black females, 45-65 years of age at elevated risk of CRC (fragments of colorectal adenoma or ≥ 1 colorectal adenoma in the past 36 months), who reside in a Chicago community area with high violent crime and report moderate to high perceived stress on the Perceived Stress Scale (PSS ≥ 14).

Setting. The study will take place at UIC College of Medicine and College of Applied Health Sciences.

Visits to research center. All participants will visit UIC at baseline and post-intervention for clinical measurements with research staff. Participants will receive an email upon scheduling the research visit with details regarding data collection. They will also receive reminder phone calls and text messages the night prior to their appointment.

Intervention Protocol.
The intervention will begin within a few weeks of the baseline data collection.

Mindfulness intervention. **UIC PI Biggers** is conducting an NIH-funded study (*K01HL149775*) to examine the utility of Mindfulness for reducing cardiovascular disease risk among Black adults with type 2 diabetes. Based on her experience, we will use a hybrid approach to increase weekly exposure to Mindfulness through weekly synchronous and asynchronous content. The Mindfulness content for the group sessions and web-based intervention are informed by Jon Kabat Zinn's Mindfulness Based Stress Reduction program.[46] Participants will receive text messages to remind them of weekly intervention visits and to complete asynchronous, web-based materials.

Mindfulness group sessions. The group sessions will be held both in-person (3 sessions) and remote (6 sessions) and led by Dr. Jasmin Searcy. The in-person sessions will be held at the Institute for Health Research and Policy. The remote group sessions will be held over Zoom. Sessions will be held on the same day and time each week. One in person session will be a group retreat held on a Saturday from 10-4P.

Asynchronous web-based Mindfulness content. To increase weekly exposure to Mindfulness beyond the group sessions, we will leverage and adapt NU PI Yanez's (Northwestern University Partner) web-based mindfulness intervention, *My Journey*.[47] In the first 3 months of funding, we will modify and optimize the website to shift the focus to CRC risk reduction (previously developed for racially-ethnically and socio-economically diverse female cancer survivors). The web-based intervention is based on Kabat's Zinn's Mindfulness program and has been tested for useability. The web-content is divided into 8 weeks with the content dovetailing with the content of the group sessions (Table 1). The participants will be encouraged to engage with the web intervention for at least 30 minutes each week. During the initial in-person group session, the interventionist will show participants how to access and navigate the website. The web intervention provides back-end analytics at the individual level to track usage metrics. Staff will track usage, and contact participants (phone, text, email) who fail to engage with web-intervention to encourage use. To allow participants to comfortably view the web-based intervention and to fully engage in the remote group sessions, headphones with microphone will be provided.

7.0 Data and Specimen Collection

Table 3. Assessment and timing of clinical outcomes		**Active Phase (8 weeks)**								
Study week	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Post-intervention**
Aim 1										
Intervention feasibility		x	x	x	x	x	x	x	x	
Intervention adherence		x	x	x	x	x	x	x	x	

Intervention acceptability					x					x
Aims 2 & 3 (hair cortisol, circulating markers and anthropometrics)										
Body weight (kg), BMI (kg/m^2)	x									x
Height	x									
Body composition measurement (DXA)	x									x
Hair cortisol	x									x
Circulating CORT	x									x
Circulating epinephrine and norepinephrine	x									x
High sensitivity C-reactive protein	x									x
Fasting glucose	x									x
Resting heart rate	x									x
Diet	x									x
Physical activity and sleep (FitBit)	x									x
Aim 4										
Stool sample collection	x									x
Microbial DNA isolation	x									x
Fecal microbiota composition/16S rRNA amplicon sequencing	x									x
Intestinal inflammation	x									x

Aim 1. Aim 1. Test the feasibility and acceptability of a MBSR intervention among Black females at elevated risk of CRC. No biological specimens are collected for Aim 1. All data will be related to feasibility, adherence to the group sessions and digital content and acceptability of the study.

Feasibility, adherence and acceptability. We will collect detailed records of number of the individuals eligible, approached (phone, email, EHR patient portal), screened and the number of individuals who decline and their reason(s) for non-enrollment. Once an individual is enrolled, attendance at study visits, completeness of data, session attendance and asynchronous intervention usage metrics and loss to follow-up/withdrawal will be closely monitored. To track the progress of participants through the trial, we will adhere to and update weekly the Consolidated Standards of Reporting Trials (CONSORT) participant flow diagram.[48] Individuals who voluntarily withdraw will be asked to provide reason(s) for revoking their enrollment. Rates of enrollment and retention are key feasibility outcomes. Weekly remote group session attendance and asynchronous Mindfulness intervention usage metrics are key acceptability outcomes. Participants will also complete the acceptability of intervention measure (scores range from 4-20 points with higher scores reflecting higher acceptability).[49] Participants will receive compensation for data collection visits and related transportation costs. These activities will allow for the assessment of success and failure points to guide future work.

Expected results. The study will be deemed feasible if ≥ 30% of those approached enroll at a minimum rate of 1-3 women/week for each wave and ≥ 80% of women enrolled are retained with complete data collection at both assessment time-points. The intervention will be deemed acceptable if women attend ≥ 80% of the Mindfulness group sessions, engage with ≥ 80% of the asynchronous Mindfulness content and score ≥ 16 on the acceptability survey.

Aim 2. Explore changes (baseline to postintervention) in perceived and objective measures of stress including heart rate, hair cortisol and circulating EPI, NE, and CORT and perceived stress from baseline to post-intervention.

Stress markers. Lab and Core personnel will be blinded to both treatment assignment and time-point. ***HPA axis activity***: We will measure circulating CORT in serum via mass spectrometry at the RRC Mass Spectrometry Core. The Core will follow standard sample preparation and analysis procedures and uses standards from Sigma-Aldrich (St. Louis, MO). CORT will be extracted by protein precipitation protocol, followed by dryness under nitrogen and reconstitution in HPLC-grade water acetonitrile and formic acid before subjected to LC/MS analysis. The sample analysis will be carried out in the LC-MS/MS (Agilent 1290 UPLC coupled to AB Sciex QTRAP 6500). ***Hair cortisol:*** We will assess hair cortisol from a 2 cm scalp hair sample (one month's growth represents cortisol deposition over the previous month).[50, 51] Hair cortisol is a robust marker of the recent past (i.e., weeks or months) or an ongoing stressor, that is responsive to MBSR.[52] Hair will be taken from the crown and vortex of the head and stored at -80°C until analysis. Hair health will also be considered when collecting hair samples. Each hair sample will be weighed, washed twice with isopropanol, and air-dried for a minimum of 24 hours. Methanol will be added to the powdered hair and the cortisol extracted. Tubes are centrifuged, after which methanol extract is removed to a clean tube and evaporated using a vacuum evaporator. The dried extract is reconstituted in assay buffer, filtered to remove particulate material, and then frozen for subsequent assay. The CORT content of the extract is analyzed in duplicate along with control via immunoassay (Enzo Lifesciences, Farmingdale, NY), which is converted to pg cortisol/mg dry hair weight. The ELISA-based measurement of is more sensitive compared to mass spec.[53] Baseline and post-intervention samples for a participant will be assayed on the same plate. We have successfully collected hair from the target population through a study funded by the UIC Center for Health Equity Chicago NIMHD U54. ***SNS activity***: We will measure circulating catecholamines, EPI and NE, in serum via mass spectrometry at the RRC Mass Spectrometry Core following the methods described above.

Resting heart rate. Heart rate will be assessed in duplicate using an automated blood pressure cuff (Omron, Hoffman Estates, IL). Participants will rest quietly for 10 minutes prior to the first measurement with a 5-minute rest between measurements. The average of the two measures will be calculated.

Perceived stress. Perceived stress will be determined using two measures. The PSS queries participants' perceptions of feeling stressed during the last month. Responses were on a 5-point scale from "never" to "very often." Scores will be summed to indicate current stress levels, with higher scores suggesting greater perceived stress (≥ 14 indicates moderate to high perceived stress). We will also administer the chronic stress burden survey[54, 55] that asks participants about ongoing stressors related to important life domains (health, work, relationships) that have lasted for at least 2 months. A score will be created by summing the number of ongoing stressors reported (range 0–8), which can be further collapsed into the number of stressors (0, 1, 2, ≥ 3).[56]

Expected results. We expect that the planned assessments will be feasible given our experience with the target population. We expect that, participants will have lower objective and perceived measures of stress post-intervention.

Aim 3. Explore changes in adiposity and immune and metabolic biomarkers from baseline to post-intervention. The goal of this aim is to explore changes in body composition, fasting glucose and systemic inflammation from baseline to post-intervention.

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Anthropometrics and body composition. Height will be measured (baseline only) in duplicate using a fixed stadiometer to the nearest 0.1 cm. Body weight will be assessed to the nearest 0.1 kg using a calibrated digital scale (Tanita BWB-800, Arlington Heights, IL). Whole body

composition will be assessed with participants in a fasted state and following a urine void using the GE iLunar DXA scanner which will allow for assessment of total body fat, body fat distribution and estimated visceral adiposity.

Fasting glucose. Fasting glucose will be assayed from serum (Quest Diagnostics, Wood Dale, IL).

Systemic inflammation. We will assess serum high-sensitivity C-reactive protein (hs-CRP) via nephelometry at a commercial lab (Quest Diagnostics, Wood Dale, IL).

Expected results. We expect that participants will have lower visceral adiposity % body fat, fasting glucose and CRP post-intervention.

Aim 4. Explore the impact on gut microbiota composition and colonic inflammation. This goal of this aim is to explore changes in gut microbiota diversity and composition and colonic inflammation post-intervention.

Stool nucleic acid extraction. Microbial genomic DNA will be extracted from stool using the PowerSoil DNA Isolation Kit (Qiagen) following the manufacturer's instructions by the RRC Genomics Core. Nucleic acid quality and quantity will also be assessed.

Microbial amplicon sequencing and bioinformatics processing. We will conduct 16S rRNA amplicon sequencing on the extracted microbial DNA at baseline and post-intervention. Sample prep and analysis will be conducted by the RRC Genomics Core. The V4 region of the 16S rRNA gene will be sequenced with the Illumina MiniSeq platform. Environmental controls will be included in the sequences to distinguish from any contaminants. 16S rRNA reads will be processed with DADA2,[57] which allows for determination of amplicon sequence variants (ASVs) present. ASVs with a low number of counts or with low abundance (< 0.5%) will be removed from downstream analysis. ASVs will be summarized at different phylogenetic levels and normalized using cumulative sum scaling.[58] Variation in community structure [alpha (i.e., Shannon) and beta diversity (e.g., Bray-Curtis distances) in response to the intervention will be determined within and between groups with R vegan and phyloseq packages.[59] Compositional differences will be determined using zero-inflated generalized liner models correcting for covariates (e.g., BMI) in R using metagenomeseq.[58]

Colonic inflammation. Fecal calprotectin is a non-invasive marker of intestinal inflammation.[60] From stool collected at baseline and post-intervention, fecal calprotectin will be assayed using a commercially available immunoassay kit (Alpco Diagnostics, Salem, NH). The lower level of detection for this assay is 32.5 µg/g. Values below the lower limit of detection were assigned at the value of 16.25 µg/g per assay instructions. Values above 100 µg/g are suggestive of intestinal inflammation.[61]

Expected results. We anticipate that participants will show a change in their gut microbiota composition (i.e., increased levels of Lactobacillus and Actinobacteria and decreased levels of Proteobacteria) and a reduction in fecal calprotectin s. We will begin to explore how microbial changes correlate with body composition, metabolic, and immune-related changes.

Additional Questionnaires

At baseline, subject sociodemographic status, mental health [stress (Perceived Stress Scale), We have identified factors that may influence intervention adherence and response. Participants will complete surveys related to health history (baseline only), medication and supplement use, use of behavioral health services, spirituality (PEW Surveys Questions Religion and Spirituality 2017),[62] p adverse childhood experiences,[64] discrimination,[65] resilience,[66] fear of crime,[68]

sleep,[69] anxiety,[70] and depressive symptoms.[71] Because diet and physical activity can affect stress, body weight, glucose metabolism and the gut microbiome we will measure dietary behavior at baseline and post-intervention, using the NCI Diet History Questionnaire-III[72, 73] We will examine intake of macro- and micronutrients as % kcal or per 1000 kcal. We will also calculate diet quality using the most current Healthy Eating Index (HEI).[74] We will also measure steps over a 7-day period with Fitbit (San Francisco, CA) with data transmitted through the Fitabase platform (San Diego, CA). To collect information about stool sample collection, participants will complete the Bristol Stool Scale at baseline and 8 week visits.

8.0 Expected Risks/Benefits

Potential Benefits:

There may be no benefit to participation. However, it is possible that Mindfulness will translate to a reduction in stress. It is possible that a reduction in stress may translate to decreased central adiposity and improved metabolic and lower systemic inflammation. It is important to note that the primary goal of this study is to assess the feasibility and acceptability of the Mindfulness intervention in the target population.

Potential Risks:

Breach of confidentiality of the subjects' records and bio-specimens. It is possible that research subjects would be concerned for a loss of privacy concerning collected research data/health information or biospecimen samples and through using the web-based *MyJourney* Mindfulness intervention or Fitabase Fitbit data platform.

Hunger or modest dizziness from fasting 12 hours. It is possible that participants experience hunger or modest dizziness from fasting from food and caloric beverages for 12 hours.

Pain or infection from venous blood draw. Risks pertaining to a venous blood draw include discomfort, bruising, and bleeding. Some subjects may be uncomfortable with having their blood drawn may feel lightheaded, dizzy or even faint. In rare instances (<1%), infection from the site of blood draw may occur.

Anthropometric assessments. Risks pertaining to anthropometric assessments (height, weight) are minimal. However, some individuals feel embarrassed having their weight measured.

Risk of radiation from DXA scan. The DXA scan to measure body composition uses X-rays that yield precise, high-quality images of body composition (*i.e.*, fat, muscle and bone.) The scan emits very low amounts of x-ray radiation that is equivalent to natural background radiation and similar exposure to what would be incurred on a trans-Atlantic flight.

Questionnaires and hair sampling. Responding to socio-demographic, health related questions, questionnaires on diet and hair sampling may cause some subjects discomfort or psychological distress.

Stool. Discomfort with handling stool. Subjects may feel discomfort or emotional distress when collecting stool. Mishandling stool may lead to infections.

Strategies to Reduce Risk:

We will take care to explain the entire study, the participant's involvement in the study, and the various risks and benefits. Participants will be told that their participation is completely voluntary and that they can choose to withdraw at any time without affecting any current or future dealings with the University of Illinois Chicago or University of Illinois Hospital and Health Sciences System. All research team members engaging with research participants and collecting research data will have completed human subjects and HIPAA training requirements. All team members will have been trained in the informed consent process, all data collection procedures including questionnaire administration.

Loss of confidentiality.

The confidentiality of subjects will be safeguarded using unique subject identification numbers/codes (ID #) rather than names on all biospecimens and data forms. A list of names of subjects and their locator form will be kept in a locked file separate from the raw data and destroyed within 2 years of the study's conclusion. Research staff who have access to the data will not have access to subject names. All subject biospecimen data will be kept in Tussing-Humphreys locked lab until analysis. The biospecimens will be labeled with ID, date, and specimen type only. All questionnaire data will be directly entered into the REDCap data management system using data structure developed by the study team. The *MyJourney* intervention and Fitabase data platform were designed for research purposes and have a backend research platform to obtain engagement data. At the end of each wave of participants, data will be downloaded to a CSV file and will include the participants unique study ID, uploaded to REDCap and removed from the intervention platform. Participants will be provided a study ID number, and they will determine their password for *MyJourney* and no identifiable information is collected through the web intervention or Fitabase. Only the investigators and members of the research team will have access to subject data files and biospecimens. Care will be taken in the presentation of data to not include any potentially identifying information. Overall, the risk of accidental disclosure of electronic personal health information is very small. Any breach of confidentiality would be taken seriously and would be reported promptly to both the IRB and the DSMC. The IRB and DSMC will determine necessary steps to make reparations, including notifying affected participants, and additional data protections.

Venous blood draw.

Blood will be obtained via venipuncture at baseline and post-intervention. There is usually minimal discomfort, and minimal risk of bleeding, infection, or phlebitis due to routine phlebotomy. To minimize risk of discomfort, bruising or bleeding, venous blood collection will be performed by an experienced phlebotomist or registered nurse. Subjects will be sitting or in the supine position during the blood draw to avoid any fall related injury as a result of dizziness or fainting. In rare instances (<1%), infection from the site of the blood draw may occur. This procedure will take place in our clinical laboratory at Applied Health Sciences by research staff trained in phlebotomy.

Hunger and dizziness from fasting.

Participants will be provided a small snack and beverage to break the fast after venous blood has been obtained.

Anthropometric assessments.

To minimize discomfort related to body measurements, assessments will be conducted by a trained and experienced research team member in a private area.

Risk of radiation from DXA scan.

A DXA scan emits a small amount of radiation deemed minimal risk for a non-pregnant adult. However, women will take a urine pregnancy test if they report prior to scanning if the report a menstrual period within the previous 12 months. This precaution is to avoid accidental fetal exposure to radiation. Drs. Lisa Tussing-Humphreys have extensive training in performing DXA scans and specifically with operating the GE Lunar iDXA machine located at the UIC Applied Health Sciences building and has extensively trained her research team.

Questionnaires and hair sampling.

The research team has extensive experience in administering health and socio-demographic related questionnaires and will work to minimize any participant distress. Questionnaires will be conducted in a private area and subjects can choose not to respond to a given question or an entire questionnaire if they are experiencing discomfort/distress. The team also has experience with collecting hair sample for cortisol analysis. To reduce distress related to sampling hair, the participant is shown the total sample in a falcon tube and how the hair will be sampled using a salon mannequin.

Stool.

Participants will be provided detailed instructions regarding how to properly collect the sample and are provided a pictogram to bring into the restroom detailing proper collection methods. Gloves are also provided, and proper handwashing advised before and after collection of the sample. After sample collection, participants will complete the Bristol Stool Questionnaire on paper to detail date and time of collection as well as quality of the sample. The survey will be returned with the stool sample. Data will be entered into REDCap and the paper form will be coded with participant study ID to be stored in a locked filing cabinet at Applied Health Sciences until the end of the study when the surveys will be destroyed.

9.0 Data Collection and Management Procedures

Sources of data include body weight and body composition measurements, blood samples, stool samples, dietary records, and questionnaire responses. Stool kits will be provided to participants at their baseline visit and picked up by research staff. Questionnaire data will be entered directly into REDCap. To protect participant identity, code numbers only will identify all laboratory specimens, evaluation forms, reports, and other records. Participant identities will not be used in any reports or publications resulting from this study. All participant records will be kept in locked files; code sheets linking the patient's name to a patient identification number will be stored separately in a locked file cabinet. Only study personnel will have access to the files. Blood specimens and stool samples will be stored at the Applied Health Sciences Building in a locked -80˚C freezer. Specimens will not be labeled with any personal identifiers. Only the participant ID and study week will be on the label of the blood specimens. Code sheets linking the participant's name to a participant identification number will be stored separately in a locked file cabinet for 2 years after the end of the intervention and then destroyed.

10.0 Data Analysis

Data will be analyzed using the statistical software, SAS V9.4 (SAS Institute) and R. We will summarize feasibility and acceptability metrics using descriptive statistics such as frequencies, percentages, means, and standard deviations (**Aim 1**). The endpoints include recruitment rate among eligible persons approached, adherence (i.e., % attendance at sessions and interaction with asynchronous content), % retained through post-intervention and scores on the acceptability survey. In **Aims 2 & 3,** analysis will be largely descriptive. We will evaluate distributions, identify any outliers, and look for patterns of missing data. Then, we will investigate changes in the variables from baseline to post-intervention. We will examine the trend plot of each participant and summarize trends to understand patterns of change for the Aim 2 & 3 measures. For the **Aim 4**, we will investigate changes in microbial community diversity and composition, and intestinal inflammatory changes from baseline to post-intervention. We will explore how the microbial and inflammatory changes correspond to changes in the stress, anthropometric, glucose and systemic inflammation measures.

Statistical analysis of the collected data will be performed by Dr. Nelson Chen a member of the UICC Biostatistics Shared Resource and Evaluation Core for the NCI Chicago CHEC U54 which is funding this study.

11.0 Quality Control and Quality Assurance

Team meetings will be held weekly in-person for the duration of the study. These meetings will be chaired by Drs. Alana Biggers and Lisa Tussing-Humphreys. Data will be monitored for completeness and accuracy of data entry. A research coordinator will be hired to oversee the study implementation. All staff working on the study will be trained on recruitment, testing procedures, specimen processing, and data management. Dr. Jasmin Searcy will implement the study. Dr. Biggers and Tussing-Humphreys will determine and certify when the staff member is ready to function independently. All procedures will be written, kept in an easy to locate study electronic Box folder, and updated and reviewed at study meetings as needed.

12.0 Data and Safety Monitoring

The risks associated with this study are minimal and the potential for serious adverse events is low. We have safety precautions in place for study procedures. The individuals who will be responsible for data safety and monitoring of this study include Alana Biggers, MD, Lisa Tussing-Humphreys, PhD, MS RD and Keith Naylor, MD. Dr. Nelson Chen (biostatistician) will share the responsibility of monitoring the data. Drs. Biggers, Tussing-Humphreys and Naylor will share primary patient safety monitoring for the intervention. Drs. Biggers and Tussing-Humphreys will assure that participants freely consent for study participation.

Data Safety Monitoring. Data Safety Monitoring will be ongoing and will be through the UICC DSMC. The following information will be reported as requested to the UICC DSMC: study event updates (e.g., changes in personnel, recruitment strategies, testing procedures), study enrollment (actual vs. expected), baseline data on subjects, recruitment and retention flow diagram, subject retention data (loss to follow up, withdrawals) and adverse health events. Adverse events will be separated by study related and non-study related. Report to IRB will occur per prompt reporting standards.

Blood and Stool Banking. Samples provided as part of this study will be stored with linked codes in a secure password-protected database owned by the Principal Investigator and the research staff (Tussing-Humphreys fridge-freezer at 1919 W. Taylor St. Chicago, IL). These samples will be stored for up to 2 years and then discarded. Any future use of the samples would

be reviewed and approved by an Institutional Review Board. These samples may be used in other future research studies, including genetic analyses and may have some commercial value. Tissue/specimen from donors will not receive any notice of future uses.

13.0 Statistical Considerations

This study is designed to evaluate the feasibility of the development of a larger study. We want to investigate and learn data management, data collection methodologies, and how to design a larger study in the future. Forty eight Black females will be recruited allowing for 20% dropout resulting in completed data collection on 40 individuals which supports the calculation of confidence intervals for feasibility and effect size components.[42] This feasibility-pilot study is not powered to detect statistically significant effects for improvement in chronic stress or the secondary/exploratory measures. The minimum detectable difference from baseline to post-intervention for these outcomes is 1 standard deviation with baseline and post-measurements that are correlated at r=0.5, alpha=0.05 and 80% power. We did not consider power for the overall and multiple pairwise comparisons between different groups nor will we correct for multiple comparisons because of the exploratory nature of the pilot study.

14.0 Regulatory Requirements

14.1 Informed Consent

Consent will be obtained prior screening by a member of the study team. The informed consent document will be captured in REDCap and stored electronically. All study team members will complete the CITI and HIPAA training courses and will be trained in to administer consent.

14.2 Participant Confidentiality

To protect participant identity, code numbers only will identify all laboratory specimens, evaluation forms, reports, and other records. Subject identities will not be used in any reports or publications resulting from this study. All patient records will be kept in locked files; code sheets linking the patient's name to a patient identification number will be stored separately in a locked file cabinet. Only study personnel will have access to the files.

14.3 Unanticipated Problems

Participants will be asked to report each adverse health events as they occur via telephone/email/text message. The investigative team will monitor adverse health events related to the study procedures, respectively. The PI will consult and determine the severity and appropriate response or action to the reported adverse health event. All serious unanticipated problems or serious adverse health events will be reported to the UIC Institutional Review Board (IRB) within 24 hours. Serious adverse health events are extremely unlikely to occur in this study; however, if such an event occurs, the PI will immediately inform the UIC Office for the Protection of Research Subjects and IRB within 24 hours. Any adverse event of a nature serious enough to warrant withdrawal from the study will also be reported to the UIC IRB in a timely manner.

UIC Office for the Protection of Research Subjects requires that all other problems (non-serious adverse events) be reported within five days of discovery and provide sufficient information to gauge severity and to complete the mandatory Office for the Protection of Research Subjects report form. UIC for the Protection of Research Subjects has procedures in place to review the report form, and the PI are notified if further review, changes to research protocol or consent form, or other action is required. The PI will notify UIC IRB require further action after any unanticipated problem/adverse event is reported.

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