Trauma History Predicts Decoupling of C-Reactive Protein and Somatic Symptoms: Results From a Cohort Study of Sexual and Gender Minority Youth

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ABSTRACT

Objective: Systemic inflammation can induce somatic symptoms (e.g., pain, nausea, fatigue) through neuroimmune signaling pathways. Previous research suggests that early-life adversity amplifies signaling between peripheral inflammation and the brain. We therefore hypothesized that greater lifetime trauma exposure at baseline would predict stronger associations between systemic inflammation and somatic symptoms at 2.5-year follow-up in a cohort study of sexual and gender minority youth assigned male at birth (n = 694).

Methods: We measured prior trauma exposure (lifetime count of traumatic event types reported at baseline), somatic symptoms (Brief Symptom Inventory somatization score), and systemic inflammation (C-reactive protein, interleukin 6, interleukin 1β, and tumor necrosis factor α). All models included age, gender, education, recent trauma exposure, substance use, body mass index, and HIV status as covariates.

Results: Higher C-reactive protein concentrations were associated with greater somatic symptoms in the main effects model (β = 0.019, 95% confidence interval [CI] = 0.006 to 0.031). Contrary to our hypothesis, we observed a negative interaction between prior trauma exposure and C-reactive protein levels in predicting somatic symptoms (β = −0.017, 95% CI = −0.030 to −0.004). Higher C-reactive protein was associated with greater somatic symptoms only in participants without prior trauma exposure at baseline (β = 0.044, 95% CI = 0.026 to 0.062). Specificity analyses revealed similar patterns when nonsomatic depressive symptoms were used as the outcome variable.

Conclusions: These results suggest that sexual and gender minority youth assigned male at birth who have a history of prior trauma exposure may experience decoupling of systemic inflammation and somatic symptoms. The absence of inflammation-related symptoms may prevent individuals from seeking necessary medical care by reducing interoceptive awareness of pathological states.

Key words: lesbian, gay, bisexual, trans, queer, plus, stress, psychoneuroimmunology, inflammation.

INTRODUCTION

Nonspecific somatic symptoms (e.g., fatigue, pain, nausea) occur frequently in individuals experiencing infectious and noncommunicable diseases (1–3). These symptoms are also common in the absence of known disease (4). The behavioral analogs of these symptoms (e.g., reduced locomotion, increased pain sensitivity, reduced food intake) are known as "sickness behavior" (5). Sickness behavior is evolutionarily conserved, occurring across a wide range of vertebrate species (6,7). Sickness behavior is thought to reflect a temporary regulatory state that serves to prioritize immune function and promote recovery from illness (8,9). Systemic inflammation is part of the immune system's frontline response to infection and tissue damage. There are multiple pathways linking peripheral systemic inflammation to the brain, and inflammation plays a key mechanistic role in triggering somatic symptoms and sickness behavior (10,11).

A growing body of evidence suggests that early-life adversity amplifies bidirectional immune-brain signaling (12). Increased immune-brain signaling may reflect elevated vigilance against internal danger (e.g., pathogens, tissue damage) and external danger (e.g., malicious conspecifics, environmental hazards) in high-threat environments (12,13). However, in the long term, greater immune-brain signaling can also promote chronic inflammation, which increases risks of a variety of adverse mental and physical health outcomes (14–18).

One previous study recruited a cohort of African American adolescents assigned female at birth who were at high risk for depression, based on family history or cognitive vulnerability (19). Those who had experienced childhood adversity exhibited stronger subsequent associations between systemic inflammation and risk of depressive episodes. Another study found that children living in poverty exhibited stronger associations between systemic inflammation and neural responsivity to threat and reward compared with

CI = confidence interval, **CRP** = C-reactive protein, **HIV** = human immunodeficiency virus, **IL-1β** = interleukin 1β, **IL-6** = interleukin 6, **MSD** = Meso Scale Discovery, **PROMIS** = Patient Reported Outcomes Measurement Information System, **SGM-AMAB** = sexual and gender minority assigned male at birth, **TNF-α** = tumor necrosis factor α

SDC Supplemental Digital Content

From the Institute for Sexual and Gender Minority Health and Wellbeing (Schrock, Mustanski), Northwestern University, Chicago; Department of Psychology (Nusslock), Institute for Policy Research (Nusslock, McDade), and Department of Anthropology (McDade), Northwestern University, Evanston; and Department of Medical Social Sciences (Mustanski), Northwestern University, Chicago, Illinois.

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children of higher socioeconomic status (20). A third study examined influenza vaccination as an inflammatory stimulus in a small sample of young adults (21). Those who had reported greater early trauma exhibited larger increases in depressed mood in proportion to increased interleukin-6 (IL-6) levels after vaccination. Collectively, these studies suggest that early-life adversity may amplify immune-brain signaling. This elevated immune-brain signaling may be one mechanism linking early-life adversity to chronic disease risk later in life (12).

Sexual and gender minority youth assigned male at birth (SGM-AMAB youth; e.g., gay and bisexual men, trans women, nonbinary individuals) are at high risk for experiencing traumatic events (22,23) and exhibit disproportionately high rates of systemic inflammation and risk of inflammation-related chronic conditions (24,25). It is possible that early trauma exposure drives increased immune-brain signaling, thereby leading to elevated systemic inflammation in SGM-AMAB youth.

Drawing on prior work, we hypothesized that greater lifetime trauma exposure measured at baseline would predict stronger associations between systemic inflammation and somatic symptoms at follow-up. We tested this hypothesis in a Chicago-based cohort study of SGM-AMAB youth (n = 694).

METHODS

Data for this study were collected through RADAR, a Chicago-based cohort study of SGM-AMAB youth. The RADAR study aims to understand a set of interrelated health concerns (e.g., human immunodeficiency virus [HIV], substance use, mental health) that occur at high rates among SGM-AMAB youth. Baseline data collection for RADAR began in 2015. Initial enrollees included members of two prior cohort studies, Project Q2 and Crew 450, as well as a third cohort of newly recruited participants who were 16 to 20 years of age; were assigned male at birth; reported a sexual encounter with a man in the previous year or identified as gay, bisexual, or transgender; and spoke English (26,27). Recruitment was expanded through enrollee referrals to friends and romantic partners who met the selection criteria. Upon recruitment into the study, participants were invited to a community-based site for data collection. All participants provided informed consent, and all study protocols were approved by Northwestern University's Institutional Review Board. The deidentified data and statistical code for this study are available from the corresponding author upon reasonable request.

Timeline

Lifetime traumatic event count was assessed at baseline, and this count was used to operationalize prior trauma exposure. Past-year traumatic event count was assessed at visit 3 (1-year follow-up) and visit 5 (2-year follow-up), and these past-year counts were combined to calculate a score indexing recent trauma exposure. Surveys on substance use were collected every 6 months, and HIV screening was conducted every 6 months. At visit 6 (2.5 years after the initial visit), height and weight were measured and an antecubital venous blood sample was drawn to measure inflammatory markers. Somatic symptoms and nonsomatic depressive symptoms were measured at the same visit at which the blood sample was collected (visit 6). Participants were included in the analytic sample for this study if they had data available for all variables of interest. The data collection timeline is summarized in Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A928.

Covariate Selection

We included variables in our statistical models that are potential confounders of the relationship between inflammation and somatic symptoms. Age, gender, education (as an indicator of socioeconomic status), race/ethnicity, and alcohol use were included as covariates in our models based on existing recommendations in the literature (28). HIV status, polydrug use, smoking, and marijuana use were also included as covariates because each of these variables is a plausible cause of both somatic symptoms and systemic inflammation.

Traumatic Events

Traumatic events were assessed using an index of traumatic experiences adapted from the posttraumatic stress disorder module of the Computerized Diagnostic Interview for *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (29). These items were modified to assess exposure to traumatic events unrelated to military combat. Similar adaptations of the Computerized Diagnostic Interview have been used to measure trauma exposure in studies of sexual and gender minorities (30) and in other populations (31). Participants reported whether they had experienced each of the following: a) being shot or stabbed; b) being mugged or threatened with a weapon, or experiencing a break-in or robbery; c) being raped or sexually assaulted; d) being in a disaster like a fire, flood, earthquake, tornado, hurricane, bombing, or plane crash; e) experiencing an unexpected sudden death of a close friend or relative; f) being diagnosed with a life-threatening illness; g) being in a serious accident; h) seeing someone being seriously injured or killed; h) unexpectedly discovering a dead body; or i) being kicked out of a caregiver's house. The latter item was added because of its particular importance for sexual and gender minority youth, who experience high rates of homelessness.

Our research question is focused on developmental calibration of inflammation-related symptoms. Traumatic events can have direct effects on somatic symptoms, so we wanted to control for recent trauma exposure in our analyses. We therefore separated recent trauma exposure from prior trauma exposure. A prior trauma score was calculated by summing the number of lifetime traumatic event types a participant reported at the baseline visit. A recent trauma score was calculated as the mean number of past-year traumatic event types reported at visit 3 and visit 5. A minority of participants (n = 66; 9.51%) had available data from only one of the two visits (visit 3 or visit 5). For these cases, the trauma count from the nonmissing visit was used as their recent trauma score. Including participants with data from only one of the two visits allows us to reduce the impact of biased missingness on our statistical models. To generate comparable effect estimates for prior and recent trauma, we standardized prior trauma score and recent trauma score to have a mean of 0 and a standard deviation of 1 in statistical analyses. The same checklist of traumatic event types was used when assessing prior trauma exposure and recent trauma exposure.

Systemic Inflammation

Plasma markers of systemic inflammation were measured in duplicate using the MESO QuickPlex SQ 120 electrochemiluminescence Meso Scale Discovery (MSD) immunoassay platform (Rockville, Maryland). C-reactive protein (CRP) was measured using the MSD V-PLEX Plus Human CRP kit (detection range,

0.00000133–49.6 mg/L). An MSD V-PLEX Custom Proinflammatory Panel 1 kit (human) was used to measure IL-6 (detection range, 0.06–488 pg/ml), interleukin 1β (IL-1β; detection range, 0.05–375 pg/ml), and tumor necrosis factor α (TNF-α; detection range, 0.04–248 pg/ml). The mean intra-assay coefficient of variation was 6.61% for CRP, 9.05% for IL-6, 12.90% for IL-1β, and 5.30% for TNF-α. The mean inter-assay coefficient of variation was 15.68% for CRP, 16.96% for IL-6, 11.58% for IL-1β, and 17.98% for TNF-α. A small proportion of samples were below the lower limit of detection for CRP (0.55%), IL-6 (0.97%), IL-1β (2.35%), and TNF-α (0.28%). Values below the lower limit of detection were imputed with half the lower limit. We included IL-1β, IL-6, and TNF-α because they are inflammatory signaling molecules that play key roles in initiating and maintaining systemic inflammation (7). We included CRP because it is a downstream inflammatory protein that can be upregulated, directly or indirectly, by all three of these proinflammatory cytokines (IL-1β, TNF-α, and IL-6) and is frequently used as a biomarker of inflammation-related chronic disease risk (32,33).

Somatic symptoms were measured using the six-item somatization scale from the Brief Symptom Inventory (34). Participants were presented a list of symptoms (faintness or dizziness, pains in the chest, nausea or upset stomach, trouble getting your breath, numbness or tingling in parts of your body, and feeling weak in parts of your body) and asked to rate on a scale of 0 (not at all) to 4 (extremely) how much each symptom had bothered them in the past 7 days, including the day of the interview. A total somatic symptom score was created by computing each participant's mean response value to the six items.

Nonsomatic depressive symptoms were measured using the Patient Reported Outcomes Measurement Information System (PROMIS) Depression—Short Form 8a instrument, which measures the presence and severity of eight nonsomatic depressive symptoms (worthlessness, helplessness, feeling depressed, hopelessness, feeling like a failure, unhappiness, feeling like you had nothing to look forward to, and feeling that nothing could cheer you up) over the past 7 days (35). Participants were asked to report how often in the past week they had experienced each of the feelings mentioned previously on a 5-point scale ranging from "never" to "always." Raw scores were calculated by adding up the scores of all completed items and dividing by the number of items completed. Raw scores were then converted to PROMIS t-scores, following the PROMIS manual.

Substance Use

Marijuana use was assessed using numeric scores on the Cannabis Use Disorders Identification Test—Revised, which measures patterns of cannabis use in the past 6 months (36). We calculated a cumulative marijuana use score by summing the Cannabis Use Disorders Identification Test–Revised score across all completed visits and dividing by the number of completed visits. This approach allows for the estimation of cumulative use patterns while accommodating participants with different numbers of completed visits (37). Cumulative alcohol use was calculated in the same manner using numeric scores on the Alcohol Use Disorders Identification Test (38). Cigarette use was assessed using survey items taken from the Monitoring the Future Study (39). We converted categorical responses about cigarette use in the past 30 days to cigarette count equivalents: "none" = 0; "less than one" = 0.5, "one to five" = 3, "about one-half pack" = 10, "about one pack" = 20, "about one and one-half packs" = 30, and "two packs or more" = 40. A cumulative cigarette use score was calculated by summing this cigarette count across all completed visits and dividing by the number of completed visits.

A urine sample was collected at each visit and analyzed using the Multi-Drug Screen Test (DOA-264) and the Ecstasy Drug Test (DMD-114) from Innovacon, Inc. (San Diego, California). The Multi-Drug Screen Test detects metabolites of cannabis (THC, 3- to 10-day detection window), cocaine (3–5 days), benzodiazepine (3–7 days), amphetamine (1–4 days), methamphetamine (3–-5 days), and opiates (1–4 days) (40). The Ecstasy Drug Test detects metabolites of methylenedioxymethamphetamine (1–2 days) (40). We created a polydrug use score by summing the number of nonmarijuana drugs that were detected in a participant's urine sample at a given visit (range, 0–6). We created a cumulative polydrug score by summing the polydrug score across completed visits and dividing by the number of completed visits.

To generate statistical model coefficients that are comparable across substance use categories, we standardized cumulative marijuana use score, cumulative alcohol use score, cumulative cigarette use score, and cumulative polydrug use score so that each had a mean of 0 and standard deviation of 1.

Body Mass Index

At visit 6, height and weight were measured using an Adam Equipment MDW-250L digital physician scale and manual stadiometer (Oxford, Connecticut) with standard anthropometric protocols. Body mass index was calculated using the standard formula: weight in kilograms per height in meters squared.

HIV Status

HIV tests were conducted at visit 6 using the Alere Determine HIV1/2 Ab/Ag Combo fourth-generation point-of-care test on a fingerstick blood sample (Waltham, Massachusetts). If a participant tested positive on the point-of-care test, follow-up HIV testing of blood collected by venipuncture was conducted according to Centers for Disease Control and Prevention guidelines to confirm the positive result.

Demographics

Age, gender, race/ethnicity, and educational attainment were measured using a demographic questionnaire administered at visit 6.

Statistical Analysis

Somatic symptom scores had a distribution that was left-censored at 0 (336 participants had a score of 0). We therefore used tobit regression models for data analysis, which are designed to predict outcome variables with censored distributions (41). Tobit regression models were specified in the R package "AER" (version 1.2-9). For each coefficient, we calculated a 95% confidence interval (CI). All models included age, gender, race/ethnicity, education, body mass index, HIV status, alcohol use, marijuana use, smoking, polydrug use, and recent trauma exposure as covariates. In specificity analyses predicting nonsomatic depressive symptoms, we specified tobit regression models for depressive symptom t-scores with a distribution that was left-censored at 38.2 (258 participants had a score of 38.2).

RESULTS

At the time of analysis, 1165 participants had enrolled in RADAR and completed a baseline visit, and 721 had completed visit 6 (2.5-year follow-up) and provided a plasma sample. Of those 721 participants, 694 had complete data available for the variables of interest for this study and were included in the analytic sample. Descriptive statistics for the analytic sample (n = 694) are presented in Table 1.

Main Effects Models

Higher CRP was associated with greater somatic symptoms (B = 0.019, 95% CI = 0.006 to 0.031). The corresponding coefficients for IL-1β (B = −0.020, 95% CI = −0.067 to 0.028), IL-6 (B = 0.050, 95% CI = −0.022 to 0.122), and TNF-α (B = 0.047, 95% CI = −0.020 to 0.114) had 95% CIs that contained 0. Coefficients and 95% CIs for all models with CRP as the dependent variable are presented in Table 2.

Interaction Models

We observed an interaction between prior trauma exposure and CRP in predicting somatic symptom scores (B = −0.017, 95% CI = −0.030 to −0.004). We also observed an interaction between prior trauma exposure and TNF-α (B = −0.099, 95% CI = −0.194 to −0.004) in predicting somatic symptom scores. The corresponding interaction terms for IL-1β (B = −0.013, 95% CI = −0.053 to 0.027) and IL-6 (B = −0.044, 95% CI = −0.110 to 0.022) had 95% CIs that contained 0.

Models Stratified by Prior Trauma Exposure

To probe the interaction effects observed for CRP and TNF-α, we conducted follow-up analyses stratified by prior trauma exposure. Higher CRP was associated with higher somatic symptom scores only in the low prior trauma group (B = 0.044, 95% CI = 0.026 to 0.062; Figure 1). Higher CRP was not associated with higher somatic symptom scores in the moderate prior trauma group (B = 0.002, 95% CI = −0.028 to 0.033) or in the high prior trauma group (B = −0.0003, 95% CI = −0.021 to 0.020). For TNF-α, the effect estimate was largest in the low prior trauma group (B = 0.136, 95% CI = −0.045 to 0.317), followed by the moderate prior trauma group (B = 0.036, 95% CI = −0.041 to 0.114), but both sets of 95% CIs contained 0. TNF-α was not associated with somatic symptoms in the high prior trauma group (B = 0.004, 95% CI = −0.151 to 0.158).

Specificity Analysis: Models Predicting Nonsomatic Depressive Symptoms

To investigate the specificity of the patterns we identified for CRP and somatic symptoms, we tested whether prior trauma exposure moderated the cross-sectional association between CRP and nonsomatic depressive symptoms. We observed an interaction between prior trauma exposure and CRP in predicting depressive

TABLE 1. Selected Descriptive Statistics for a Sample of Sexual and Gender Minority Youth Assigned Male at Birth (n = 694), Stratified by Level of Prior Traumatic Event Exposure

	Low Prior Trauma (n = 242)	Moderate Prior Trauma (n = 173)	High Prior Trauma (n = 279)	Total (n = 694)
Age at baseline, mean (SD), y	20.93 (2.94)	21.01 (2.67)	21.48 (2.99)	21.17 (2.90)
Gender, *n* (%)				
Man	222 (91.74)	151 (87.28)	239 (85.66)	612 (88.18)
Woman	13 (5.37)	11 (6.36)	26 (9.32)	50 (7.20)
Nonbinary	7 (2.89)	11 (6.36)	14 (5.02)	32 (4.61)
Race, *n* (%)				
White	65 (26.86)	42 (24.28)	48 (17.20)	155 (22.33)
Black	64 (26.45)	57 (32.95)	117 (41.94)	238 (34.29)
Latinx	86 (35.54)	56 (32.37)	86 (30.82)	228 (32.85)
Multiracial	16 (6.61)	12 (6.94)	22 (7.89)	50 (7.20)
Other	11 (4.55)	6 (3.47)	6 (2.15)	23 (3.31)
Education, *n* (%)				
Less than high school	8 (3.31)	14 (8.09)	17 (6.09)	39 (5.62)
High school or equivalent	37 (15.29)	27 (15.61)	62 (22.22)	126 (18.16)
Some college	138 (57.02)	91 (52.60)	147 (52.69)	376 (54.18)
Undergraduate degree or higher	59 (24.38)	41 (23.70)	53 (19.00)	153 (22.05)
Living with HIV, *n* (%)	39 (16.12)	38 (21.97)	71 (25.45)	148 (21.33)
C-reactive protein, median (MAD), mg/L	0.93 (1.02)	1.07 (1.17)	0.87 (1.01)	0.96 (1.06)
Somatic symptom score, mean (SD)	0.24 (0.45)	0.35 (0.49)	0.42 (0.60)	0.34 (0.53)
Recent trauma count, mean (SD)	0.17 (0.36)	0.31 (0.50)	0.63 (0.81)	0.39 (0.64)

SD = standard deviation; MAD = median absolute deviation.

Percentages are computed column-wise. Low prior trauma = 0 lifetime traumatic event types reported at baseline. Moderate prior trauma = 1 lifetime traumatic event types reported at baseline; High prior trauma = 2+ lifetime traumatic event types reported at baseline. All categorical variables have mutually exclusive categories.

TABLE 2. Tobit Regression Models With C-Reactive Protein as the Independent Variable and Somatic Symptom Score as the Dependent Variable in a Sample of Sexual and Gender Minority Youth Assigned Male at Birth (n = 694)

	Main Effects Model (n = 694)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Intercept	−0.583	−1.300	0.134
Age	0.012	−0.015	0.039
Gender (ref = man)			
Woman	−0.160	−0.440	0.128
Nonbinary	0.273	−0.039	0.585
Race (ref = White)			
Black	−0.208	−0.428	0.013
Latinx	−0.008	−0.198	0.182
Multiracial	0.167	−0.124	0.458
Other	−0.040	−0.445	0.365
Education (ref = less than high school)			
High school or equivalent	−0.047	−0.389	0.295
Some college	0.113	−0.209	0.436
Undergraduate degree or higher	−0.059	−0.420	0.301
Body mass index	0.01	−0.001	0.021
Living with HIV	0.085	−0.111	0.281
Polydrug use score	−0.067	−0.172	0.038
Cigarette use score	0.028	−0.058	0.114
Marijuana use score	0.059	−0.020	0.138
Alcohol use score	0.014	−0.069	0.096
C-reactive protein	0.019	0.006	0.031
Prior trauma score	0.062	−0.015	0.138
Recent trauma score	0.161	0.087	0.235
Sigma	−0.208		

	Interaction Model (n = 694)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Intercept	−0.584	−1.295	0.128
Age	0.012	−0.015	0.039
Gender (ref = man)			
Woman	−0.172	−0.454	0.111
Nonbinary	0.258	−0.051	0.568
Race (ref = White)			
Black	−0.220	−0.439	−0.001
Latinx	−0.017	−0.205	0.172
Multiracial	0.158	−0.132	0.447
Other	−0.044	−0.446	0.359
Education (ref = less than high school)			
High school or equivalent	−0.046	−0.385	0.293
Some college	0.122	−0.199	0.442
Undergraduate degree or higher	−0.054	−0.411	0.304
Body mass index	0.010	−0.001	0.021
Living with HIV	0.070	−0.125	0.265
Polydrug use score	−0.068	−0.172	0.036
Cigarette use score	0.027	−0.059	0.112
Marijuana use score	0.062	−0.016	0.140
Alcohol use score	0.009	−0.073	0.091
C-reactive protein	0.018	0.006	0.031

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TABLE 2. *(Continued)*

	Interaction Model (n = 694)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Prior trauma score	0.113	0.027	0.198
Recent trauma score	0.165	0.092	0.238
C-reactive protein by prior trauma score	−0.017	−0.030	−0.004
Sigma	−0.216		
	Stratified Model: Low Prior Trauma (n = 242)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Intercept	0.397	−0.871	1.665
Age	−0.025	−0.069	0.019
Gender (ref = man)			
Woman	−0.167	−0.791	0.458
Nonbinary	0.390	−0.215	0.994
Race (ref = White)			
Black	0.130	−0.235	0.495
Latinx	0.045	−0.244	0.335
Multiracial	0.159	−0.295	0.614
Other	0.065	−0.472	0.602
Education (ref = less than high school)			
High school or equivalent	−0.003	−0.808	0.802
Some college	0.279	−0.495	1.052
Undergraduate degree or higher	−0.064	−0.888	0.760
Body mass index	−0.007	−0.027	0.012
Living with HIV	−0.146	−0.513	0.220
C-reactive protein	0.044	0.026	0.062
Polydrug use score	−0.051	−0.266	0.164
Cigarette use score	0.128	−0.082	0.337
Marijuana use score	0.055	−0.066	0.176
Alcohol use score	0.103	−0.032	0.237
Recent trauma score	0.134	−0.064	0.331
Sigma	−0.331		
	Stratified Model: Moderate Prior Trauma (n = 173)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Intercept	−0.256	−1.546	1.034
Age	0.003	−0.048	0.055
Gender (ref = man)			
Woman	−0.137	−0.662	0.387
Nonbinary	0.012	−0.498	0.523
Race (ref = White)			
Black	−0.205	−0.602	0.193
Latinx	0.038	−0.274	0.351
Multiracial	0.106	−0.408	0.520
Other	−0.466	−1.204	0.272
Education (ref = less than high school)			
High school or equivalent	−0.152	−0.680	0.377
Some college	−0.177	−0.651	0.296
Undergraduate degree or higher	−0.176	−0.703	0.351
Body mass index	0.021	0.001	0.041

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TABLE 2. *(Continued)*

	Stratified Model: Moderate Prior Trauma (n = 173)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Living with HIV	0.044	−0.317	0.404
C-reactive protein	0.002	−0.028	0.033
Polydrug use score	−0.148	−0.357	0.061
Cigarette use score	0.046	−0.131	0.222
Marijuana use score	0.092	−0.075	0.259
Alcohol use score	−0.021	−0.167	0.124
Recent trauma score	0.147	−0.012	0.306
Sigma	−0.346		
	Stratified Model: High Prior Trauma (n = 279)		
	Coefficient	Lower Limit (2.5%)	Upper Limit (97.5%)
Intercept	−1.671	−2.884	−0.457
Age	0.047	0.003	0.091
Gender (ref = man)			
Woman	−0.183	−0.613	0.246
Nonbinary	0.261	−0.246	0.768
Race (ref = White)			
Black	−0.415	−0.780	−0.050
Latinx	−0.068	−0.410	0.274
Multiracial	0.059	−0.439	0.558
Other	0.117	−0.676	0.911
Education (ref = less than high school)			
High school or equivalent	0.084	−0.479	0.646
Some college	0.280	−0.267	0.828
Undergraduate degree or higher	0.138	−0.483	0.760
Body mass index	0.020	0.002	0.037
Living with HIV	0.181	−0.121	0.483
C-reactive protein	0.000	−0.021	0.020
Polydrug use score	−0.075	−0.227	0.077
Cigarette use score	0.002	−0.116	0.120
Marijuana use score	0.079	−0.050	0.209
Alcohol use score	−0.055	−0.195	0.085
Recent trauma score	0.187	0.095	0.279
Sigma	−0.144		

HIV = human immunodeficiency virus.

symptom scores (B = −0.217, 95% CI = −0.425 to −0.009). Higher CRP was associated with higher depressive symptom scores only in the low prior trauma group (B = 0.426, 95% CI = 0.086 to 0.765). Higher CRP was not associated with higher depressive symptom scores in the moderate prior trauma group (B = 0.009, 95% CI = −0.504 to 0.522) or the high prior trauma group (B = −0.0005, 95% CI = −0.278 to 0.277).

Sensitivity Analyses

One participant had a CRP value (>60 mg/L) that was considerably higher than the other CRP values in the sample. We reran our adjusted CRP models excluding this participant. The main effect of CRP on somatic symptoms (B = 0.022, 95% CI = 0.009 to 0.036) and the interaction effect between CRP and prior trauma (B = −0.016, 95% CI = −0.030 to −0.002) were very similar to the analogous effects in our original analysis. The association between CRP and somatic symptoms (B = 0.0003, 95% CI = −0.026 to 0.026) in the high prior trauma group (which originally contained the excluded participant) was very similar to the analogous association in the original analysis.

We also reran our CRP models without covariates to investigate whether the observed patterns were sensitive to the covariates included in the model. The main effect of CRP on somatic symptoms (B = 0.021, 95% CI = 0.009 to 0.034) and the interaction effect between CRP and prior trauma (B = −0.013, 95% CI = −0.027 to −0.0003) were similar to the analogous effects in our original analysis. The coefficients in the low (B = 0.039, 95% CI = 0.021 to 0.057), moderate (B = 0.010, 95% CI = −0.020 to 0.040), and

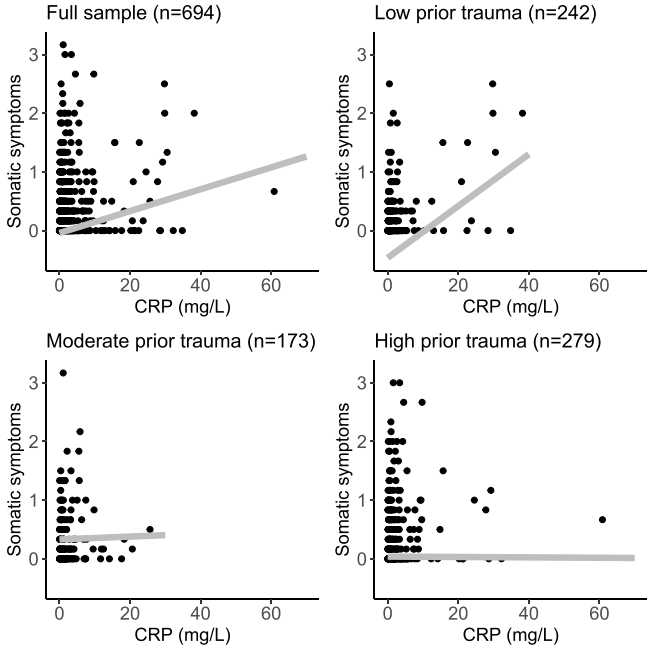

FIGURE 1. Scatterplots depicting associations between plasma CRP and somatic symptom scores. Data are from RADAR, a Chicago-based cohort study of sexual and gender minority youth assigned male at birth (n = 694). The plotted lines depict marginal effects of CRP on somatic symptoms in tobit regression models controlling for age, gender, race/ethnicity, education, body mass index, HIV status, alcohol use, marijuana use, smoking, polydrug use, and recent traumatic event exposure. Primary analyses revealed that total lifetime traumatic events reported at baseline moderated the cross-sectional association between CRP and somatic symptom score at 2.5-year follow-up. To probe this interaction, follow-up analyses were stratified by prior trauma exposure. The "low prior trauma" group reported no lifetime traumatic events at baseline. The "moderate prior trauma" group reported one lifetime traumatic event type at baseline. The "high prior trauma" group reported at least two lifetime traumatic event types at baseline. The y axis depicts a participant's mean item score on the Brief Symptom Inventory somatization scale. CRP = C-reactive protein; HIV = human immunodeficiency virus.

high (B = 0.009, 95% CI = −0.011 to 0.029) prior trauma groups were also similar to the analogous coefficients in the original analysis.

Our "prior trauma" and "recent trauma" variables are correlated with one another, which could cause problems of multicollinearity thereby distorting the model's outputs. To investigate this possibility, we reran our models without including the recent trauma variable. The main effect of CRP on somatic symptoms (B = 0.021, 95% CI = 0.008 to 0.033) and the interaction effect between CRP and prior trauma (B = −0.016, 95% CI = −0.029 to −0.003) were similar to the analogous effects in our original analysis. The coefficients in the low (B = 0.045, 95% CI = 0.027 to 0.063), moderate (B = 0.003, 95% CI = −0.029 to 0.034), and high (B = 0.004, 95% CI = −0.017 to 0.025) prior trauma groups were also similar to the analogous coefficients in the original analysis.

It is possible that trauma exposure in general could be the actual moderator, regardless of recency. To investigate this possibility, we stratified the sample into four groups. The "neither" group consisted of participants who reported neither prior nor recent traumatic events. The "recent only" group consisted of participants who reported no lifetime history of traumatic events at baseline but reported at least one recent traumatic event at follow-up. The "prior only" group reported at least one lifetime traumatic event at baseline but reported no recent traumatic events at follow-up. The "both" group reported at least one prior lifetime traumatic event at baseline and at least one recent traumatic event at follow-up. In the "neither" group (B = 0.039, 95% CI = 0.017 to 0.061) and the "recent only" group (B = 0.045, 95% CI = 0.017 to 0.072), greater CRP was associated with greater somatic symptoms. In the "prior only" group (B = 0.0002, 95% CI = −0.024 to 0.025) and the "both" group (B = 0.003, 95% CI = −0.020 to 0.026), there was no detectable association between CRP and somatic symptoms.

DISCUSSION

In this study, we hypothesized that prior trauma exposure would predict stronger cross-sectional associations between systemic inflammation and somatic symptoms. Contrary to our hypothesis, we found a negative interaction between prior trauma exposure and CRP in predicting somatic symptoms. In stratified analyses, higher CRP was associated with greater somatic symptoms only among those who reported no prior traumatic events at baseline.

We found similar patterns in a specificity analysis using nonsomatic depressive symptoms as the outcome variable. Higher CRP was associated with greater nonsomatic depressive symptoms only among those who reported no prior traumatic events at baseline. This suggests that the decoupling of CRP and symptoms may extend to both somatic symptoms and nonsomatic depressive symptoms. Previous studies investigating the relationship between systemic inflammation and depressive symptoms have produced mixed results (42). These studies often fail to account for variation in lifetime trauma exposure, which may help explain

why associations between systemic inflammation and depressive symptoms are detectable in some samples but not others.

Possible Interpretations and Directions for Future Research

One interpretation of our findings is that lifetime traumatic event exposure leading up to early adulthood may predict subsequent suppression of inflammation-induced symptoms. Previous studies with animal models have reported that animals suppress inflammation-induced sickness behavior in the presence of threat cues (43). For example, one study found that inducing systemic inflammation in rhesus monkeys led to increased lethargy in a quiet setting, but this increase in lethargy disappeared when the inflamed monkeys were exposed to threat cues from a human experimenter (44). A study of dominant and subordinate male mice housed in pairs found that the dominant mice reduced the total frequency of active behaviors in response to inflammation, but the subordinate mice did not (45). The authors suggested that the dominant mice could afford to prioritize recuperation by reducing activity, whereas the subordinate mice had to maintain social defensive behaviors because of the potential threats posed by the dominant mouse. In humans, dominant individuals tend to disproportionately victimize individuals they perceive as being vulnerable (46). For a human in a high-threat environment, suppressing symptoms when experiencing low-grade inflammation may be a social defensive strategy to avoid appearing vulnerable in the eyes of potential aggressors. The patterns observed in this study may reflect a developmental response to threat cues that parallels the proximal short-term response evident in animal models.

Although suppressing inflammation-induced symptoms might reduce one's perceived vulnerability, this suppression could also have negative long-term health consequences. Many inflammation-induced symptoms and behaviors are thought to reflect a temporary regulatory state that serves to promote somatic maintenance and recovery (8,9). Forgoing these opportunities for prioritizing maintenance may delay the resolution of the underlying pathologies that are causing inflammation. Over time, these extended windows of exposure to unresolved proinflammatory pathologies may increase cumulative damage across multiple physiological systems, leading to chronically elevated inflammation and greater chronic disease risks (14–18). High rates of early-life trauma exposure (22,23), in tandem with suppression of inflammation-induced symptoms, may help explain why SGM-AMAB communities experience disproportionately high rates of systemic inflammation and inflammation-related chronic conditions (24,25).

An adjacent literature has reported a pattern of "skin-deep resilience" among individuals from disadvantaged backgrounds (47). In these studies, disadvantaged youth with higher levels of conscientiousness and teacher-rated psychosocial competence exhibit higher levels of educational attainment, less problematic alcohol use, and fewer depressive symptoms (48,49). However, the same individuals also experience higher rates of negative physical health indicators, including elevated systemic inflammation and allostatic load (a measure of wear and tear on the body) (48,49). The patterns observed in our study may also reflect a form of skin-deep resilience—suppressing inflammation-induced symptoms may promote psychosocial adjustment and safety in high-threat environments. However, suppressing inflammation-induced symptoms could also delay the resolution of the underlying proinflammatory pathologies, thereby increasing long-term health risks.

Previous studies suggested that greater early-life adversity predicts stronger subsequent associations between systemic inflammation and brain states (e.g., depressive episodes, depressed mood, neural responsivity to threat and reward) (19–21). In contrast, our results suggest that a history of traumatic events predicts decoupling of CRP and somatic symptoms. We found a similar decoupling pattern when nonsomatic depressive symptoms were used as the outcome variable. There are multiple study design differences that could explain why our results diverge from those of previous studies, including how adversity was operationalized and the composition of our sample. Our measure of trauma exposure was narrowly focused on specific events that are likely to be highly impactful. Previous studies used more general indicators of adversity (e.g., poverty, parental separation, familial psychopathology, stressful life events) (19–21). Our sample was composed exclusively of individuals who were assigned male at birth, whereas previous studies included only participants assigned female at birth (19) or featured majority-female samples (20,21). In addition, our sample had only participants who identified with a minoritized sexual orientation or gender identity, but previous studies did not purposively sample these groups. It is possible that suppressing inflammation-related symptoms is a more salient adjustment strategy for those who are socialized as men than it is for those who are socialized as women. It is also possible that the added danger of having a stigmatized sexual orientation or gender identity makes suppression of inflammation-related symptoms a more salient adjustment strategy. People who are already vulnerable because of stigmatized identities may be more likely to suppress symptoms that could make them appear even more vulnerable. Further work is needed to investigate how specific types of early adversity interact with contextual differences to predict immune-brain signaling.

Another possibility is that our findings reflect dysfunctional immune-brain communication among those with a history of prior trauma exposure, rather than active suppression of inflammation-induced symptoms. Further research is needed to test whether exposure to early life trauma disrupts specific immune-brain signaling pathways, leading to dysfunctional immune-brain communication later in life.

Limitations

This study should be interpreted in the context of its limitations. Our longitudinal design allowed us to separate recent trauma exposure from prior trauma exposure, but systemic inflammation and somatic symptoms were measured at only one time point. This meant that we could only examine cross-sectional associations between inflammation and somatic symptoms. Future studies should measure inflammation and somatic symptoms at multiple time points so that they can distinguish within-person and between-person patterns. We did not have data on sleep disruption, anti-inflammatory medication use, or antidepressant use. We were therefore unable to include these factors as covariates in our models. Further studies are needed to assess whether the patterns observed in this study replicate in other samples, with other sets of covariates, and generalize to other groups (e.g., sexual and gender minority youth assigned female at birth, people exposed to humanitarian crises

early in life). Participants reported their history of traumatic events upon entering the cohort at an average age of 21 years, but we lack data on the age at which each traumatic event occurred. We are therefore unable to further narrow the age range in which trauma exposure predicts later decoupling of CRP and somatic symptoms. Further studies are needed to identify potential critical age ranges for trauma exposure as a predictor of subsequent decoupling of CRP and somatic symptoms. Another limitation is that our measures of somatic symptoms and depressive symptoms were not designed to capture sickness behaviors or symptoms that are canonically associated with acute inflammation (e.g., fatigue, loss of appetite, anhedonia). Some of our items overlap with these canonical symptoms. For example, nausea and upset stomach overlap with loss of appetite. Faintness and bodily feelings of weakness overlap with fatigue. Nonsomatic depressive symptoms overlap with anhedonia. However, the correspondence between our items and classic sickness behaviors/symptoms is incomplete. Future studies should incorporate more direct measures of sickness behaviors and symptoms (e.g., the Sickness Questionnaire) (50). A further limitation is that our sample included relatively few participants who were at the higher end of the CRP distribution. The positive association between CRP levels and somatic symptoms may largely be driven by a relatively small number of participants with high levels of CRP. Future studies should collect samples that include more individuals with elevated CRP (e.g., inpatient clinical studies) to test whether similar patterns persist.

CONCLUSIONS

We found that prior trauma exposure predicted decoupling of CRP and somatic symptoms in a sample of SGM-AMAB youth. This suggests that SGM-AMAB youth with a history of trauma exposure leading up to early adulthood may suppress somatic symptoms arising from low-grade inflammation. This suppression of inflammation-driven symptoms may undermine long-term health by delaying the resolution of underlying inflammatory pathologies. Suppression of inflammation-driven symptoms may also prevent individuals from seeking necessary medical care by reducing interoceptive awareness of pathological states. Our findings highlight the importance of understanding how early environments shape the development of symptom regulation. Understanding individual differences in symptom regulation will open novel avenues for individually tailored prevention and treatment.

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