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Perceived Control and Inflammation: Mediating and Moderating Effects in the Relationship Between Cumulative Trauma and Depression

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Abstract

Objective: The effects of trauma exposure on depression risk and severity are well-established, but psychosocial and biological factors that impact or explain those relationships remain poorly understood. This study examined the moderating and mediating effects of perceived control and inflammation in the relationship between trauma and depression.

Methods: Moderation analyses and longitudinal mediation analyses were conducted on data from 945 adults who completed all three waves (spanning around 19 years) of the MIDUS Study and the MIDUS Biomarker Study. Data were collected during a phone interview, self-report surveys distributed in the mail, and an in-person blood draw. Two dimensions of perceived control — mastery and constraints — were examined separately in all analyses.

Results: Perceived control did not significantly moderate the relationship between trauma and depression severity at MIDUS 2 ($b = .03$, $SE = .02$, $p = .091$). Constraints significantly mediated the relationship between trauma and MIDUS 3 depression ($IE = 0.03$, $SE = .01$, $p = .016$) but not after accounting for MIDUS 2 depression. Perceived control did not have a significant moderating effect in the relationships between trauma and inflammation or inflammation and depression.

Conclusions: Findings from this study revealed that perceived control may be better characterized as an explanatory factor rather than a buffer in trauma-associated depression. Perceived constraints in particular may be a useful treatment target for trauma-associated depression. Further research is needed to examine whether these results generalize to populations other than among mostly non-Hispanic white adults in the United States.

Key words: Trauma, perceived control, constraints, mastery, depression, inflammation

Abbreviations: CRP = C-reactive protein; IL-6 = Interleukin 6; CES-D = Center for Epidemiologic Studies Depression Scale; CIDI-SF = Composite International Diagnostic Interview Short Form; IE = Indirect Effect

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Introduction

Traumatic life events — high-magnitude stressful experiences that induce perceived psychological or physical harm to oneself or others (1) — often have lasting negative effects on one's mood. For example, trauma is associated with an increased risk of depression in children and adolescents (2), greater likelihood of diagnosis and severity of depression in adulthood (3), and higher risk of recurrent episodes and poor treatment outcomes in individuals with depression (4). While the association between trauma and depression risk is well-established, less is known about the pathways through which trauma leads to depression and what factors might affect these pathways in adults. To better characterize possible mechanisms for potential treatment targets, the current study explores the roles of two factors that may partially explain and/or influence the relationship between trauma and depression. Specifically, the current investigation examines whether *perceived control* acts as a moderator or a mechanism in the link between trauma and depression. Additionally, the effects of perceived control on trauma-and-depression-associated-*inflammation* are examined.

Defining Perceived Control

In a review, Skinner (1996) identified over 100 control-related constructs and described how different theoretical traditions emerged with slightly different versions of these constructs. Skinner identified three themes among these constructs: 1) The belief about one's ability to implement a behavior that might exert control, 2) The belief about the link between one's behavior and desired outcomes, and 3) The belief regarding one's ability to achieve desired outcomes. For the current study, our definition of perceived control includes all three of those beliefs.

Mastery and Constraints

In recent years, some researchers have argued that two commonly-measured dimensions of perceived control — *mastery* and *constraints* — display distinct associations with health and well-being and should therefore be analyzed separately (5). Mastery has been defined as the belief that life opportunities are under one's control rather than being ruled by fate (5,6). Measures of mastery typically include items that capture both the belief regarding one's ability to implement control-exerting behaviors and beliefs about the link between those behaviors and the intended outcomes (7). Constraints has been defined as the belief that barriers prevent one from exerting control over one's life circumstances (5). For example, those with high levels of perceived constraints would be more likely to believe that other people interfere with their ability to achieve goals. We review literature below on perceived control more broadly and comment on studies that have examined these two dimensions of perceived control separately.

Roles of Perceived Control in the Link Between Trauma and Depression

Several studies have demonstrated negative associations between perceived control and depression, such that those with a greater sense of control report fewer depressive symptoms (8–10)—a finding that has been documented in analyses on the MIDUS data (11). While depressed mood has been shown to reduce individuals' perceived control (12) and prospectively predict decreased perceived control (13), perceived control may also reduce one's risk of worsening depressive symptoms. For example, results of one study of 2052 individuals in the Netherlands indicated that higher perceived control longitudinally predicted lower depression (14). In two other studies, changes in perceived control were associated with improved treatment outcomes in individuals with depression (15,16). Among the only two studies that analyzed mastery and

constraints separately, constraints seemed to display stronger relationships with depression than did mastery (8,13). Taken together, these findings indicate that perceived control — and constraints in particular — may affect the maintenance of depression.

Given this link between perceived control and depression, researchers have tested whether perceived control operates as a buffering factor (moderator) in the relationship between trauma and depression, such that those high in perceived control are less adversely affected. Several studies have shown preliminary evidence for buffering effects of perceived control on childhood maltreatment (17–19). Other research has found preliminary evidence that perceived control partially explains the relationship between trauma and depression, serving as a pathway through which trauma exerts its effects (17,20,21). Of note, most of this research has focused on children and adolescents, and none of this work has examined whether perceived control protects against the effects of cumulative lifetime trauma on depression into adulthood. Furthermore, none of these studies have examined mastery and constraints separately as either buffering or mediating factors. More research is needed to better characterize the role of perceived control (and each of these two dimensions separately) in the relationship between cumulative lifetime trauma and depression in adults. Further clarity in this area could provide clinicians and researchers with more specific treatment targets to buffer or reduce the effects of a wider range of trauma on depression in adults.

Role of Inflammation in the Link between Trauma and Depression

Part of the human body's natural response to infection or tissue damage involves the release of proinflammatory cytokines — small proteins that initiate an inflammatory response to

protect an injured tissue and/or fight off an infection (22). Measuring the amount of these cytokines circulating in the bloodstream provides a measure of inflammatory activity. In periods of infection or illness, high levels of proinflammatory cytokines are indicative of a healthy immune response. However, the *sustained* release of these proteins and associated chronic inflammation can adversely affect one's health. For example, heightened levels of circulating cytokines have been associated with a greater risk of future cardiovascular events and disease (23). Therefore, identifying risk and protective factors of chronic inflammation to prevent these negative consequences is highly important.

Both trauma and depression have been identified as risk and maintenance factors for chronic inflammation. Trauma exposure has been shown to cause long-term alterations in stress reactivity and stress physiology (24–26), which may have downstream effects on circulating proinflammatory cytokines and consequent chronic inflammation (27). Additionally, inflammation has been shown to induce symptoms of depression (28–31), and depression also predicts higher levels of inflammation (32–34). Using data from the MIDUS study, several researchers have documented significant associations between inflammation and depression. For example, one paper reported a negative association between C-reactive protein (CRP) and anhedonia and a positive association between CRP and somatic complaints (35). Other studies using MIDUS data demonstrated that inflammation predicted future within-person 9-year change in Major Depressive Disorder diagnosis status (36) and that childhood maltreatment was related to inflammatory activity through negative affect (37). Finally, a network analysis of MIDUS data revealed positive correlations between childhood maltreatment and interleukin-6 (IL-6) on the one hand, and between IL-6 and somatic symptoms of depression on the other (38). These

studies together demonstrate that inflammation may serve as a key biological mechanism and maintenance factor in trauma-associated depression and that these findings have been well-established using MIDUS data.

Perceived Control and Inflammation

While perceived control has been shown to act as a protective factor for many psychological and physical conditions, only a handful of studies have investigated perceived control's protective function in the context of trauma-and- depression-associated-inflammation. Results from one study using the MIDUS sample revealed no statistically significant moderating effect of perceived control on the relationship between subjective autonomic arousal and symptoms of depression and anxiety (39). While these results suggest that perceived control may not affect relations between existing stress responses and mood, whether perceived control could buffer the effects of trauma exposure on autonomic arousal and downstream inflammatory processes was not assessed. Findings from one study that did investigate this question indicate that perceived control may buffer the effects of trauma on inflammatory activity (40). More specifically, although constraints (but not mastery) predicted inflammatory activity longitudinally, mastery (but not constraints) buffered the effect of trauma on inflammation. That is, the relationship between trauma and inflammation was attenuated for those higher in mastery but did not differ at different levels of constraints. These results provide preliminary evidence that perceived control, and its dimension of mastery specifically, may affect the relationship between trauma and inflammation. However, the role of perceived control in the relationship between inflammation and depression remains to be established. Research is needed to examine these effects and characterize the role of perceived control in the links between trauma,

inflammation, and depression, as more information in this area could inform intervention development targeting perceived control as a protective factor.

The Present Study

The goal of this investigation was to characterize the roles of perceived control and inflammation in the relationship between trauma and depression. While previous research has shown buffering effects of perceived control on childhood maltreatment in children and adolescents (17–19), no study to our knowledge has investigated the buffering effects of perceived control in the relationship between cumulative lifetime trauma and depression in adults. Additionally, while some studies have shown that perceived control might partially explain the relationship between trauma and depression (17,20,21), there has not been research yet investigating whether this mediating effect lasts into adulthood. More work is needed to determine whether perceived control's protective effects generalize to US adults who have been exposed to lifetime trauma. Therefore, our first aim was to examine perceived control's role by evaluating both mediating and moderating pathways of perceived control in the relationship between cumulative lifetime trauma and depression in a large US adult sample. We hypothesized that perceived control would moderate the relationship between trauma and depression severity, such that the positive relationship between trauma and depression severity would be attenuated among individuals with a greater sense of control compared to those with a lower sense of control (See Figure 1A). We also hypothesized that perceived control would partially longitudinally mediate the relationship between trauma and subsequent depression (See Figure 1B).

Furthermore, while one study of older adults demonstrated that perceived control buffered the effect of trauma on inflammation (40), no studies to our knowledge have examined this buffering effect in adults across the lifespan. Demonstrating a protective effect of perceived control on the relationship between trauma and inflammation across adulthood could provide support for intervention development targeting perceived control after trauma exposure earlier in adulthood to reduce its negative consequences on long-term health. Additionally, no studies to our knowledge have examined whether perceived control affects the relationship between inflammation and depression. Given the downstream effects of perceived control on behaviors associated with both inflammatory activity and depression (41,42), perceived control may be important for better characterizing the relationship between inflammation and depression. Therefore, the second aim of the study was to evaluate the moderating role of perceived control in the relationships between trauma and inflammation, and in inflammation and depression. We hypothesized that perceived control would moderate the relationship between 1) trauma and inflammation (See Figure 1C), and 2) inflammation and depression (See Figure 1D). A third exploratory aim of the current study was to further probe the role of perceived control in these relationships by examining each of the two dimensions, mastery and constraints. By examining each of these two dimensions separately, the result of this study could provide further specificity for treatment targets and intervention development. Given that studies examining these two dimensions separately in this area of research are sparse, no specific hypotheses were made regarding the potentially distinct associations between each of these dimensions of perceived control and trauma, inflammation, and depression.

Methods

Participants

The current investigation used data from the Midlife Development in the United States Study (MIDUS), a nationally representative longitudinal study investigating the psychosocial and biological factors that contribute to healthy aging. Three waves of data have been collected thus far. The first wave of data collection (MIDUS 1) started in 1995 and comprised 7,108 English-speaking adults between the ages of 25 and 74 living in the United States. The sample included four subsamples: a national random digit dialing (RDD) sample ($n = 3,487$); oversamples from five cities ($n = 757$); siblings of participants in the RDD sample; and a sample of RDD twin pairs ($n = 1,914$). The second wave of data collection (MIDUS 2) occurred from 2004 to 2006 and included five different smaller projects. In one of the five projects, the MIDUS 2 Biomarker Project, participants completed a 24-hour overnight visit at one of three General Clinical Research Centers at either UCLA, Georgetown, or University of Wisconsin based on where they lived. A third wave of data collection (MIDUS 3) began in 2013, in which participants who completed MIDUS 1 and MIDUS 2 were invited back to complete all of the same measures from MIDUS 1.

Data for the current investigation were from participants who completed MIDUS 1, the MIDUS 2 Biomarker Project, and MIDUS 3. Data from a total of 945 participants who completed all procedures and measures at all three timepoints were included in analyses. The current analysis of publicly available deidentified data did not meet criteria for human subjects research and thus did not require IRB approval.

Procedures

MIDUS 1 participants were initially contacted in 1995 using a random-digit-dial sampling technique selected from telephone banks in the United States. Those who agreed to participate completed a 30-minute telephone interview and were mailed questionnaires that took an average of two hours to complete.

Participants from MIDUS 1 were then invited for another wave of data collection in 2004. Of the original 7,108 participants in MIDUS 1, 4,032 participants completed another 30-minute phone interview and self-administered questionnaires as part of MIDUS 2. All participants who completed the MIDUS 2 phone interview and self-administered questionnaires were invited to participate in the MIDUS 2 Biomarker Project. For the current study's sample, participants completed procedures for the MIDUS 2 Biomarker Project an average of 26.4 months ($SD = 14.7$) after completing the MIDUS 2 self-administered questionnaire. Participants gave written informed consent at the beginning of their first in-person visit. On day 1 of the site visit, participants provided information on their current medication and their medical history, completed self-report measures, and underwent a physical exam (at the Midwest site only). On day 2, participants provided a fasting blood draw. Additional procedures were conducted that were not relevant to the present study's aims, including a 12-hour urine collection, a psychophysiology experimental protocol, and a bone scan (a full description of the MIDUS 2 Biomarker project's procedures is documented online by the MIDUS study investigators (43)).

In 2013, participants from MIDUS 1 and 2 were invited to complete another phone interview and self-administered questionnaires (MIDUS 3). A total of 2,732 participants completed the phone interview and self-administered questionnaires.

Measures

Trauma. Consistent with previous studies examining the effects of trauma, the present study operationalized trauma exposure as the total number of potentially traumatic experiences that participants endorsed (Turner & Lloyd, 1995). The composite measure of trauma exposure from the MIDUS study used by Elliot et al. (2018) was employed for the present study, which was created based on items found in measures of trauma exposure (44,45). Five items from the MIDUS 1 self-administered survey captured traumatic events in childhood (emotional abuse, physical abuse, parental alcohol abuse, parental drug abuse, and parental divorce). These data were extracted from responses on 15 items on the Conflicts Tactics Scale (46), a self-report measure that asks participants to report how often they experienced various types of conflicts with others in their childhood and who was involved in the conflict (e.g., guardians, siblings, or others). The response scale was modified for the MIDUS study to a four-point likert scale ranging from “often” (1) to “never” (4), with the option to indicate “does not apply” (8). Following the same procedures as Elliot et al. (2018), physical abuse was counted if participants reported the abuse occurring “sometimes” or “often” (47), and emotional abuse was counted if it was reported to have occurred “often” in childhood. Severe physical abuse such as being choked or burned was totalled as an additional trauma exposure in addition to moderate physical abuse, such as being pushed or slapped. Parental death in childhood was also captured in the MIDUS 1 self-administered questionnaire and was included as a trauma exposure as well. The rest of the

items in the trauma composite measure were assessed in the MIDUS 2 self-administered questionnaire and asked about events that may have occurred at any point in participants' lives and are widely recognized as traumatic (child death, child with a life threatening illness, physical assault, sexual assault, lost home to a natural disaster, and combat experience). Higher scores on this count measure represent more trauma exposure. No studies have evaluated the validity of this particular measure to our knowledge; however, given that the traumatic experiences selected for this composite measure were based on validated measures of cumulative trauma (44,45), and this count has demonstrated effects consistent with other measures (48), this composite measure seems to capture exposure to trauma.

Depression. The present investigation used two different measures of depression: one that assesses for Major Depressive Disorder (MDD) based on the diagnostic criteria of the third edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; 1), and the other that captures the dimensionality and full spectrum of depressive experiences. This decision was made for two reasons: 1) Relying only on the clinical measure of depression would have neglected important variance in the range of symptoms above and below clinical levels of depression, and 2) The dimensional measure of depression was only administered in the second wave of data collection, which precluded longitudinal mediation analyses using the three timepoints with this measure. Therefore, both measures of depression were employed in separate models.

The Composite International Diagnostic Interview Short Form (CIDI-SF) was administered in a 30-minute phone interview at all three waves of data collection. Participants

were asked whether, in the past 12 months, they had experienced a period of sadness or depression or loss of interest in things that typically give them pleasure for at least two consecutive weeks. If they endorsed having experienced a two-week period of sadness or loss of interest in the last 12 months, they were asked follow-up questions about that two-week period to assess whether they experienced those feelings at least most of the day and nearly every day. Participants who endorsed experiencing those symptoms at that frequency were asked follow-up questions to assess whether they experienced each of the other seven symptoms of depression listed in the DSM-III-R. For each participant who reached this portion of the interview, the sum of the number of symptoms of depression endorsed was calculated to produce a symptom count score. Those who did not endorse experiencing a two-week period of sadness or loss of interest most of the day and nearly every day in the prior 12 months had scores of 0.

While the CIDI-SF has the advantage of following diagnostic criteria for depression, it may be less sensitive to subclinical levels of depression. The MIDUS-2 Biomarker Project administered the following depression measure that better captures the full spectrum of depression: The Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a 20-item self-report survey that is commonly used to measure depression in a general population (49). Using a four-point Likert scale ranging from “rarely or none of the time” (1) to “most or all of the time” (4), participants reported how frequently in the prior week they experienced various thoughts, feelings, or behaviors commonly associated with depression. Higher scores indicate greater depression. The CES-D has demonstrated good construct validity and reliability in other studies (49,50) and appears robust to measurement across multiple racial and ethnic groups (51). The CES-D had good internal consistency ($\alpha = .90$ in the current analytic sample).

Perceived control. The MIDUS Sense of Control Scale (52) is a 12-item self-report measure that captures the extent to which individuals feel in control over their life circumstances and outcomes and includes statements such as, “Whether or not I am able to get what I want is in my own hands,” and reverse-coded statements such as “What happens in my life is often beyond my control.” Participants were asked to rate how much they agree with each of the twelve statements on a 7-point Likert scale ranging from “strongly disagree” (1) to “strongly agree” (7). Reverse-coded items were reverse-scored, and total scores were then calculated by summing the scores of each item. Higher scores indicate greater perceived control. The MIDUS Sense of Control Scale demonstrated good internal consistency in the current analytic sample ($\alpha = .87$) and is considered a valid measure of perceived control (52). This scale also provides scores for the two dimensions of perceived control, mastery ($\alpha = .75$ in current analytic sample) and constraints ($\alpha = .85$ in current analytic sample). Additional analyses in the present study replaced perceived control with each of its two dimensions in all models (5,13).

Inflammation. A fasting blood draw was used to measure circulating markers of inflammation. Samples were stored between -60 and -80 degrees Celsius before being shipped on dry ice to the MIDUS Biocore Lab where they were processed. The current study measured inflammation with C-reactive protein (CRP) and interleukin-6 (IL-6), which are the two most empirically-supported inflammatory markers associated with stress and depression (53–56). IL-6 was measured from serum with a Quantikine® High-sensitivity ELISA kit #HS600B (R & D Systems, Minneapolis, MN). CRP was processed through plasma with BNII nephelometer from Dade Behring with a particle enhanced immunonephelometric assay. Samples that fell below the assay range were then processed with immunoelectrochemiluminescence with a high-sensitivity

assay kit (Meso Scale Diagnostics #K151STG). For extensive information on the measurement procedures of CRP and IL-6 in the MIDUS 2 Biomarker Study, see the study's documentation available online (43).

Covariates. Previous research has demonstrated that numerous demographic variables, including age, gender, and socioeconomic status, are associated with perceptions of control, trauma exposure, and/or depression (52,57–59). Therefore, to control for potential confounding effects, the following variables were included as covariates in models testing the role of perceived control in the relationship between trauma and depression: age, gender, household income, education level, and parental education level. To parse out the effects of perceived control and trauma on current depression above and beyond previous history of depression, depression at the previous timepoint (CIDI-SF) was also included as a covariate. Psychiatric treatment status was included as a covariate as well to control for treatment effects in the analyses. Given previous research showing relationships between medical conditions and medication on inflammation levels (60–62), the following additional covariates were included in models with CRP or IL-6 as either predictors or outcomes: history of heart disease, history of a diabetes diagnosis, currently taking blood pressure medication, anti-inflammatory medication, or any other medication.

Analytic Approach

Data preparation. Following procedures described in Hostinar et al. (2015), inflammation values that were greater than four standard deviations from the mean were winsorized and replaced with the value at the 99.9th percentile (14 cases for CRP, 12 cases for

IL-6). All highly skewed outcome variables were log-transformed to normalize their distributions. Continuous variables were centered for multiple regression analyses. Household income was standardized in regression models to provide more easily interpretable estimates. To retain all observations in our analytic sample for fully adjusted models, multiple imputation of 20 imputed datasets was employed with the mice package in R (64). We used the classification and regression trees (CART) method to allow for greater flexibility (i.e., accommodate possible interaction and non-linear effects between variables; 65).

Statistical analyses. All analyses were conducted using R version 4.1.2. Bivariate correlations of all study variables were first examined. Pearson's correlations were conducted on continuous variables, and Spearman's correlations were conducted for pairs that included at least one ordinal variable. Independent samples t-tests were conducted to test differences in the means of study variables for dichotomous demographic variables.

A piece-wise approach for the main study analyses was employed to adequately fit both linear regression models and zero-inflated Poisson regression models. Linear regressions were used for cross-sectional moderation analyses for MIDUS 2 data, and longitudinal mediation analysis was employed with trauma predicting T2 perceived control using linear regression and T2 perceived control predicting T3 depression using zero-inflated Poisson regression (described further below).

First, the main effect of trauma on T2 (from MIDUS 2) depression (CES-D) was tested with a linear model. Interaction terms between the hypothesized moderator (i.e., perceived

control, mastery, and constraints) and the predictor (trauma) were then included in unadjusted models. Specified covariates were then included in fully adjusted models. Regression diagnostics were examined to ensure that any deviations from the assumptions of linear regression were within reasonable limits. Models with and without transformed variables were compared to assess whether transforming highly skewed variables contributed to better model fit and/or improved regression diagnostics. If the transformed variables did not improve model fit nor improve regression diagnostics, then the variable was left untransformed to allow for easier interpretability.

To examine the potential longitudinal mediating role of perceived control in the relationship between trauma and depression, the *maczic* package in R was used (66,67). This package allows one to fit both linear regression and zero-inflated Poisson regression when testing mediation. Since only those who endorsed having experienced a two-week period of sadness or anhedonia were asked about the remaining depression symptoms, the meaning of depression scores of 0 on the CIDI-SF represents two groups of people: 1) Those who had experienced no symptoms of depression, and 2) Those who experienced some symptoms of depression but not sadness or anhedonia more days than not in a two-week period. Therefore, given the distribution and the double-meaning of 0 in this variable, zero-inflated Poisson regression was determined to be more suitable than linear regression. A linear regression model was first fit with trauma predicting T2 perceived control as the “a path”, and a zero-inflated Poisson regression model was also fit with T2 perceived control predicting T3 depressive symptoms (CIDI-SF at MIDUS 3) as the “b path.” The indirect effect of trauma on T3 depression through T2 perceived control was estimated by pooling the estimates across the 20

imputed datasets using the mitml package in R (68). Specified demographic, health, and treatment covariates were included in the adjusted model. Finally, to examine whether perceived control mediated the relationship between trauma and depressive symptoms above and beyond previous history of depressive symptoms, T2 depressive symptoms were included as a predictor in the fully adjusted model. To examine the contributions of mastery and constraints, each model was then tested again replacing perceived control with each of its two dimensions in their own models and controlling for the other dimension.

Finally, to examine the moderating role of perceived control in the relationship between trauma and inflammation, and inflammation and depression, the same stepwise approach described above for moderation analysis was employed. Models with CRP and IL-6 were examined separately for perceived control, mastery and constraints. The amount of time in between the MIDUS 2 questionnaire and the Biomarker Study session was also tested as a covariate to examine its influence on any of the hypothesized relationships. No changes were observed, so the original models were retained.

Power Analysis

Using G*Power 3.1.9, we performed a sensitivity power analysis to determine the minimum detectable effect size given the current study's analytic sample size. We set alpha to .05, power at .8, sample size at 945, and the number of predictors at 15 (which was our largest model fully adjusted for potential confounding variables). The Cohen's f^2 needed to detect an effect was 0.00832, which is smaller than effect sizes documented in previous research on the

relationship between perceived control and physiological variables (41). Therefore, the current study's analyses were deemed sufficiently powered.

Results

Analytic Sample

Characteristics of the analytic sample and descriptive statistics of the study variables are presented in Table 1. At T2 (the timepoint during which the moderation analyses were conducted), participants included were on average 54.3 years old ($SD = 11.1$; at MIDUS 2), 56% female, 91.7% non-Hispanic white, 2.7% Black, 0.3% Native American, 0.2% Asian or Pacific Islander, 2.0% other, 0.8% multiracial, and 3.8% Hispanic. Participants in the original baseline sample (MIDUS 1) were on average 46.4 years old ($SD = 13.0$; at MIDUS 1), 52% female, 90.7% white, 5.3% Black, 0.6% Native American, 0.9% Asian or Pacific Islander, 1.9% other, and 0.7% multiracial. Data on Hispanic ethnicity were not captured at MIDUS 1.

Bivariate Correlations and T-tests

Bivariate correlations of the variables used in the current study were in the expected directions and magnitudes (see Table S1, Supplemental Digital Content, <http://links.lww.com/PSYMED/A997>). Independent samples t-tests revealed some gender differences in the study variables, with males showing higher levels of perceived control ($t = 2.17, p = .030$), lower levels of constraints ($t = -2.11, p = .035$), and lower CRP ($t = -4.90, p < .001$) than females.

Moderating Effect of Perceived Control on Trauma and Depression.

As expected (see Figure 1A for hypothesized model tested), greater levels of trauma exposure were associated with more depression symptoms at T2 ($b = .13, p < .001$). However, in an adjusted model with relevant covariates, perceived control did not significantly moderate the effect of trauma on depression ($b = .03, p = .091$; see Table S2, Supplemental Digital Content, <http://links.lww.com/PSYMED/A997>). This non-significant interaction effect appeared to be driven primarily by constraints ($b = .03, p = .085$; see Table S3, <http://links.lww.com/PSYMED/A997>) and less so by mastery ($b = .02, p = .27$; see Table S4, <http://links.lww.com/PSYMED/A997>). The interaction between constraints and trauma in predicting depression reflects a more pronounced effect than the interaction between mastery and trauma.

Mediating Effect of Perceived Control on Trauma and Depression.

In an unadjusted model using zero-inflated Poisson mediation analysis (see Figure 1B for hypothesized model tested), perceived control at T2 significantly mediated the relationship between lifetime trauma exposure and depression nine years later at T3 (IE = 0.031, $SE = 0.012, t = 2.57, p = .010$). After including relevant covariates, the indirect effect of T2 perceived control on the relationship between trauma and T3 depression was no longer statistically significant (IE = 0.016, $SE = 0.009, t = 1.88, p = .060$). Finally, the mediating effect of perceived control on trauma and depression further diminished after including previous wave of depression in the adjusted model (IE = 0.007, $SE = 0.007, t = 0.91, p = .36$).

When examining constraints and mastery separately, a pattern similar to the results of the moderation analysis emerged, such that constraints (as opposed to mastery) seemed to primarily account for the mediating effect of perceived control in the relationship between trauma and T3 depression. Again, when replacing perceived control with constraints in the mediation model, the unadjusted indirect effect was significant ($IE = 0.045$, $SE = 0.014$, $t = 3.18$, $p = .001$). The indirect effect of constraints was significant when including relevant covariates ($IE = 0.032$, $SE = 0.013$, $t = 2.42$, $p = .016$) but was no longer significant after controlling for the previous wave of depression ($IE = 0.019$, $SE = 0.011$, $t = 1.67$, $p = .095$). In contrast, mastery did not significantly mediate the relationship between trauma and depression even in the unadjusted model ($IE = 0.001$, $SE = 0.004$, $t = 0.23$, $p = .82$).

Inflammation, Trauma, and Depression.

In contrast to our hypothesis, higher levels of trauma were not associated with greater CRP ($b = .04$, $p = .10$). Additionally, perceived control did not significantly interact with trauma to predict CRP in either crude or adjusted models (see Table S5, Supplemental Digital Content, <http://links.lww.com/PSYMED/A997>; see Figure 1C for hypothesized model tested). Additionally, trauma exposure was not associated with IL-6 and did not significantly interact with perceived control in either crude or adjusted models (see Table S6, <http://links.lww.com/PSYMED/A997>). These results were similar when examining mastery (see Tables S7 and S8, <http://links.lww.com/PSYMED/A997>) and constraints (see Tables S9 and S10, <http://links.lww.com/PSYMED/A997>) separately.

In considering the effects of inflammation and perceived control on T2 depression (see Figure 1D for hypothesized model tested), main effects but no statistically significant interactions were observed. CRP was positively associated with depression ($b = .06, p = .027$) when included in its own model (see Table S11, Supplemental Digital Content, <http://links.lww.com/PSYMED/A997>). When controlling for the effect of perceived control on depression, the relationship between CRP and depression maintained statistical significance ($b = .06, p = .011$). In the same model, perceived control was also negatively associated with depression ($b = -0.42, p < .001$). However, contrary to our hypothesis, perceived control did not significantly moderate the effect of CRP on T2 depression ($b = .04, p = .17$). Similar to the null findings on the relationship between trauma and IL-6, there was no statistically significant association between IL-6 and depression nor interaction with perceived control in predicting depression in crude or adjusted models (see Table S12, <http://links.lww.com/PSYMED/A997>). These results were consistent when replacing perceived control with mastery (see Tables S13 and S14, <http://links.lww.com/PSYMED/A997>) and constraints for CRP and IL-6 (see Tables S15 and S16, <http://links.lww.com/PSYMED/A997>).

Exploratory Analysis: Childhood Trauma.

Since much of the research that has shown moderating effects of perceived control has focused on childhood trauma (17–19), we conducted follow-up exploratory analyses that replaced the trauma variable with a sum variable of only the events that occurred in childhood. The findings using the childhood trauma measure were consistent with the cumulative lifetime trauma measure.

Adjustments for Multiple Comparisons.

Given the state of the research and the novelty of the current study's approach, we elected to report and discuss point estimates uncorrected for multiple comparisons. This approach is conducive to highlighting potential relationships of interest for future research. However, this approach also increases the risk for labeling a relationship as statistically significant when, in reality, it may not be meaningful. Thus, we also employed Benjamini-Hochberg's false discovery rate method ($FDR = .05$; 69) to determine statistical significance in accord with the number of comparisons made in the analyses. It should be noted that the mediating effect of constraints in the relationship between trauma and depression would not be labeled statistically significant after adjusting for multiple comparisons with this method. This important caveat highlights the need for replication of this finding in future studies before concluding that it may be theoretically meaningful.

Discussion

The overarching objective of the current investigation was to elucidate the roles of perceived control and inflammation in the relationship between trauma exposure and depression in a national sample of adults in the United States. Findings from the current study lend some support for the importance of perceived control as an explanatory mechanism in the relationship between cumulative lifetime trauma and depression but provided no support for the buffering effects of perceived control on trauma and in inflammatory processes related to trauma and depression.

Our first aim was to examine the role of perceived control by evaluating both moderating and mediating pathways in the relationship between trauma and depression. Contrary to our expectations, we did not observe a buffering effect of perceived control on the relationship between trauma and depression severity. This finding may be best understood in the context of trauma's multifaceted and intersecting effects, including but not limited to interpersonal difficulties (70), disordered eating (71), and substance abuse (72), all of which may exacerbate symptoms of depression. These exacerbating effects of trauma on depression severity may weaken the relative contribution of perceived control in depression.

Our finding contrasts with previous studies that demonstrated buffering effects of perceived control on the relationship between trauma and depression severity (17–19). One potential explanation for this discrepancy is the differences in the current study's population compared to previous studies on children (17), female adolescents (19), and women who had endured childhood sexual trauma (18). Perhaps perceived control has a particularly salient buffering effect of trauma on depression for children and adolescents, who may have yet to develop the downstream consequences of trauma that manifest and compound over the course of a lifetime (70,72). Furthermore, perhaps perceived control is particularly helpful for reducing depression for those who have experienced interpersonal trauma (e.g., sexual trauma, physical assault) compared to other types of traumas (e.g., natural disaster) because of one's awareness of more apparent behavioral strategies that may prevent trauma re-occurrence (18). The contrast between the current study's findings on cumulative trauma exposure and other findings on specific trauma experiences suggests that the type of traumatic experience may be relevant for the protective nature of perceived control. Severity of trauma exposure may also represent an

important factor to consider when examining the protective effects of perceived control and other factors in trauma sequelae, as previous research has shown diminished protection from resilience factors against more severe traumatic experiences (73). Taken together with results from previous studies, the finding of the current study that perceived control did not buffer the effect of trauma on depression in a sample of US adults provides greater understanding of when, how, and for whom perceived control may or may not be helpful.

We also hypothesized that perceived control would partially mediate the relationship between trauma and subsequent depression nine years later. Findings from our study lend some support to this hypothesis. Perceived constraints significantly mediated the relationship between trauma and subsequent depression even after controlling for several potentially confounding variables. However, this finding did not remain significant in the fully adjusted model that included MIDUS 2 depression. The lack of a statistically significant indirect effect of perceived constraints when controlling for MIDUS 2 depression suggests that while constraints may contribute to the trauma-associated maintenance and chronicity of depression, the directionality of the relationship between constraints and depression should be considered.

This relationship between constraints and depression may be bidirectional, such that constraints contributes to reduced depression and depression increases constraints (13,14). Therefore, the indirect effect of constraints in the longitudinal relationship between trauma and depression may be explained by the synergistic relationship between constraints and depression, such that constraints may concurrently fluctuate with depression. These findings contrast with

previous studies that have shown explanatory effects of perceived control in the relationship between trauma and depression among children (17,21) and adolescents (20).

The current study differs from previous studies investigating these effects by directly testing mediation while controlling for the auto-regressive effect of depression in a large sample of US adults. Given the difference in both methodology and samples in the current study compared to previous studies, it is difficult to determine what might explain the discrepancy in findings. Notwithstanding that ambiguity, these results provide further information on the potential mediating role of constraints in the relationship between trauma and depression over time.

Our second aim was to describe the role of inflammation in the relationship between trauma and depression and to evaluate how perceived control influences those relationships. Our study found a positive association between CRP and depression (53,74) but no associations between CRP and trauma or between IL-6 and trauma and depression. These findings reflect similar results in the literature that have shown inconsistent relationships with depression and various inflammatory markers (75,76). Our finding that CRP was associated with depression was not surprising given previous reports of this association in the MIDUS data with different methods of capturing depression (35–37). These results provide further evidence that CRP in particular may be sensitive to depression.

Contrary to our expectations, we observed no buffering effects of perceived control on the relationship between trauma exposure and inflammation or inflammation and depression.

This finding is surprising given previous research that has examined these links (40). One potential reason for this discrepancy is that the sample used for the current study was younger than the sample in Elliot et al. (2017). Perhaps the buffering effect of perceived control on the relationship between trauma and inflammation does not emerge until later in life, when the consequences of trauma have accumulated over time and display larger effects on inflammatory systems (63,77).

Finally, our study showed that constraints was a particularly salient dimension of perceived control in all analyses relative to mastery, and that constraints may be a particularly relevant risk and maintenance factor of depression. These findings suggest that, compared to mastery beliefs, perceived barriers to achieving desired goals may be a stronger explanatory factor in the relationship between cumulative trauma and depression in adults. These results are consistent with previous studies that have found constraints more strongly associated with depression than is mastery (8,13). Results from our study extend this literature to include the effects of trauma on both constraints and associated depression severity.

Results from the current study provide several novel contributions to the literature on the role of perceived control in the relationship between trauma and depression. Our observation that perceived control did not significantly moderate the effect of trauma on depression suggests that the buffering effects previously demonstrated may not extend to mostly white US adults. Additionally, our finding that constraints partially mediated the relationship between trauma and depression nine years later suggests that constraints may be a relevant maintenance factor for depression in the context of trauma among US adults. These findings taken together suggest that

constraints in particular may be a clinically relevant factor worth exploring for the prevention and treatment of depression in US adults.

Despite notable contributions of this study, the limitations of this study are worth acknowledging. To start, the sample used here was relatively homogenous, with most of the sample comprising non-Hispanic white participants. Systemic racism represents a structural set of constraints and disadvantage that impinges on people of color's ability to exert control over their life circumstances (78). The protective nature of perceived control may therefore represent and function differently among racial minorities who are chronically exposed to systems of oppression (79–81). Future work should specifically recruit racial and ethnic minorities to examine whether perceived control and inflammation behave in the same ways described here. Additionally, the finding that constraints mediated the relationship between trauma and depression did not survive adjustment for multiple comparisons. Therefore, these findings should be considered preliminary, and additional studies would need to replicate these findings to enhance confidence in the generalizability of the results.

Notwithstanding these limitations, the current study provides more clarity on the role of perceived control, and especially each of its dimensions, in the relationships between cumulative trauma and depression. These findings extend the work of previous research on children and adolescents to US adults. Findings described here suggest that constraints may serve as a key mechanism in the relationship between trauma and depression. Findings from the current study also provided evidence against a potential buffering effect of perceived control on the relationship between trauma and inflammation or on inflammation and depression. This study

provides useful information for future research investigating perceived control as a mechanism or buffering factor in the harmful effects of trauma and inflammation on depression severity.

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FIGURE CAPTION

Hypothesized Models for role of Perceived Control, in the Relationships between Trauma, Inflammation, and Depression

Note. CIDI-SF = The Composite International Diagnostic Interview Short Form; CES-D = Center for Epidemiologic Studies Depression Scale.

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Figure 1

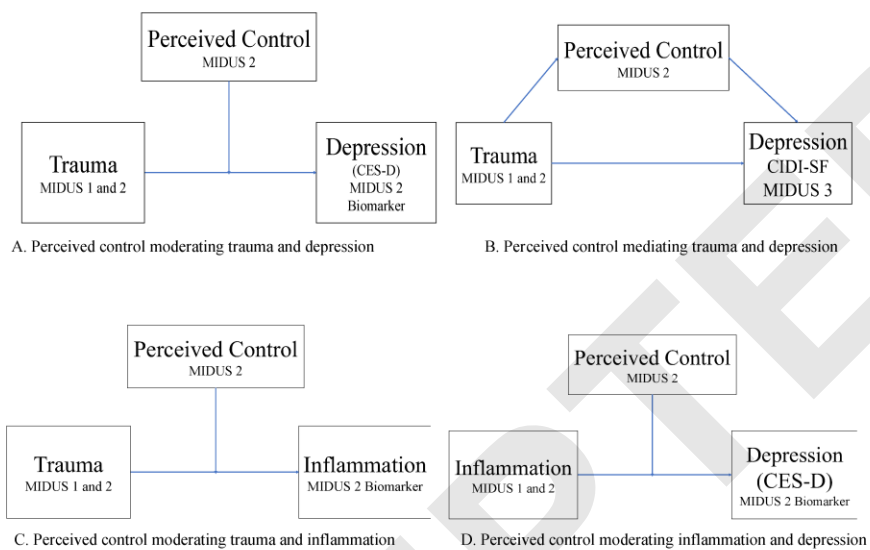


Table 1

Descriptive Statistics

Variable	M (SD) or number (%)	n
Age (years)	54.33 (11.06)	945
Gender (female)	525 (56)	945
Race		916
White	861 (94.0)	
Black	25 (2.7)	
Native American	3 (0.3)	
Asian or Pacific Islander	2 (0.2)	
Other	18 (2.0)	
Multiracial	7 (0.8)	
Ethnicity		943
Hispanic	36 (3.8)	
Education level	7.58 (2.42)	944
Mother's education level	5.3 (2.49)	920
Father's education level	5.24 (3.02)	874
Treatment Status (no treatment)	620 (65.6)	945
Trauma	2.93 (1.56)	945
T2 Perceived Control	5.69 (0.94)	945
T2 Mastery	5.81 (1.01)	945
T2 Constraints	2.37(1.08)	945
T2 CES-D	7.56 (7.44)	945
T3 CID-SF	0.61 (1.74)	945
T2 CRP	2.57 (3.72)	945
T2 IL-6	2.58 (2.35)	945

Note. Demographic statistics are reported from analytic sample with missing data; descriptive statistics on study variables are pooled estimates from 20 multiply imputed datasets; Age is reported at MIDUS 2; Education was measured as an ordinal variable, with 5 corresponding to a high school graduate, 7 corresponding to around 3 years of a 4-year degree, and 8 corresponding to a completed associates degree; Treatment status was a binary variable with 1 = did not report using antidepressants or engaging with therapy at T2; CES-D = Center for Epidemiologic Studies Depression Scale; CIDI-SF = Composite International Diagnostic Interview Short Form (Depression); CRP = c-reactive protein; IL-6 = interleukin 6.