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# How Discrimination Gets Under the Skin: Biological Determinants of Discrimination Associated With Dysregulation of the Brain-Gut Microbiome System and Psychological Symptoms

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## Abstract

**BACKGROUND:** Discrimination is associated with negative health outcomes as mediated in part by chronic stress, but a full understanding of the biological pathways is lacking. Here we investigate the effects of discrimination involved in dysregulating the brain-gut microbiome (BGM) system.

**METHODS:** A total of 154 participants underwent brain magnetic resonance imaging to measure functional connectivity. Fecal samples were obtained for 16S ribosomal RNA profiling and fecal metabolites and serum for inflammatory markers, along with questionnaires. The Everyday Discrimination Scale was administered to measure chronic and routine experiences of unfair treatment. A sparse partial least squares-discriminant analysis was conducted to predict BGM alterations as a function of discrimination, controlling for sex, age, body mass index, and diet. Associations between discrimination-related BGM alterations and psychological variables were assessed using a tripartite analysis.

**RESULTS:** Discrimination was associated with anxiety, depression, and visceral sensitivity. Discrimination was associated with alterations of brain networks related to emotion, cognition and self-perception, and structural and functional changes in the gut microbiome. BGM discrimination-related associations varied by race/ethnicity. Among Black and Hispanic individuals, discrimination led to brain network changes consistent with psychological coping and increased systemic inflammation. For White individuals, discrimination was related to anxiety but not inflammation, while for Asian individuals, the patterns suggest possible somatization and behavioral (e.g., dietary) responses to discrimination.

**CONCLUSIONS:** Discrimination is attributed to changes in the BGM system more skewed toward inflammation, threat response, emotional arousal, and psychological symptoms. By integrating diverse lines of research, our results demonstrate evidence that may explain how discrimination contributes to health inequalities.

Structural racism contributes to health inequities and partially manifests as everyday, mundane experiences of discrimination (1–3). Self-reported discrimination is a risk factor for mental and physical disorders. However, the understanding of how discrimination gets embedded in biology and affects mental/physical health remains unclear.

Previously, the mechanistic understanding of the link between discrimination and disease was mainly centered on the hypothalamic-pituitary-adrenal (HPA) axis (4–6). However, recent studies have highlighted that the gut microbiome is extremely sensitive to stressors in influencing long-term health and inflammation (7–9). Stress can impact the bottom-up communication between the microbiome and the brain through several pathways, including changes in HPA activity, specific microbial metabolites, and vagus nerve and immuneinflammatory mechanisms (7,10–14).

Similarly, changes in brain activity can also influence the body and the gut. Neuroimaging studies suggest that discrimination rewires the brain, causing dysregulation of stress networks (15–21). These top-down signals from the brain influence gastrointestinal processes, including motility (22), intestinal permeability (23), and microbial gene expression (24–31). Dysbiosis in the brain-gut microbiome (BGM) system hampers host homeostasis due to its role in immune modulation and activation (32,33). Therefore, the major goal of this work is to examine how discrimination affects biology beyond the well-studied HPA axis by examining how discrimination alters the BGM system.

We propose a model highlighting the influence of discrimination on the bidirectional signaling between the brain and gut microbiome as mediated by inflammation. A novel aspect of this model reflects the dysregulation in connections between the central and enteric nervous systems (Figure 1).

Furthermore, discrimination has been predominantly studied in Black individuals as compared with White individuals, and few have studied how it may affect racial groups differently. It would seem logical that the effects of discrimination on health would be stronger among people of color than among White individuals, but the literature is mixed in this regard (34). Some studies show that discrimination is associated with increased C-reactive protein levels among Black individuals (35), whereas other studies show no differences (36,37). One study showed that among Asian immigrants, discrimination was related to increased obesity, which is not as commonly seen in other races (38), while other studies have shown that among Latinx individuals, discrimination is associated with outcomes such as depression and substance use (39,40). This raises an intriguing question as to why discrimination may have varying effects across different races/ethnicities. Obesity, substance abuse, and depression have all been linked to the BGM system. Therefore, these differences may be related to differences in how dysregulation of the BGM system occurs within each race/ethnicity.

To study a holistic view of how discrimination can affect biology, we performed a detailed analysis of discrimination on the BGM system in a racially diverse population to test whether 1) experiences of everyday discrimination will be associated with increased alterations in stress brain connectivity pathways (resting-state functional magnetic resonance imaging [fMRI]) and stress-related gut microbiome (16S sequencing and fecal metabolites) as mediated by increased inflammatory processes (peripheral blood mononuclear cells [PBMCs]), 2) these associations will be related to increased adverse behavioral and psychological measures, and 3) these associations will vary across Asian, Black, Hispanic, and White individuals.

## METHODS AND MATERIALS

### Ethics Approval and Consent to Participate

All procedures were approved by the Institutional Review Board (16–000187, 15–001591) at the University of California, Los Angeles, Office of Protection for Research Subjects. All participants provided written informed consent.

### Participants

The final sample comprised 154 adults from the 165 who were initially enrolled in the study. Participants were recruited from the Los Angeles community and clinics.

Participant data included fMRI for resting-state connectivity, anthropometrics, blood samples for genetic expression of inflammation via PBMCs, stool samples (microbiome and metabolomics), and survey questionnaires, including a diet history (Table S1 in Supplement 1). Participants self-reported race/ethnicity (Asian American, Black, Hispanic, or White). Discrimination was measured using the Everyday Discrimination Scale.

### Statistical Analysis

Group differences in demographic characteristics; brain, microbial taxa, and differential abundance testing for metabolomics; and PBMCs were determined individually (adjusting for sex, age, body mass index, and diet). For fMRI and metabolite data, sparse partial least square linear discriminant analysis (sPLS-DA) was done to analyze brain and metabolite data using the Mixomics package in R. Because the number of variables far exceeds the number of study participants, sparse multivariate nonparametric models exhibit the most robust statistical power and consistency (41). sPLS-DA operates using a supervised framework to find linear combinations of a limited set of variables that predicts predefined groups (42). sPLS-DA is a well-established method for both data reduction and classification analysis for both fMRI and metabolite data (42,43). Microbiome data were analyzed using QIIME2 and DESEq2 in R. PBMC data were analyzed using a priori–specified domains of immune function that have repeatedly been found to vary in response to psychosocial risk factors (44). For PBMC, Mann-Whitney $U$ test was performed between participants with low or high discrimination, and $p$ values were adjusted for multiple hypothesis testing using Bonferroni correction. Data were analyzed for factors associated with discrimination as well as within-group differences associated with discrimination. Factors that were associated with high levels of discrimination were then compared across races.

Integrated analyses involving associations between different datasets were performed using Spearman's correlation controlling for multiple hypothesis testing and presented as circos plots. Further details are provided in Supplemental Methods in Supplement 1.

## RESULTS

### Participant Differences Associated With Discrimination

Of the 154 participants (80 with high discrimination and 74 with low discrimination), the high discrimination group had higher levels of anxiety ($p = .009$), depression ($p = .009$), perceived stress ($p = .001$), visceral sensitivity ($p < .001$), early-life adversity ($p = .009$), neuroticism ($p = .01$), and worse scores for mental health ($p = .01$) and physical health ($p = .02$) than the low discrimination group (Table 1). There were no significant differences in sex, age, body mass index, education, marital status, and diet. When examining across race/ethnicity within the high levels of discrimination group, Hispanic individuals reported the highest levels of early-life adversity, levels significantly higher than in Asian individuals ($p = .04$). Black individuals reported the highest levels of resilience, levels significantly

higher than in Asian individuals ($p = .02$). Black individuals reported the lowest levels of neuroticism, levels significantly lower than in Asian ($p = .02$), Hispanic ($p = .001$), and White ($p = .01$) individuals. Black individuals had the lowest levels of trait anxiety, depression, and perceived stress and significantly lower than in Hispanic individuals ($p = .03$, .03, and .02, respectively). Black individuals also had the highest reported scores for mental health, scores significantly higher than in Hispanic individuals ($p = .003$). There were no significant differences in extraversion, socioeconomic status, and self-reported physical health in individuals who experienced high levels of discrimination across the races.

For Asian, Black, and Hispanic participants, race was the most common reason for discrimination. For White participants, gender and age were the most common reasons for discrimination (Table S2 in Supplement 1). The average Everyday Discrimination Scale score for participants who had high levels of discrimination was similar across the different races ($p = .18$).

## Discrimination Is Associated With Altered Brain Connectivity

In the aggregated sample, high discrimination as compared with low discrimination was associated with increased connectivity between the default mode network (DMN) (supramarginal gyrus, superior temporal sulcus, lateral aspect of the superior temporal gyrus, inferior temporal sulcus, middle temporal gyrus, precuneus, and transverse temporal sulcus) and the sensorimotor network (SMN) (precentral gyrus, Heschl's gyrus, subcentral gyrus, paracentral lobule, superior frontal gyrus, posterior lateral sulcus, and inferior and superior part of the precentral sulcus). High discrimination was also associated with increased connectivity between the central autonomic network (CAN) (medial orbital gyrus, gyrus rectus, frontomarginal gyrus, and orbital sulcus) and the emotion regulation network (ERN) (several subregions of the anterior cingulate cortex, orbital part of the inferior frontal gyrus, and parahippocampal gyrus), salience network (SAL) (anterior insula, anterior midcingulate cortex), and occipital network (OCC) (middle and superior occipital sulcus, superior occipital gyrus, and occipital pole). High discrimination as compared with low was associated with decreased connectivity between regions of the central executive network (CEN) (intraparietal sulcus, subparietal sulcus, superior parietal lobule, and middle frontal gyrus) to various regions of the CAN, SMN, and OCC. (Loadings and variables of importance from the sPLS-DA are listed in Tables S3–S7 in Supplement 2.)

More specific discrimination-based differences were observed in brain connectivity when stratified by race/ethnicity (Figure 2). For Black participants, high levels of discrimination as compared with low were related to higher connectivity within the CEN (orange) and with the DMN (blue). For Hispanic participants, high discrimination as compared with low was associated with higher connectivity within regions of the DMN and between regions of the DMN with regions from the CEN, SAL (yellow), CAN (red), and OCC (purple). For Asian participants, high discrimination, as compared with low, was associated with higher connectivity within regions of the SMN (green) and within the OCC. In addition, there was higher connectivity between regions of the CEN with CAN and DMN. For White participants, high discrimination as compared with low was associated with higher connectivity involving various brain regions within the ERN (pink) and reward network

(RN, gray), which was unique to this group and within the SMN, DMN, SAL, CAN, CEN, and OCC, which was also seen in the other groups.

Similar patterns were observed when investigating differences across races in the high discrimination group only: Black individuals had greater connectivity in the CEN, DMN, and OCC but decreased connectivity in the CAN compared with White individuals. Hispanic individuals, compared with Asian individuals, had greater connectivity in the DMN and OCC, but decreased connectivity in the SMN, and compared with White individuals, they had greater connectivity in the CEN and DMN. Asian individuals, compared with White individuals, had greater connectivity in the SMN (details in Table S8 in Supplement 2).

## Discrimination Is Associated With Gut Microbiome and Metabolite Changes

Microbiome and metabolite differences related to discrimination were only apparent when stratified by race/ethnicity (Figure 3).

Black participants had 9 bacterial species that were different by discrimination. High levels of *Prevotella*, *Coprococcus*, and *Tyzzerella* and lower levels of species belonging to *Bacteroides*, *Parabacteroides*, and Ruminococcaceae were observed in the high discrimination group compared with those found in the low discrimination group. For Black participants, high discrimination was also associated with a reduced level of hydroxy-*N6,N6,N6,*-trimethyllysine as compared with low discrimination.

In Hispanic individuals, high discrimination as compared with low was associated with a higher level of *Bacteroides stercosis* and lower levels of valerate, levulinate, 3-(4-hydroxyphenyl)lactate, pregnanolone/allopregnanolone sulfate, and isovalerate.

For Asian participants, 11 fecal metabolites were higher in participants with high discrimination than in partipants with low discrimination. These include 3-beta-hydroxy-5-cholestenoate, beta-sitosterol, campesterol, cholesterol, desmosterol, fucosterol, palmitoyl-sphinganine, and palmitoyl-sphingosine.

For White participants, a high level of discrimination as compared with low was associated with changes in 7 bacterial species (reduction in *Prevotella copri*, *Bacteroides salyersiae*, *Blautia stercosis*, *Faecalibacterium prausnitzii*, and unknown species of *Prevotella* and Ruminococcaceae and an elevation in *Catenibacterium mitsuokai*).

Bacteria and metabolite differences across races in individuals experiencing high levels of discrimination are summarized in Tables S9 and S10 in Supplement 1. In this analysis of individuals who experienced high levels of discrimination, *P copri* was the highest in Black and Hispanic individuals and was the lowest in White individuals ($p = .04$). Similarly, of the metabolites analyzed in individuals who experienced high levels of discrimination, only isovalerate, valerate, and fucosterol were statistically different between the races. Isovalerate and valerate were significantly lower in Hispanic than in White individuals ($p = .04$ and .04, respectively), and fucosterol was significantly higher in Asian than in White individuals ($p = .03$).

## Effects of Discrimination on Inflammatory Markers

Of the a priori set of immune markers, which included 19 genes involved in inflammation and 32 genes involved in type I interferon responses, 4 markers were associated with high discrimination as compared with low discrimination (Figure 4).

In Black participants, high discrimination as compared with low was associated with elevated levels of prostaglandin-endoperoxidase synthase 1 (*PTGS1*). In Hispanic participants, high discrimination as compared with low was associated with elevated levels of interferon-induced protein 35 (*IFI35*) and interleukin 1β (*IL1B*). In White participants, high discrimination as compared with low was associated with a reduction in interferon regulatory factor 8 (*IRF8*). There were no inflammatory markers that were different in Asian participants.

Examining only individuals who experienced high levels of discrimination across races, Black individuals had the highest level of *PTGS1*, which was significantly higher than in White individuals ($p = .03$). Hispanic individuals had the highest level of IL1B, which was significantly higher than in White individuals ($p = .001$). There was no statistical difference in the expression level of *IFI35* or *IRF8* in individuals who experienced high levels of discrimination across races.

## Association Networks Differ by Discrimination and by Race/Ethnicity

The association networks within the BGM system with high discrimination levels and by race/ethnicity are represented in the connectograms (Figure 5).

In Black participants, hydroxy-*N6,N6,N6*,-trimethyllysine was negatively associated with the DMN and CEN, and inflammatory markers IRF8 and IL-1β were positively associated with resilience, which was also positively associated with the DMN and CEN. There were positive connections between stress and anxiety with several bacterial species (*Para-bacteroides* and *Bacteroides*).

Among Hispanic participants, inflammatory marker IRF8 was associated with higher levels of anxiety and neuroticism and with the lipid metabolite valerate. Higher levels of physical symptoms (Patient Health Questionnaire and Short Form Survey 12 Physical Component Score) were positively associated with the DMN and with the anterior midcingulate cortex (key region of the SAL), but high socioeconomic status was also positively associated with the DMN.

In Asian participants, there were several positive associations between metabolites related to cholesterol (lipid pathway), microbial species (*Prevotella*, Ruminococcaceae), and anxiety (state and trait), neuroticism, depression, and physical symptoms. Asian individuals who experienced high discrimination also had several connections to the SMN and OCC.

White participants had several associations between the gut microbiome (*Coprococcus*, *Ruminococcus*, Ruminococcaceae, *Parabacteroides*, *Alistipes*, *Bacteroides*) and widespread brain networks (including the ERN and RN) and with anxiety, depression, neuroticism,

early-life adversity, stress, visceral sensitivity, and physical symptoms. It was the only group that demonstrated negative associations between resilience and other variables.

## DISCUSSION

We examined the association between everyday experiences of discrimination and alterations in the BGM system. Generally, discrimination was associated with anxiety, depression, and worse measures of physical and mental health. However, these associations varied across race/ethnicity, with Black individuals having no association between discrimination and mental health.

A history of discrimination was associated with widespread connectivity differences in several networks, but with race/ethnic differences contributing to the greatest variance. The differences seen in the BGM system between the different racial/ethnic groups could be due to the varying types of discrimination experienced by the different groups. A key feature of our work is the inclusion of multiple forms of discrimination. While racial discrimination is important, our study allowed participants to report on discrimination based on other factors (e.g., gender, age, religion). This was critical for capturing the spectrum of experiences for our diverse sample. For minorities, skin color and race were the most common reason for discrimination. For White individuals, gender and age were the most common reasons. Discrimination based on race and skin color can occur as early as in childhood, a period of time that is critical for the development of the BGM system (45), while discrimination based on gender and age is more common in young adulthood (46). One of the most common reasons suggested to explain the cause of negative physical health outcomes associated with discrimination is an increase in allostatic load and the involvement of multiple biological systems (47). Discrimination based on race and skin color, which can occur in early childhood, could lead to a longer period of stress and allostatic load than other forms of discrimination (46,48). These differences may alter the BGM system in a way that may enhance vulnerability to various behaviors and psychological symptoms.

### Discrimination and Altered Brain Connectivity

Discrimination was linked with heightened self-reflectiveness and pain-related processing, as indicated by increased connectivity in the DMN and SMN (49–54). While self-generated thoughts can be a source of creative insight and introspection, they can lead to distress and negatively impact performance of specific tasks (55). These results suggest that alterations within the DMN and SMN may reflect difficulties with cognitive and affective appraisal of pain in relation to discrimination. Discrimination was also associated with heightened emotion regulation (ERN), autonomic (CAN), alertness (SAL), and attention toward salient stimuli (OCC). Experiences of discrimination are typically stressful (56), leading to anxious emotions and heightened cognitive load (57). However, the discrimination-related patterns in the brain showed strong differences when examined by racial/ethnic groups.

In Black participants, discrimination was associated with higher connectivity within the DMN and CEN. The DMN is important in self-recollection of past experiences (58–61) and may be key in navigating stressful experiences (62–65), while the CEN contributes to emotion regulation and inhibitory control in stressed-evoked situations (16,66–68).

Attributing negative treatment externally can reduce negative emotions and self-blame (19). Our data showed that Black individuals are more likely to attribute discrimination to race relative to other groups (69,70), possibly using this as a coping mechanism to regulate distress accompanying discrimination.

In Hispanic participants, discrimination was associated with greater connectivity within the DMN, CEN, SAL, CAN, and OCC. Psychosocial stress is associated with cognitive impairment (71), and the SAL might be involved in regulation of heightened vigilance associated with discrimination. Hispanic individuals who experienced more discrimination were more likely to have early-life trauma, higher levels of anxiety, depression, stress, and visceral sensitivity than those who experienced less discrimination, similar to the hyperactivity of SAL regions observed in patients with anxiety, depression, and posttraumatic stress disorder (72–74). The CAN can be triggered by challenges to unpleasant social/environmental situations (75) and may indicate altered regulatory functions via viscerosensory mechanisms. These responses are not only critical for adapting to internal or external challenges, but also initiate signals that trigger emotion, affect decision making, and promote social behavior (76). Alterations in CAN highlight a risk factor for both mental and physical health problems. The alterations in the OCC suggest enhanced attention toward threatening stimuli experienced during discrimination (21).

In Asian individuals, discrimination was associated with higher connectivity within the SMN. The SMN is engaged in interoceptive, autonomic, sensory, motor, and reward processing (77–80). Increased SMN connectivity indicates disrupted sensory functions associated with somatization, similarly observed in stressed individuals and patients with major depressive disorder (81,82). The anterior insula, together with the SMN, has been implicated in social pain and, as a result, in physical pain due to distress associated with exclusion (83–85).

White participants who experienced high levels of discrimination displayed a chaotic enhanced resting-state connectivity in numerous large-scale networks including the ERN and RN, which may underscore the hypersensitivity and inability to cope with discrimination in comparison with other races/ethnicities. Disruptions in the communication between large-scale networks may reflect difficulty with reacting and coordinating efficiently to experiences of discrimination (86). Accordingly, some research shows that race-related stress can have a more negative effect on mental health for White than for Black individuals (87,88).

## Discrimination-Associated Gut Microbiome and Metabolite Changes

*P copri* was the only bacterium species that was significantly different across races. *P copri* was the highest in Black and Hispanic individuals who experienced discrimination as compared with White individuals who experienced discrimination. *P copri* produces a superoxide reductase and phosphoadenosine phosphosulfate reductase (89). These enzymes let *P copri* utilize reactive oxygen species, allowing it to thrive in inflammatory environments as well as increase inflammation (89). *P copri* is considered highly inflammatory and has been found in rheumatoid arthritis and hepatic fibrosis (90,91).

When examining metabolites, Black individuals with high discrimination had lower levels of hydroxy-*N6,N6,N6*-trimethyllysine, and Hispanic individuals had lower levels of branched-chain fatty acids as compared with Black and Hispanic individuals with low discrimination, respectively. Hydroxy-*N6,N6,N6*-trimethyllysine is a by-product of carnitine biosynthesis. Carnitine has anti-inflammatory and cardioprotective properties (92) and has been associated with reductions in interleukin 6 and tumor necrosis factor alpha (93). Hispanic individuals had the lowest levels of branched-chain fatty acids and had significantly lower levels than White individuals who also experienced similar levels of discrimination. Branched-chain fatty acids can have anti-inflammatory and anticancer properties and are important to colonic motility and health (94,95).

Unlike the patterns observed in Black and Hispanic individuals, the microbiome and metabolite panel of Asian and White individuals are less related to inflammation. In Asian individuals, high discrimination was associated with higher levels of metabolites that have been implicated in lipid metabolism. This profile may suggest dietary preference for foods high in fat in Asian individuals who experience high levels of discrimination. In White individuals, discrimination was associated with the lowest levels of *P copri*.

## Discrimination-Associated Inflammatory Changes

In Black individuals, discrimination was associated with higher levels of *PTGS1*, and in Hispanic individuals, discrimination was associated with higher levels of *IL1B*. Both of these were higher in Black and Hispanic individuals who experienced high levels of discrimination, as compared with White individuals who experienced similar levels of discrimination. PTGS1 is also known as cyclo-oxygenase 1 (*COX1*) and is the enzyme that catalyzes the conversion of arachidonate to prostaglandins. High levels of prostaglandins are produced in response to injury or infection and are major drivers of inflammation (96). Similarly, IL-1β is a proinflammatory cytokine that has been implicated in pain, inflammation, and autoimmune conditions (97). These findings suggest that discrimination may lead to a chronic state of inflammation, specially in Black and Hispanic individuals.

## Discrimination-Related Changes Within the BGM System and Clinical Implications

The BGM patterns highlight that high levels of discrimination in Black participants are associated with higher levels of inflammatory biomarkers as compared with Black participants with lower levels of discrimination. Despite the increase in inflammatory markers, the group as a whole showed the lowest levels of anxiety and depression, irrespective of discrimination. Black participants as a group had the highest resilience scores of any race. These findings suggest that the effect of discrimination on mental health in this group is likely being buffered by top-down processes related to resilience and cognitive flexibility (98–101).

In Hispanic participants, high discrimination was associated with peripheral markers (inflammation-*IRF8* and gut microbes) and several clinical behaviors (anxiety, physical health symptoms), but socioeconomic status and DMN activity related to better coping strategies and cognitive control could be overriding these negative effects. Similarly, some

studies have demonstrated that socioeconomic status can be protective against discrimination (35,102–106).

In Asian participants with high discrimination, there were positive associations between metabolites related to cholesterol and to several clinical measures (anxiety, depression, physical symptoms) and with SMN activity (social pain and visceral somatosensory processes) (50). This suggests that Asian individuals with high discrimination are possibly eating foods that are high in fat to deal with the associated feelings of anxiety, depression, and somatosensory/visceral signals, which is consistent with studies demonstrating the emphasis on physical symptoms as a way to deal with painful emotional and stressful situations.

In White participants with high discrimination, there were several widespread associations within the BGM system, and it was the only group that included connections to the ERN and RN (a network associated with emotional stress). This pattern, together with the negative association with resilience, highlights the decreased regulatory deficiency in reacting and coordinating efficiently to novel and stressful experiences of discrimination in White participants.

### Limitations

While this is the first study to examine discrimination across different racial groups in relation to the BGM system, there are several limitations to the current study. Black individuals were underrepresented in the study. This low sample size could make the analysis for Black individuals underpowered to discern small effect sizes as well as raise the possibility of sampling bias. However, we do not present any data that conflict with previously published works regarding Black individuals and discrimination, but rather expand on their relation to the BGM system. Future studies looking into the BGM system and discrimination should attempt to increase the representation of Black individuals. Finally, while a major strength of this article is the incorporation of multiple biological systems, we did not examine other systems that are likely involved in discrimination such as the HPA axis and the autonomic nervous system. But this body of work shows that discrimination has a holistic effect on the body and the mind, and therefore, discrimination's effect on health is complex and multifactorial.

## Conclusions

Unfair treatment is experienced by all people. Our findings provide a preliminary framework for understanding how unfair treatment is perceived and processed in the brain and how these are, in turn, related to inflammation, gut microbiome, and psychological symptoms. Of course, much more work remains, but it provides an initial step toward understanding how social inequalities become a whole-body experience and gives some understanding of how expressions of "racism makes me sick to the stomach" might have an actual manifestation in the body.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Funding was acquired by AG. TSD, GCG, and AG were involved in conceptualization of the study; TSD and AG developed the methodology; and TSD, AG, ZC, VS, YZ, YG, and SC performed the formal analysis. AG was responsible for resources/data curation. TSD, GCG, HB-S, MW, VO, LAK, JSL, BN, XZ, SC, EAM, and AG contributed to writing and original draft preparation. TSD, YZ, and AG contributed to visualization. The entire study was supervised by AG. All authors read and approved the final manuscript.

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The datasets generated during and/or analyzed during the current study are not publicly available due to an ongoing collaboration with multiple principal investigators involving participant identifiers at the G. Oppenheimer Center for Neurobiology of Stress and Resilience. However, data are available from the corresponding author on reasonable request.

Participants or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

AG is a scientific consultant to Yamaha. EAM is a scientific advisory board member of Danone, Axial Biotherapeutics, Amare, Mahana Therapeutics, Pendulum, Bloom Biosciences, Seed, and APC Microbiome Ireland.

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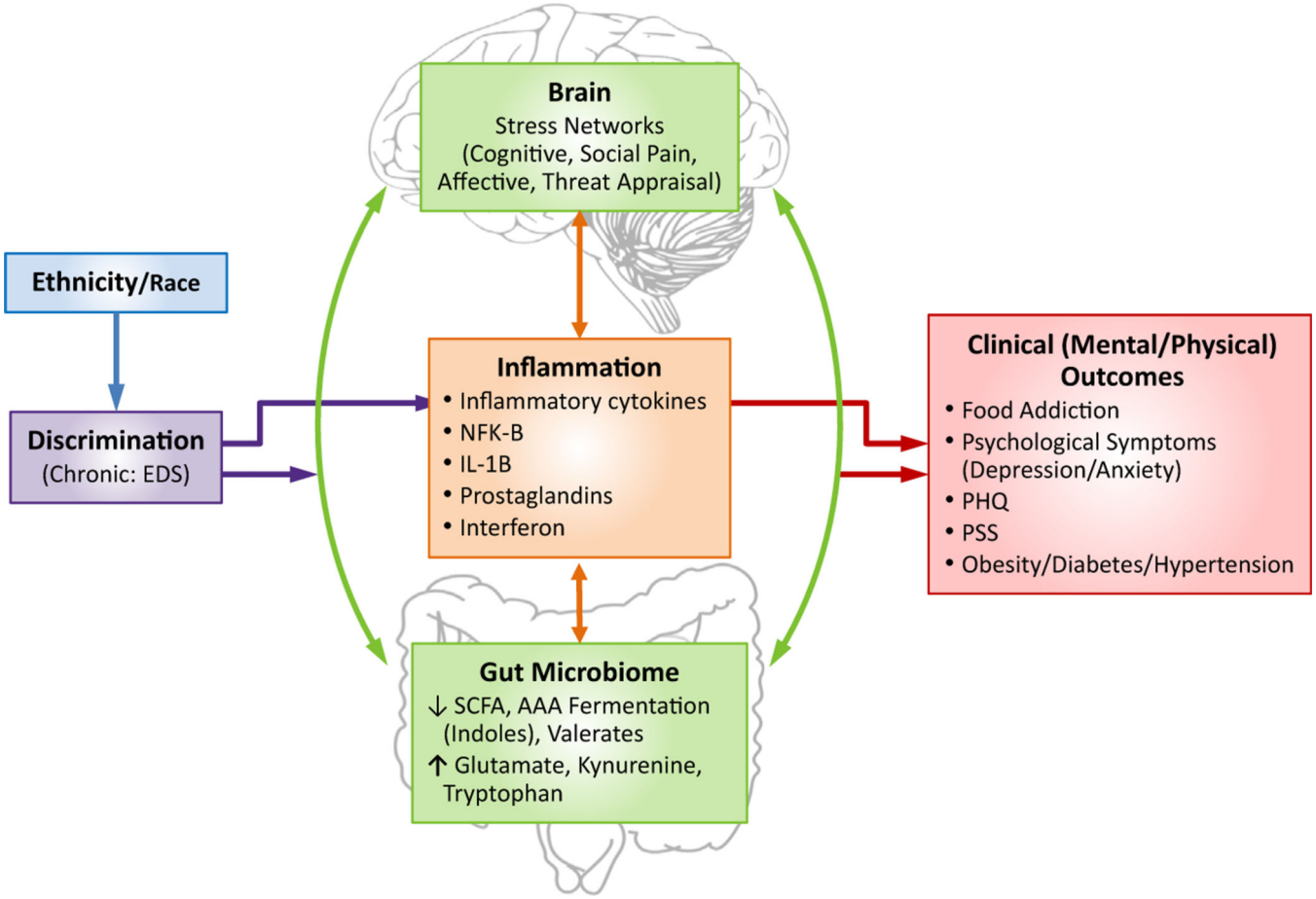


**Figure 1.**

Conceptual model linking the brain-gutmicrobiome system to discrimination and clinical outcomes. AAA, aromatic amino acid; EDS, Everyday Discrimination Scale; IL-1 β, interleukin 1β; NFK-B, nuclear factor kappa light chain enhancer of activated B cells; PHQ, Physical Health Question-naire; PSS, Perceived Stress Scale; SCFA, short-chain fatty acids.

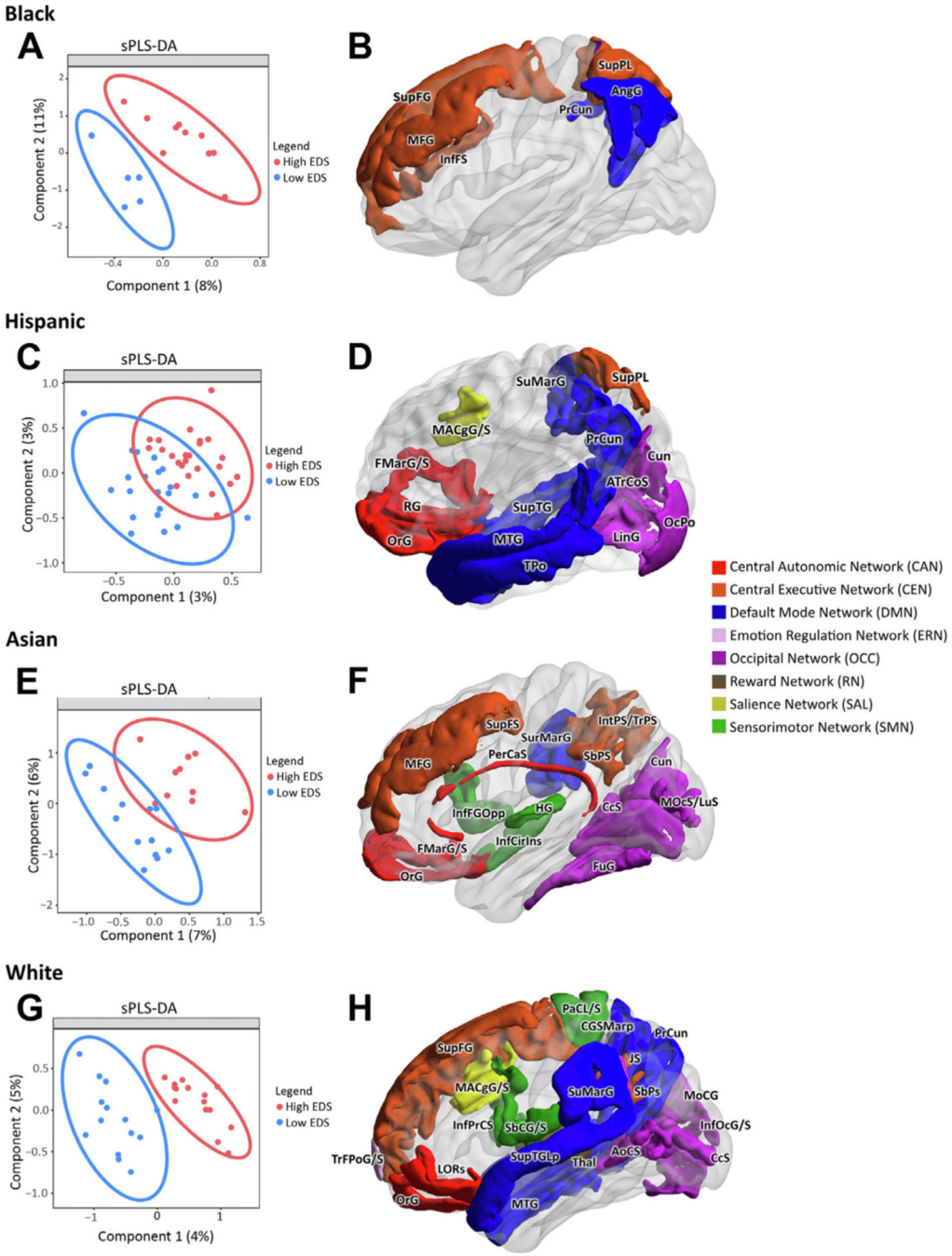


**Figure 2.**

Brain regions associated with discrimination by race/ethnicity. Sparse partial least square linear discriminant analysis (sPLS-DA) plots, restingstate pairwise differences by levels of discrimination, and anatomical diagram of brain regions associated with discrimination across the different races/ethnicities: Black **(A, B)**, Hispanic **(C, D)**, Asian **(E, F)**, and White **(G, H)**. AngG, angular gyrus; AoCS, anterior occipital sulcus; ATrCos, anterior transverse collateral sulcus; CcS, calcarine sulcus; CgSMarp, marginal branch of the cingulate sulcus; Cun, cuneus; EDS, Everyday Discrimination Scale; FMarG/S, fronto-marginal gyrus and

sulcus; FuG, fusiform gyrus; HG, Heschl's gyrus; InfCirInS, inferior segment of circular sulcus of the insula; InfFGOpp, opercular part of the inferior frontal gyrus; InfFS, inferior frontal sulcus; InfOcG/S, interior occipital gyrus/sulcus; InfPrCS, inferior part of the precentral sulcus; IntPS/TrPS, intraparietal sulcus (interparietal sulcus) and transverse parietal sulci; JS, sulcus intermedius primus (of Jensen); LinG, lingual gyrus; LORs, lateral orbital sulcus; MACgG/S, middleanterior part of the cingulate gyrus and sulcus; MFG, middle frontal gyrus; MoCG, middle occipital gyrus; MOcS/LuS, middle occipital sulcus and lunatus sulcus; MTG, middle temporal gyrus; OcPo, occipital pole; OrG, orbital gyri; PaCL/S, paracentral lobule and sulcus; PerCaS, pericallosal sulcus; PrCun, precuneus; RG, gyrus rectus; SbCG/S, subcallosal gyrus/sulcus; SbPs, subparietal sulcus; SuMarG, supramarginal gyrus; SupFG, superior frontal gyrus; SupFS, superior frontal sulcus; SupPL, superior parietal lobule; SupTG, superior temporal gyrus; SupTGLp, lateral aspect of the superior temporal gyrus; Thal, thalamus; TPo, temporo-parietooccipital; TrFPoG/S, transverse frontopolar gyri and sulci.

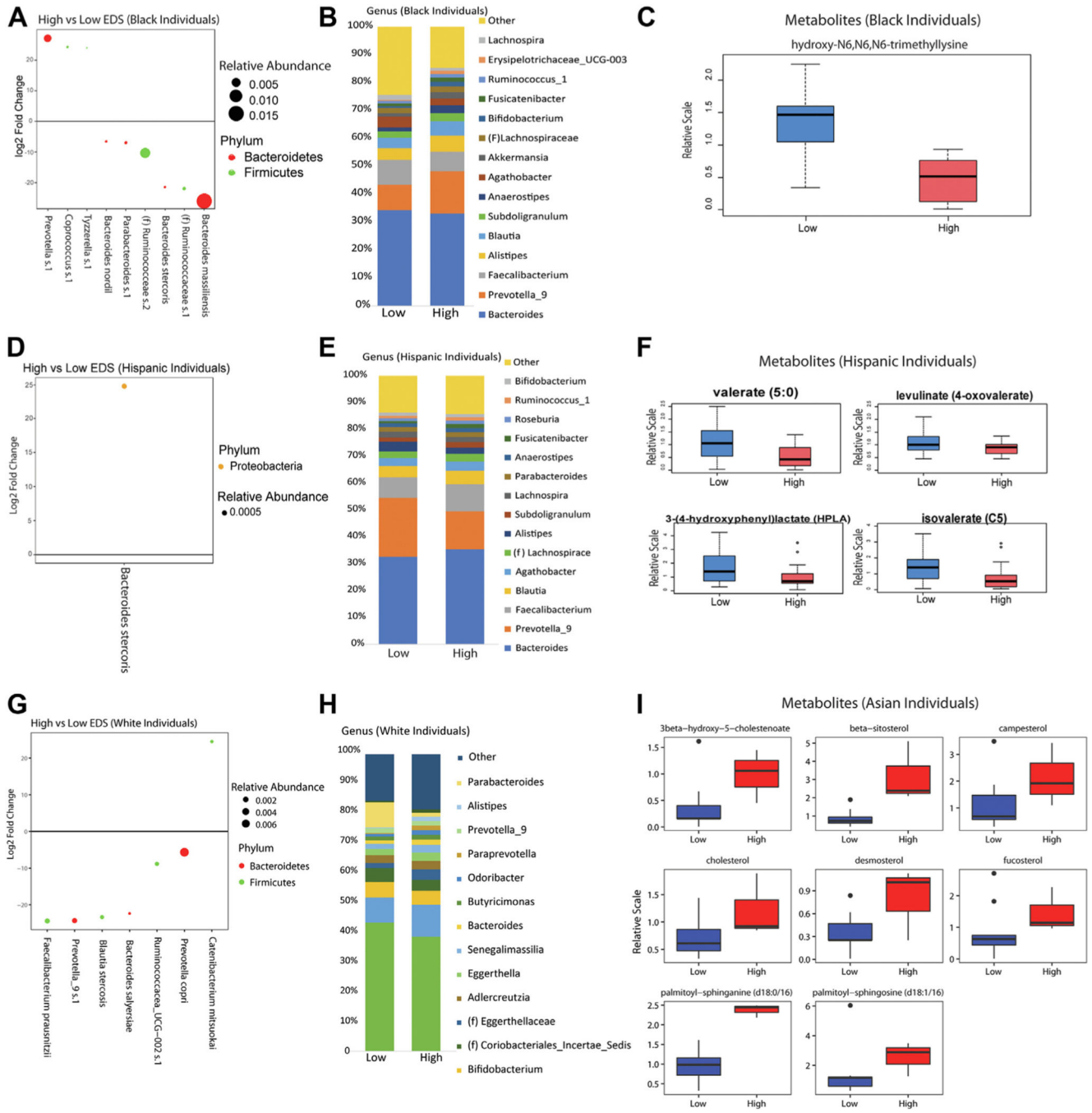


**Figure 3.**

Microbiome and fecal metabolites associated with discrimination by race/ethnicity. **(A)** Differential abundance testing by DESEq2 of bacterial taxa associated with discrimination in Black individuals. **(B)** Taxonomic plot of genera with a relative abundance ≥ 1% by discrimination in Black individuals. Similar analysis represented for Hispanic **(D, E)** and White **(G, H)** individuals. Fecal metabolites by discrimination in Black **(C)**, Hispanic **(F)**, and Asian **(I)** individuals. Asian individuals had no microbiome differences by

discrimination level, and White individuals had no metabolites that were different by discrimination level. EDS, Everyday Discrimination Scale.

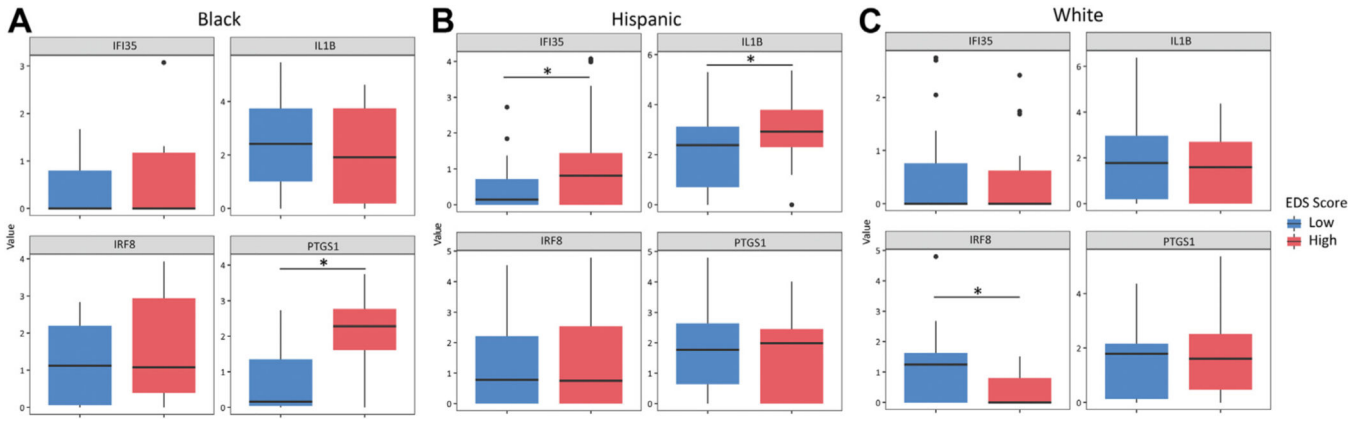


**Figure 4.**

Expression levels of several inflammatory markers extrapolated from peripheral blood mononuclear cells for Black **(A)**, Hispanic **(B)**, and White **(C)** participants. *$p$ value < .05. EDS, Everyday Discrimination Scale.

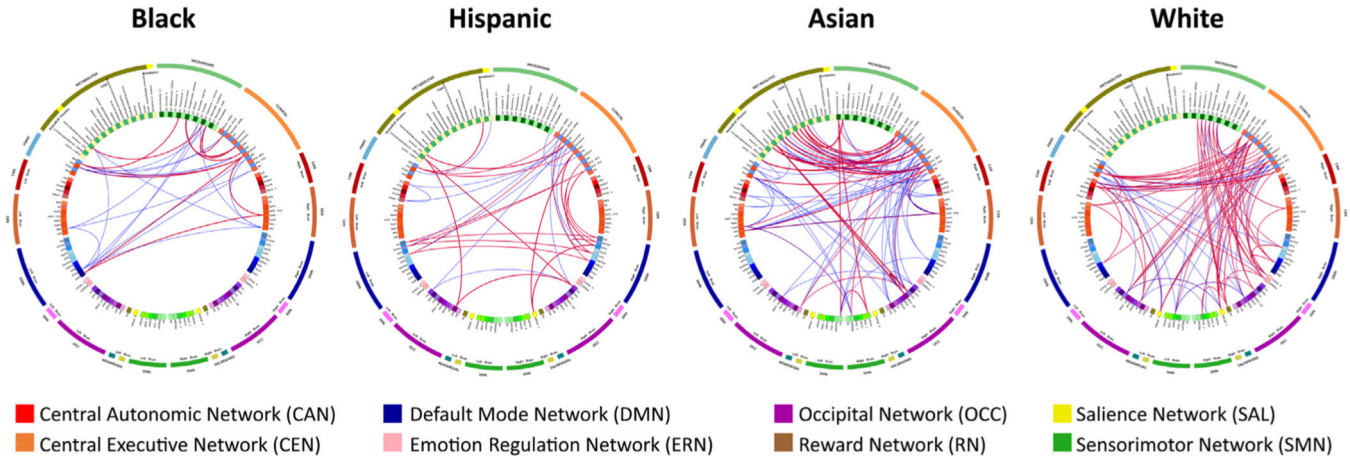


**Figure 5.**

Networks depicting high discrimination associated with brain-gut microbiome immune factors. Networks relating brain, peripheral blood mononuclear cells, microbiome, and clinical questionnaire data by race in those individuals experiencing high discrimination. Red lines are positive associations, and blue lines are negative associations.

**Table 1.**

Participant Characteristics and Clinical Questionnaires

| Characteristics | All Participants | | | Asian Participants | | | Black Participants | | | White Participants | | | Hispanic Participants | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Low EDS, *n* = 74** | **High EDS, *n* = 80** | ***p*** | **Low EDS, *n* = 18** | **High EDS, *n* = 13** | ***p*** | **Low EDS, *n* = 7** | **High EDS, *n* = 13** | ***p*** | **Low EDS, *n* = 19** | **High EDS, *n* = 21** | ***p*** | **Low EDS, *n* = 29** | **High EDS, *n* = 33** | ***p*** |
| EDS, Mean (SD) | 2.1 (2.1) | 12.9 (5.7) | <.001[a] | 1.8 (2.1) | 13.6 (7.6) | <.001[a] | 2.9 (1.9) | 15.6 (6.9) | <.001[a] | 2.2 (2.3) | 11.6 (3.9) | <.001[a] | 2.1 (2.1) | 12.4 (5.2) | <.001[a] |
| Female, *n* = 111 | 49.50% | 50.50% | .55 | 53.85% | 46.15% | .37 | 42.90% | 57.10% | .26 | 45.80% | 54.20% | .79 | 50.00% | 50.00% | –.39 |
| Male, *n* = 43 | 44.20% | 55.80% | | 80.00% | 20.00% | | 16.70% | 83.30% | | 50.00% | 50.00% | | 37.50% | 62.50% | |
| Age, Years, Mean (SD) | 32.6 (10.3) | 30.5 (10.3) | .21 | 22.3 (9.5) | 29.0 (9.8) | .63 | 32.6 (10.3) | 30.5 (10.3) | .21 | 32.6 (10.3) | 30.5 (10.3) | .21 | 32.6 (10.3) | 30.5 (10.3) | .21 |
| BMI, Mean (SD) | 29.9 (5.9) | 29.9 (5.8) | .98 | 24.7 (4.0) | 25.0 (5.1) | .83 | 29.9 (5.9) | 29.9 (5.8) | .98 | 29.9 (5.9) | 29.9 (5.8) | .98 | 29.9 (5.9) | 29.9 (5.8) | .98 |
| Education | | | | | | | | | | | | | | | |
| Some high school | 40.00% | 60.00% | .88 | 0.00% | 0.00% | .26 | 0.00% | 0.00% | .37 | 0.00% | 0.00% | .80 | 0.00% | 100.00% | .45 |
| High school graduate | 47.30% | 52.70% | | 100.00% | 0.00% | | 20.00% | 80.00% | | 36.40% | 63.60% | | 50.00% | 50.00% | |
| College graduate | 47.90% | 52.10% | | 55.56% | 44.44% | | 50.00% | 50.00% | | 51.70% | 48.30% | | 44.10% | 55.90% | |
| Marital Status | | | | | | | | | | | | | | | |
| Never married | 43.90% | 56.10% | .39 | 65.22% | 34.78% | .22 | 25.00% | 75.00% | .43 | 34.60% | 65.40% | .03[a] | 43.20% | 56.80% | .38 |
| Married | 51.30% | 48.70% | | 40.00% | 60.00% | | 50.00% | 50.00% | | 87.50% | 12.50% | | 44.40% | 55.60% | |
| Divorced | 56.30% | 43.80% | | 0.00% | 100.00% | | 33.30% | 66.70% | | 60.00% | 40.00% | | 71.40% | 28.60% | |
| Widowed | 100.00% | 0.00% | | 0.00% | 0.00% | | 100.00% | 0.00% | | 0.00% | 0.00% | | 0.00% | 0.00% | |
| Questionnaire Scores, Mean (SD) | | | | | | | | | | | | | | | |

| Characteristics | All Participants | | | Asian Participants | | | Black Participants | | | White Participants | | | Hispanic Participants | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low EDS, *n* = 74 | High EDS, *n* = 80 | *p* | Low EDS, *n* = 18 | High EDS, *n* = 13 | *p* | Low EDS, *n* = 7 | High EDS, *n* = 13 | *p* | Low EDS, *n* = 19 | High EDS, *n* = 21 | *p* | Low EDS, *n* = 29 | High EDS, *n* = 33 | *p* |
| ETI total | 3.6 (4.3) | 5.5 (4.4) | .009[a] | 2.2 (2.7) | 3.3 (3.3) | .32 | 3.3 (4.1) | 3.9 (4.5) | .76 | 4.2 (4.7) | 5.6 (3.9) | .30 | 4.3 (4.9) | 6.9 (4.7) | .04[a] |
| CDRISC | 80.5 (12.0) | 76.9 (13.3) | .09 | 76.2 (13.8) | 72.6 (13.1) | .48 | 88.0 (9.4) | 84.9 (10.2) | .52 | 81.8 (11.2) | 75.2 (14.4) | .12 | 79.7 (11.2) | 76.5 (12.9) | .32 |
| IPIP Neuroticism | 20.1 (6.3) | 23.1 (7.6) | .01[a] | 20.8 (7.5) | 24.8 (6.3) | .13 | 17.4 (3.0) | 15.9 (5.8) | .53 | 18.8 (6.4) | 23.7 (7.1) | .03[a] | 21.5 (5.8) | 24.8 (7.7) | .07 |
| IPIP Extraversion | 36.1 (7.0) | 34.3 (7.1) | .12 | 31.8 (7.5) | 33.3 (5.9) | .55 | 36.3 (6.4) | 38.8 (8.1) | .50 | 38.5 (4.4) | 34.2 (6.7) | .03[a] | 37.2 (7.6) | 33.0 (7.1) | .03[a] |
| SES | 6.3 (1.4) | 5.8 (1.5) | .06 | 6 (0.8) | 5.7 (1.1) | .59 | 6.5 (0.5) | 6.5 (1.3) | .99 | 6.7 (1.6) | 6.2 (2.2) | .50 | 6.1 (1.5) | 5.4 (1.4) | .08 |
| PHQ | 4.5 (3.8) | 5.9 (4.2) | .03[a] | 4.3 (4.0) | 5.2 (4.4) | .58 | 2.9 (2.2) | 4.8 (3.9) | .20 | 5.1 (4.9) | 5.6 (4.4) | .72 | 4.7 (3.1) | 6.8 (4.2) | .04[a] |
| STAI Trait | 30.9 (7.5) | 35.6 (10.7) | .002[a] | 34 (9.2) | 36.5 (8.1) | .43 | 27.4 (3.8) | 27.2 (6.2) | .94 | 31.6 (8.4) | 36.7 (11.2) | .12 | 29.6 (5.9) | 37.8 (11.6) | .001[a] |
| HAD Anxiety | 4.2 (3.6) | 5.9 (3.7) | .005[a] | 4.8 (4.2) | 4.2 (3.1) | .63 | 3.1 (3.2) | 4.5 (4.2) | .46 | 3.8 (3.6) | 6.0 (3.2) | .04[a] | 4.6 (3.3) | 7.1 (3.8) | .008[a] |
| HAD Depression | 1.8 (1.8) | 2.9 (2.9) | .009[a] | 2.5 (2.4) | 1.7 (1.7) | .31 | 1.3 (1.5) | 1.5 (2.4) | .86 | 1.1 (1.6) | 2.8 (2.4) | .01[a] | 2.1 (1.4) | 4.0 (3.3) | .007[a] |
| PSS | 10.8 (5.7) | 14.8 (6.4) | .001[a] | 12.3 (7.3) | 14.3 (5.2) | .41 | 10.1 (3.9) | 10.5 (5.4) | .89 | 10.3 (5.5) | 15.1 (4.8) | .005[a] | 10.8 (5.0) | 16.5 (7.4) | .001[a] |
| SF12 Physical | 54.2 (3.1) | 52.4 (5.6) | .02[a] | 53.5 (4.3) | 50.7 (7.9) | .22 | 52.7 (1.6) | 53.0 (4.1) | .88 | 55.4 (2.9) | 53.6 (4.2) | .12 | 54.1 (2.6) | 52.1 (5.7) | .10 |
| SF12 Mental | 53.1 (6.3) | 49.7 (9.4) | .01[a] | 52.4 (5.8) | 52.1 (6.4) | .89 | 54.9 (4.6) | 56.8 (4.5) | .38 | 51.8 (7.3) | 48.9 (8.3) | .25 | 53.6 (6.2) | 46.4 (10.9) | .003[a] |
| VSI | 7.2 (10.1) | 15.4 (17.7) | .0006[a] | 8.9 (13.1) | 18.8 (17.6) | .08 | 1.6 (2.9) | 11.3 (16.8) | .15 | 6.1 (7.6) | 13.0 (16.8) | .11 | 8.4 (10.3) | 17.3 (18.9) | .03[a] |

BMI, body mass index; CDRISC, Connor Davidson Resilience Scale; EDS, Everyday Discrimination Scale; ETI, Early Traumatic Inventory; HAD, Hospital Anxiety and Depression Scale; IPIP, International Personality Item Pool; PHQ, Physical Health Questionnaire; PSS, Perceived Stress Scale; SES, socioeconomic status; SF12, Short Form Healthy Survey; STAI, State-Trait Anxiety Inventory; VSI, Visceral Sensitivity Index.

[a] *p* values < .05.

KEY RESOURCES TABLE

| Resource Type | Specific Reagent or Resource | Source or Reference | Identifiers | Additional Information |
|---|---|---|---|---|
| **Add additional rows as needed for each resource type** | **Include species and sex when applicable.** | **Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use "this paper" if new.** | **Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.** | **Include any additional information or notes if necessary.** |
| Commercial Assay Or Kit | ZymoBIOMICS DNA Microprep Kit | Zymo | #D4301 | |
| Commercial Assay Or Kit | QuantSeq 3' mRNA-Seq Library Prep Kit FWD for Illumina | Lexogen | #015 | |
| Commercial Assay Or Kit | RNeasy Mini QIAcube Kit | Qiagen | #74116 | |
| Commercial Assay Or Kit | Quant-iT RiboGreen RNA Kit | Thermo Fisher | #R11490 | |
| Sequence-Based Reagent | Illumina V4 16S Primer set 515F/806R | PMID: 27822518 | N/A | |
| Software; Algorithm | QIIME2 ver. 2020.11 | https://qiime2.org/ | RRID:SCR_021258 | |
| Software; Algorithm | R | https://www.r-project.org/ | RRID:SCR_001905 | |
| Software; Algorithm | STAR 2.5.3a | https://github.com/alexdobin/STAR/releases | RRID:SCR_004463 | |
| Software; Algorithm | Circos | http://circos.ca/ | RRID:SCR_011798 | |
| Software; Algorithm | CONN | https://web.conn-toolbox.org/ | RRID:SCR_009550 | |
| Software; Algorithm | FreeSurfer | http://surfer.nmr.mgh.harvard.edu/ | RRID:SCR_001847 | |
| Software; Algorithm | SPM12 | http://www.fil.ion.ucl.ac.uk/spm/ | RRID:SCR_007037 | |
| Other | Parapak collection vials | Fischer Scientific | #23–290144 | |
| Other | Illumina Hiseq | Illumina | RRID:SCR_016386 | |