Early adversity and inflammation at midlife: the moderating role of internalizing psychopathology

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Abstract

Background. Childhood adversity has been associated with increased peripheral inflammation in adulthood. However, not all individuals who experience early adversity develop these inflammatory outcomes. Separately, there is also a link between various internalizing emotional distress conditions (e.g. depression, anxiety, and fear) and inflammation in adulthood. It is possible the combination of adult emotional distress and past childhood adversity may be uniquely important for explaining psychopathology-related immune dysfunction at midlife.

Methods. Using data from the Midlife in the United States (MIDUS) study ($n = 1255$), we examined whether internalizing, defined as past 12-month emotional distress symptomatology and trait neuroticism, moderated associations between childhood adversity and heightened inflammation in adulthood. Using latent variable modeling, we examined whether transdiagnostic or disorder-specific features of emotional distress better predicted inflammation.

Results. We observed that childhood adversity only predicted adult inflammation when participants also reported adult internalizing emotional distress. Furthermore, this moderation effect was specific to the transdiagnostic factor of emotional distress rather than the disorder-specific features.

Conclusions. We discuss the possibility that adult internalizing symptoms and trait neuroticism together may signal the presence of temporally stable vulnerabilities that amplify the impact of childhood adversity on midlife immune alterations. The study highlights the importance of identifying emotional distress in individuals who have experienced childhood adversity to address long-term immune outcomes and enhance overall health.

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Inflammatory markers encompass a variety of proteins and signaling molecules that facilitate immune activity and maintain overall health. Concentrations of inflammatory markers measured in the blood are often used to assess immune functioning. Chronic inflammation, marked by a persistent state of heightened immune activity, is associated with the development of conditions including heart disease and type 2 diabetes (Danesh et al., 2008; Theuma & Fonseca, 2003). Psychosocial stressors can activate inflammatory responses with implications for a variety of health outcomes (Liu, Wang, & Jiang, 2017; Steptoe, Hamer, & Chida, 2007). Childhood adversity in particular is an established environmental risk factor for the health conditions mentioned above and chronic inflammation later in life (Hostinar, Lachman, Mroczek, Seeman, & Miller, 2015; Kerr, McDonald, & Minnis, 2021; Lacey, Pinto Pereira, Li, & Danese, 2020). Thus, inflammation is likely a biological mechanism connecting childhood adversity to poor health during adulthood. However, not all individuals with childhood adversity exhibit later inflammation. Differences among individual vulnerabilities to stressors may play a role. Using a nationally representative sample of United States adults, we investigated whether the association between early adversity and adult inflammation is moderated by past 12-month emotional distress symptoms and trait neuroticism.

There is a reliable association between early life stress and increased health complications in adulthood (e.g. chronic inflammation); however, the severity and frequency of these outcomes can vary widely across individuals (Hostinar & Miller, 2019; Oh et al., 2018). Factors tied to stress vulnerabilities, including how individuals tend to appraise and respond to adversity, may modulate these health outcomes. For example, a recent study using data from the Midlife in the United States (MIDUS) project found that adults with a history of early adversity using more adaptive coping strategies experienced fewer physical health conditions, including autoimmune and bone conditions, compared to those using these strategies less often (Sheffler, Piazza, Quinn, Sachs-Ericsson, & Stanley, 2019). Similarly, in adults who experienced childhood maltreatment, higher self-reported control of emotions was associated with lower

inflammation (Gouin, Caldwell, Woods, & Malarkey, 2017; Jones, Marsland, & Gianaros, 2023). Therefore, the long-term effects of early life stress may vary as a function of trait-level individual differences – one's personal capacity to respond adaptively may influence the likelihood of chronic inflammation during adulthood.

Emotional distress psychopathology along with elevated personality traits of neuroticism reflect putative stress vulnerabilities capable of moderating the association between early adversity and later inflammation. Emotional distress conditions (e.g. generalized anxiety disorder [GAD] and major depressive disorder [MDD]) are more common among individuals who have experienced early adversity (Danese et al., 2008; Nanni, Uher, & Danese, 2012). Moreover, these conditions have been shown to be associated with reduced immune system functioning (Beurel, Toups, & Nemeroff, 2020). Despite this, symptoms of anxiety and depression, if included in statistical models of adversity and inflammation, are often treated as confounds (and modeled as covariates) rather than as potential moderators (Coelho, Viola, Walss-Bass, Brietzke, & Grassi-Oliveira, 2014). Conversely, in studies examining MDD and GAD as main effect statistical predictors of inflammatory markers (Costello, Gould, Abrol, & Howard, 2019; Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013; Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017; Ogłodek, Szota, Just, Szromek, & Araszkiewicz, 2016), the role of early adversity is not always examined. While some studies have examined the joint effects of emotional distress symptoms and early adversity on inflammation at midlife, inconsistencies exist. Specifically, some studies indicate that individuals with both depressive symptoms and early adversity have higher inflammation levels than those with only adversity but no depressive symptoms (Danese et al., 2008; Gill et al., 2020). However, other studies have found no differences in inflammatory markers when comparing these groups (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Coelho et al., 2014; Palmos et al., 2019).

Inconsistencies surrounding the combined influence of emotional distress symptoms and early adversity may stem in part from reliance on case-control methodology. Case-control designs group individuals based on discrete diagnostic categories such as MDD or GAD, which limits the ability to study how symptoms co-occurring across diagnoses may influence inflammatory outcomes (Moriarity & Alloy, 2020; Thylur & Goldsmith, 2022). *Transdiagnostic* internalizing (i.e. emotional distress) symptoms are psychiatric comorbidities commonly observed across depression, anxiety, and fear-based conditions (Krueger, 1999). These transdiagnostic features are often overlooked in case-control research, potentially obscuring when similar associations with inflammation exist across various internalizing conditions. Indeed, one meta-analysis found that diagnoses of clinical depression and anxiety both demonstrated similarly elevated inflammation compared to non-clinical populations (Tursich et al., 2014); this is consistent with a shared, transdiagnostic mechanism across these conditions.

Neuroticism is a broad personality trait associated with heightened emotional reactivity, tendencies towards negative affect, and increased sensitivity and reactivity to stressors (Claridge & Davis, 2001; Griffith et al., 2010). It is relatively stable during adulthood and acts as a non-specific predictor of various internalizing conditions (Costa & McCrae, 1988; Ormel & Wohlfarth, 1991). Importantly, measures of neuroticism assess content closely associated with the transdiagnostic comorbidities common across emotional distress diagnoses. In other words, neuroticism can serve as an effective marker of the shared variance across depression, anxiety, and fear-based psychopathologies (Griffith et al., 2010). Evidence for associations between neuroticism and chronic inflammation is mixed. An earlier meta-analysis, which included MIDUS data, did not observe a consistent main effect association between neuroticism and inflammation (Luchetti, Barkley, Stephan, Terracciano, & Sutin, 2014). Yet, the combined effect of neuroticism and adversity can be critical when considering associations with inflammation (Wang et al., 2022). Elliot, Turiano, and Chapman (2017) performed a moderation analysis within a subsample of MIDUS examining the personality trait of neuroticism combined with socioeconomic status (SES) to predict individual inflammation markers. Lower SES was associated with inflammation, but only when neuroticism was high. Given the known connection between lower SES and adverse childhood experiences (Walsh, McCartney, Smith, & Armour, 2019), it is possible that neuroticism specifically and transdiagnostic emotional distress more generally also reflect vulnerabilities to adverse life events on health outcomes.

The current study expands upon previous MIDUS research, which demonstrated associations between early adversity and individual markers of adult inflammation (Hostinar et al., 2015), as well as separate associations between transdiagnostic internalizing psychopathology and general health outcomes (e.g. all-cause mortality; Kim et al., 2021). Specifically, we investigated whether (Aim 1) the relationship between childhood adversity and inflammation at midlife is moderated by a latent estimate of past 12-month internalizing symptomatology and trait neuroticism using confirmatory factor analysis (CFA). In addition, we directly compared (Aim 2) transdiagnostic *v.* disorder-specific emotional distress (i.e. residual terms) when examining the connection between early adversity and inflammation in adulthood. Furthermore, our analyses used a latent estimate of chronic inflammation across multiple biomarker assays. This study is consistent with the goals of MIDUS to better understand the transdiagnostic processes of psychosocial resilience, adult well-being, and physical health. Ultimately, this may aid in identifying adults with childhood adversity who are vulnerable to worse health outcomes at midlife, thereby informing screening efforts focused on prevention and treatment.

Methods

Sample

This study used publicly available data from the MIDUS project (Ryff et al., 2007). In 1995, MIDUS recruited 7108 non-institutionalized adults via random digit dialing from the contiguous United States. In 2004, 5555 participants (75%) of the original sample were recruited for a second wave of data collection (MIDUS II). In the second wave, The Biomarker Project was initiated, involving a subsample ($n = 1054$) who underwent a 2-day study visit, including the collection of blood. Additionally, an African American subsample from MIDUS I was re-recruited and 201 of these individuals completed the Biomarkers protocol. In total, 1255 participants contributed valid biomarker data. The average time between the questionnaires/phone interviews and biomarker collection was 26.5 (S.D. = 14.0) months. For our analyses, 1.5% of the data was missing. Missing data was deemed completely at random using the vis_miss() visualization function within the R package Naniar (Tierney & Cook, 2020); multiple imputation was

employed (Slopen et al., 2010). All data transformations were performed after reporting sample characteristics in Table 1.

Measures

Inflammation

Serum markers of inflammation were collected from fasting blood samples. C-Reactive Protein (CRP) was quantified using a particle-enhanced immunonephelometric assay (BNII nephelometer, Dade Behring Inc., IL). Interleukin-6 (IL-6) was measured with the Quantikine High-sensitivity ELISA kit #HS600B (R&D Systems, MN). Fibrinogen (FGN) assessment used the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., IL). E-Selectin was measured through a high-sensitivity ELISA assay (Parameter Human sE-Selectin Immunoassay; R&D Systems, MN). Soluble Intracellular Adhesion Molecule-1 (ICAM-1) was quantified with an ELISA assay (Parameter Human sICAM-1 Immunoassay; R&D Systems, MN). Intra- and inter-assay coefficients of variance were in acceptable range (<10%) for all assays. Guided by previous MIDUS analyses (Hostinar et al., 2015), values exceeding the 99.9th percentile were replaced with values 4 S.D.s from the mean. IL-6 and CRP were log-transformed to correct for positively skewed distributions (Friedman & Herd, 2010; Slopen et al., 2010; Straka, Tran, Millwood, Swanson, & Kuhlman, 2021). All inflammatory variables were z-transformed.

Internalizing distress

Four continuous mental health measures were used to model a transdiagnostic internalizing distress factor (Kim et al., 2021). Past 12-month depression, anxiety, and panic were assessed using the Composite International Diagnostic Interview–Short Form (CIDI-SF) version 10. Thus, this assessment timeframe reflects more typical emotional functioning rather than acute states. The CIDI-SF has high agreement (91–94%) with its lengthier CIDI counterpart (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998). The fourth indicator assessed neuroticism, which was developed from existing personality inventories and exhibits acceptable internal consistency (Cronbach's $\alpha = 0.74$) (Lachman & Weaver, 2007). Neuroticism reflects a general disposition towards negative emotions and is an effective transdiagnostic marker of internalizing distress (Griffith et al., 2010). Depression, anxiety, and panic measures were log-transformed following other MIDUS analyses (Eaton, Krueger, & Oltmanns, 2011). All internalizing measures were z transformed.

Adverse childhood experiences

A cumulative sum of adverse childhood experiences (ACEs) (Felitti et al., 1998) was constructed consistent with previous MIDUS studies (Hostinar et al., 2015; Sheffler et al., 2019). MIDUS assessed eight historical experiences (before age 18): physical abuse, emotional abuse, sexual abuse, emotional neglect, physical neglect, parental divorce, parental substance abuse, and parental depression. The first five ACEs listed above were obtained from Childhood Trauma Questionnaire (CTQ) scales and collapsed into binary responses using thresholds listed in the manual (Bernstein & Fink, 1998). The CTQ is an established measure of childhood adversity demonstrates high agreement with external sources (Bernstein et al., 2003). The latter three

Table 1. Descriptive statistics of study sample

Measure	n	Mean (S.D.) or number (%)	Range
Internalizing domains			
Depressed affect	1255	0.58 (1.73)	0–7
Anxiety	1255	0.15 (0.96)	0–10
Panic	1255	0.31 (1.02)	0–6
Neuroticism	1249	2.05 (0.64)	1–4
Inflammatory markers			
IL-6 (pg/ml)	1243	3.04 (3.04)	0.16–23
CRP (µg/ml)	1235	3.02 (4.78)	0.02–61.7
FGN (mg/ml)	1235	348.92 (87.85)	45–857
E-selecting (ng/ml)	1242	43.39 (22.72)	0.09–178.05
ICAM-1 (ng/ml)	1242	288.55 (115.61)	44–1076.59
Demographics			
Age	1255	57.32 (11.55)	35–86
Gender (female)	1255	713 (57%)	0–1
Race/ethnicity :	1255		
White (non-Hispanic)		985 (78.5%)	
African American		215 (17.1%)	
And/or Black			
Native American		17 (1.4%)	
Asian		3 (0.2%)	
Other		31 (2.5%)	
Refused		4 (0.3%)	
Years of education	1252	7.47 (2.53)	1–12
Household income (ten thousands)	1213	41.5 (39.2)	0–200
Marital status :	1253		0–1
Married		811 (64.7%)	
Separated		34 (2.7%)	
Divorced		179 (14.3%)	
Widowed		77 (6.2%)	
Never married		152 (12.1%)	
Health covariates			
Body mass index	1215	28.52 (6.08)	14.23–61.43
Alcohol intake	1255	2.46 (1.55)	1–6
Exercise	1255	960 (76%)	0–1
Smoking status	1254	187 (15%)	0–1
Chronic conditions	1255	984 (78%)	0–1

Note. Descriptive statistics of study variables.

ACEs items are specific to MIDUS II questionnaires (yes/no format) with questions like 'Parent's drug use ever caused problems?' and 'Mother depression?' Only events occurring before age 18 were counted. Due to less frequent endorsement of 4 or more items as well as evidence that 4 or more ACEs is associated with worse clinical outcomes (Mersky, Topitzes, & Reynolds,

2013), total scores equal to or greater than 4 were collapsed into one category. Pre-imputation class memberships for ACEs levels were as follows: 0 ($n = 583$), 1 ($n = 286$), 2 ($n = 132$), 3 ($n = 90$), and ⩾ 4 ($n = 103$).

Covariates

Sociodemographic variables were included as covariates in follow-up analyses ([see Analyses] [https://midus.wisc.edu/] Ryff et al., 2007). Sex assigned at birth and marital status were dummy coded (0 = male, 1 = female; 0 = married, 1 = non-married). Following previous methods (Elliot & Chapman, 2016; Friedman & Herd, 2010), the most common race/ethnicity (white-non-Hispanic) was used as the reference, while less common African American, Hispanic, or other race/ethnicity identities were collapsed to 1. Household income reflected total family income in the past 12 months. Educational attainment ranged from 1 = no school/grade school to 12 = Ph.D./M.D./professional degree. Sociodemographic factors such as these have been associated with inflammation (Friedman & Herd, 2010; Nowakowski & Sumerau, 2015).

Furthermore, smoking status and past month alcohol consumption served as health covariates in follow-up analyses (see Analyses). Smoking status was dummy coded, with non-smokers as the baseline. Alcohol consumption was categorized as 1 = Never, 2 = Less than 1x/week, 3 = 1–2x/week, 4 = 3–4x/week, 5 = 5–6x/week, and 6 = Daily. Both smoking status and alcohol intake have been found to influence inflammation (Gonçalves et al., 2011; Imhof et al., 2001). Body mass index (BMI), exercise, and presence of medical conditions were also examined as health covariates due to their known associations with inflammation (Metsios, Moe, & Kitas, 2020; Pahwa, Goyal, & Jialal, 2023; Rodríguez-Hernández, Simental-Mendía, Rodríguez-Ramírez, & Reyes-Romero, 2013). Exercise was binary (1 = 20 min or more physical activity 3x/week). Various other chronic conditions were coded as 0 = No Condition and 1 = Present Condition.

Analyses

All analyses were performed using RStudio version 1.4.1717 (R version 4.1.0). We performed exploratory factor analyses (EFA; 'Psych' package) with oblimin rotations to examine the factor structure of mental health and inflammation variables. We used scree plots and initial loading cutoff values of 0.3 to guide interpretations and modeling decisions. We conducted CFAs using the 'lavaan' package to build latent measurement models of internalizing and inflammation (Rosseel, 2012). Model fit was assessed with the χ^2 goodness-of-fit statistic, confirmatory fit index ([CFI] Bentler, 1990), Tucker Lewis Index (TLI), standardized root mean square residual (SRMR), and root mean square error of approximation ([RMSEA] Steiger, 1990). In addition, Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to compare different models.

We used a series of hierarchical linear regressions to predict the factor scores of inflammation (Aim 1). In the first step, ACEs and the broad internalizing factor were used as separate main effect predictors. The interaction term with internalizing and ACEs was included in the second step. Johnson-Neyman analyses were used to probe and visualize the interaction. Sociodemographic covariates were included in the third step and health covariates were introduced in the fourth step. This was done to explore if the internalizing-ACEs interaction term

predicted inflammation over-and-above the associations between covariates and inflammation.

Inclusion of health covariates in particular can diminish effect sizes between mood indices and inflammation (Appleton, Buka, Loucks, Gilman, & Kubzansky, 2013; Winter, Riordan, Conner, & Jose, 2021). This may be due to shared processes underlying inflammation and physical health. We performed follow-up analyses considering each health covariate individually. After observing how BMI eliminated the significant internalizing-ACEs effect, we repeated hierarchical regression models using BMI as the outcome variable instead of inflammation. Therefore, we tested if internalizing distress was functioning as a similar vulnerability with ACEs when predicting BMI.

Finally, we examined whether transdiagnostic internalizing or disorder-specific features moderated the association between ACEs and inflammation (Aim 2; i.e. broad comorbidity v. disorder-specific symptoms). Two simultaneous interaction terms were incorporated into the model: ACEs interacting with the broad internalizing factor scores and ACEs interacting with each unique residual component for a specific disorder. Only one disorder residual was included at a time. The neuroticism residual was conceptualized as measurement error and was not included. Neuroticism was included solely to improve our estimate of latent internalizing distress given the item content with relevance for all three disorder-specific domains in these models. For all study models, main and interaction effects were examined at $\alpha = 0.05$.

Results

Latent measurement models

All inflammation markers were positively correlated (mean $r = 0.26$, range [0.09–0.52]; Table 2). EFA supported either a one- or two-factor solution. The one-factor CFA model showed excellent fit (Fig. 1). A two-factor model was initially considered because markers E-Selectin and ICAM-1 had EFA loadings below 0.6 in the one-factor model, but CFA fit for the two-factor model (CFI = 0.99, TLI = 0.98, RMSEA = 0.04, SRMR = 0.02, AIC = 16 788, BIC = 16 845) did not meaningfully improve over the one-factor model (AIC = 16 788, BIC = 16 840). Therefore, the shared variance of the inflammatory indicators was extracted using a single inflammation factor.

All four internalizing distress measures were positively correlated (mean $r = 0.24$, range [0.13, 0.33]; Table 2). EFA results were consistent with the one-factor solution reported in past MIDUS analyses (Kim et al., 2021). The CFA model of internalizing exhibited excellent fit (Fig. 1). Both shared (transdiagnostic internalizing distress) and unique components (depression, anxiety, and panic) were extracted for subsequent analyses.

Internalizing distress psychopathology and early adversity

We examined internalizing distress, ACEs, and their associations with inflammation (Table 3). For the first model step, internalizing ($\beta = 0.083$) and ACEs ($\beta = 0.060$) both independently predicted greater inflammation. With the second step, the interaction term between internalizing and ACEs was significantly associated with inflammation ($\beta = 0.141$; Fig. 2). Johnson-Neyman analyses revealed that a minimum of 2 ACEs was required before a significant positive association emerged between transdiagnostic internalizing distress and inflammation. Also, internalizing distress scores needed to be at the 53rd percentile before a positive association

Table 2. Bivariate correlations amongst study variables

	1	2	3	4	5	6	7	8	9	10
1. MDD	–									
2. GAD	**0.27**	–								
3. PAN	**0.24**	**0.13**	–							
4. NA	**0.33**	**0.29**	**0.22**	–						
5. IL-6	0.04	**0.06**	0.04	−0.00	–					
6. CRP	**0.07**	**0.09**	**0.09**	0.05	**0.53**	–				
7. FGN	0.05	0.02	**0.06**	−0.01	**0.44**	**0.56**	–			
8. E-Selectin	0.03	−0.01	0.03	0.05	**0.20**	**0.17**	**0.15**	–		
9. ICAM-1	0.04	0.04	**0.06**	0.04	**0.18**	**0.18**	**0.14**	**0.09**	–	
10. ACEs	**0.23**	**0.20**	**0.17**	**0.27**	**0.07**	**0.09**	0.05	0.02	**0.08**	–

MDD, major depressive disorder; GAD, generalized anxiety disorder; PAN, panic disorder; NA, neuroticism; IL-6, interleukin 6; CRP, c- reactive protein; FGN, fibrinogen; ICAM-1, intercellular adhesion molecule; ACEs, adverse childhood experiences.
Note. Bolded coefficients $p < 0.05$. Internalizing and inflammatory measures are grouped separately in shaded boxes.

emerged between ACEs and inflammation. After adding sociodemographic variables as covariates in the third step, the interaction between internalizing and ACEs remained significant ($\beta = 0.130$).

When adding multiple health covariates simultaneously in the fourth step, the statistical interaction with ACEs and internalizing became non-significant ($\beta = 0.070$). We repeated the model by instead adding one health covariate at a time. We found that the interaction between ACEs and internalizing distress was only non-significant when BMI was included. Given the positive correlation between BMI and latent inflammation ($r = 0.43$), it is possible that BMI may reflect a similar biological process as the inflammation biomarkers. Subsequently, we examined if transdiagnostic internalizing distress and ACEs similarly predicted BMI. First, the internalizing factor and ACEs were used as main effect predictors for BMI (online Supplementary Table S1). Only ACEs exhibited a positive association with BMI ($b = 0.435$,

$p < 0.001$, 95% CI [0.169–0.701], $\beta = 0.096$); internalizing distress was not significant ($b = 0.325$, $p = 0.429$, 95% CI [−0.481 to 1.13], $\beta = 0.024$). In the second model step, the ACEs-internalizing interaction term was significantly associated with BMI ($b = 0.705$, $p = 0.004$, 95% CI [0.220–1.189], $\beta = 0.051$). Johnson-Neyman analyses revealed that a minimum of 3 ACEs was required before a significant positive association emerged between the internalizing factor and BMI. Also, internalizing distress scores needed to be at the 39th percentile before a positive association between ACES and BMI emerged. Thus, we observed a similar moderation effect between transdiagnostic internalizing distress and ACEs when predicting BMI.

We also created two new ACEs subscales focused on abuse and neglect (see online Supplemental Materials). There was a significant interaction between abuse and latent internalizing ($b = 0.094$, $p = 0.003$, 95% CI [0.031–0.157], $\beta = 0.137$). Abuse predicted
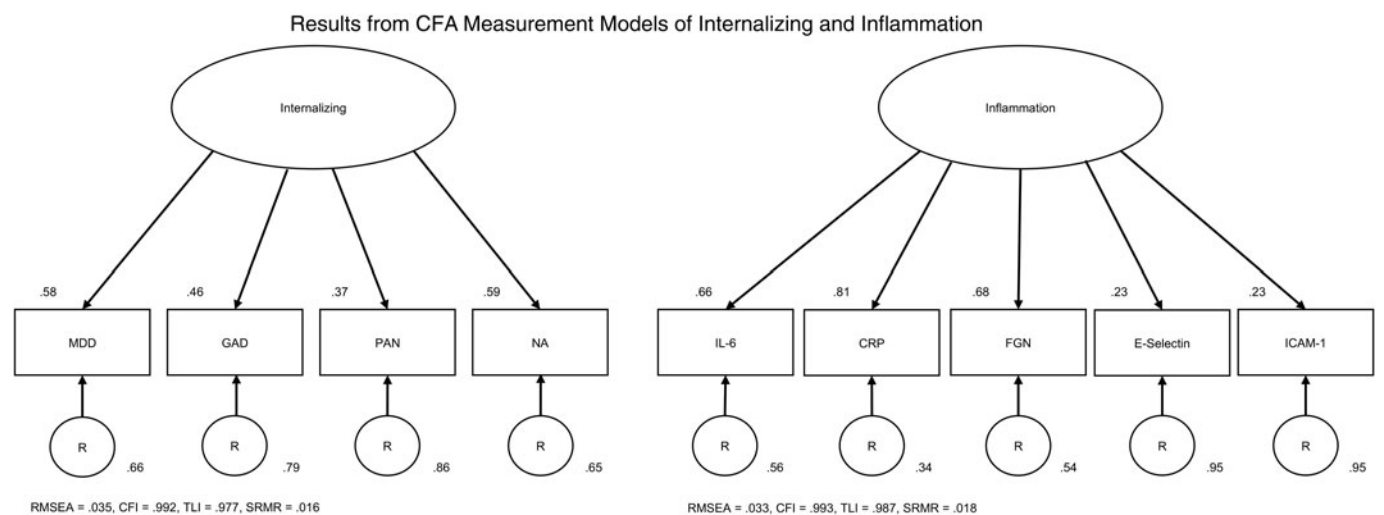

Figure 1. Results from CFA measurement models of internalizing and inflammation. Note: Arrows flowing from the latent factor to its indicators represent factor loadings. Arrows leading from each of the residuals to the indicators represent residual variance. Factor loadings and residual variances obtained using the completely standardized solution. Model fit indices are listed below each measurement model. MDD – major depressive disorder, GAD – generalized anxiety disorder, PAN – panic disorder, NA – neuroticism, IL-6 – interleukin 6, CRP – c-reactive protein, FGN – fibrinogen, ICAM-1 – intercellular adhesion molecule 1, RMSEA – root mean square error of approximation, CFI – comparative fit index, TLI – Tucker-Lewis index, SRMR – standardized root mean square residual.

Table 3. Interactions between ACEs and internalizing on inflammation

Predictor	b	β	S.E.	p
Step 1				
ACEs	**0.036**	**0.083**	**0.013**	**<0.01**
INT	**0.079**	**0.060**	**0.039**	**<0.05**
Step 2				
ACEs × INT	**0.062**	**0.141**	**0.024**	**<0.01**
Step 3				
ACEs × INT	**0.056**	**0.130**	**0.023**	**<0.05**
Sociodemographic covariates				
Step 4				
ACEs × INT	0.030	0.070	0.021	0.141
Sociodemographic + health covariates				

Note. Regression results using internalizing and ACEs as predictors. Bolded text indicates significant effect. ×: Examined for interaction. INT – latent internalizing. ACEs – adverse childhood experiences.

inflammation, but only when current internalizing was also elevated. In a separate model, neglect predicted inflammation as a main effect, but the interaction term with latent internalizing was not significant ($b = 0.063$, $p = 0.053$, 95% CI [−0.001 to 0.128], $\beta = 0.101$). Although the effect sizes are similar, abuse better explained the ACEs total score -by- internalizing moderation effect described above. Online Supplemental Tables S2–S4 summarize results comparing the broad internalizing factor score *v.* the disorder-specific residuals. The residual of depression did not interact with ACEs to predict inflammation ($b = −0.010$, $p = 0.319$, 95% CI [−0.048 to 0.016], $\beta = −0.008$), but the interaction between ACEs and broad internalizing remained significant ($b = 0.077$, $p = 0.005$, 95% CI [0.022–0.123], $\beta = 0.173$). Similarly, the anxiety residual did not significantly interact with

ACEs to predict inflammation ($b = 0.020$, $p = 0.281$, 95% CI [−0.010 to 0.041], $\beta = 0.015$), whereas broad internalizing and ACEs remained significant ($b = 0.062$, $p = 0.042$, 95% CI [0.002–0.104], $\beta = 0.140$). Lastly, the panic residual did not significantly interact with ACEs to predict inflammation ($b = 0.004$, $p = 0.754$, 95% CI [−0.019 to 0.026], $\beta = 0.001$), but broad internalizing and ACEs maintained significance ($b = 0.071$, $p = 0.012$, 95% CI [0.014–0.108], $\beta = 0.160$). In summary, the transdiagnostic internalizing distress dimension was a better predictor of vulnerabilities to ACEs than the disorder-specific residuals of anxiety, depression, or panic.

Discussion

Contrary to previous reports of a simple relationship between early adversity and midlife inflammation, our results revealed that this association depends on transdiagnostic internalizing distress. Within the MIDUS sample, heightened inflammation was best explained when ACEs were also combined with elevations on a broad factor score encompassing past 12-month internalizing symptomatology and trait neuroticism. We also observed that the disorder-specific residuals (MDD, GAD, panic) did not similarly moderate the adversity-inflammation effect.

These results point to the unique biological importance of internalizing comorbidities (DeYoung et al., 2023). Although chronic inflammation across the lifespan may be influenced by adversity, this effect may be at least somewhat conditional on the presence of processes shared across many forms of internalizing psychopathology. There are multiple possible causal sequences that could explain chronic inflammation in this sample. For example, the findings call to mind established models of resilience focused on the individual differences shaping adaptation following adversity (Luthar, Cicchetti, & Becker, 2000). Our trait-like rather than state-like index of internalizing and neuroticism may reflect stable vulnerabilities that amplified the
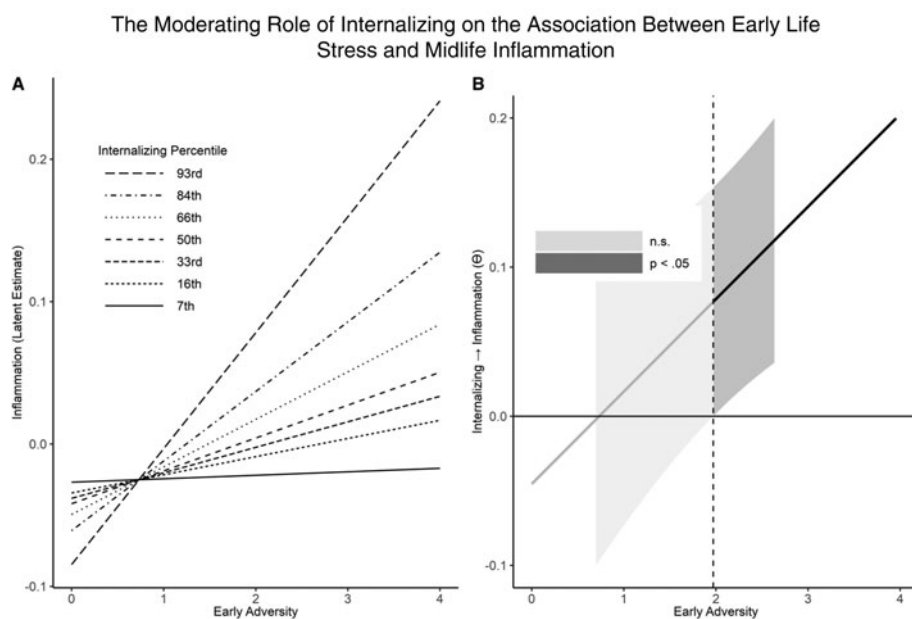

Figure 2. The moderating role of internalizing on the association between early life stress and midlife inflammation. Note: In Figure 2A, associations between early adversity and inflammation are depicted based on internalizing scores. Figure 2B presents a Johnson-Neyman plot illustrating the interaction and highlighting the threshold value of early adversity where a significant interaction emerges. n.s. – not significant.

long-term impact of adversity. A variety of transdiagnostic individual difference traits related to neuroticism are known to change the impact of stressors such as negative emotionality (Masten et al., 1999), rumination (Abela & Hankin, 2011), and maladaptive cognitive appraisal patterns (Hankin, Abramson, & Siler, 2001). Similar processes may have led to maladaptive stress responses among these MIDUS participants. Given the cross-sectional design, the extent to which features of internalizing distress were also present during childhood is unknown. It is possible adult internalizing distress is a continuation of the vulnerabilities present at the time of early stressors (Hilsman & Garber, 1995), which had long-term consequences on inflammation starting in childhood. It is also possible that current internalizing distress reflects ongoing impairments in stress regulation, which may be contributing to difficulties with managing responses to lingering psychological sequelae of past childhood adversity (e.g. intrusive reexperiencing; Ehlers and Steil, 1995). There is a need for additional prospective research to explore the longitudinal dynamics of these effects and determine whether pre- adversity internalizing distress is a true vulnerability for adversity-inflammation associations.

In contrast to a vulnerability hypothesis, a sensitization model highlights an alternative way ACEs together with internalizing may chronically exacerbate inflammation. Early adversity has a privileged role in shaping biological functioning, which can potentially sensitize reactivity to stressors later in life (Hostinar et al., 2015; Miller, Chen, & Parker, 2011). For instance, people who experienced childhood maltreatment can exhibit exacerbated acute inflammatory activity when exposed to present day stressors (Carpenter et al., 2010). Transdiagnostic internalizing psychopathology is a stressor because it disrupts role functioning and impairs quality of life. Consistent with this idea, Miller and Cole (2012) demonstrated that the onset of depressive symptoms among adult women was associated with more inflammation in those with childhood adversity. It is possible the immune response in people with ACEs has been sensitized to stress, which has led them to experience the impairment of internalizing psychopathology differently. Future studies of the inflammatory cascade may benefit from measurement approaches designed to tease apart the specific effects of current psychopathology v. the disability-related consequences of psychopathology.

For our second aim, we directly compared transdiagnostic and disorder-specific features of psychopathology. Inflammation was most closely associated with clinical symptomatology spanning across internalizing disorder measures. Therefore, the intercorrelations between internalizing symptoms and trait neuroticism were more than just a statistical phenomenon – these transdiagnostic associations best explained chronic inflammation following childhood adversity even when directly competing against symptoms specific to depression, anxiety, and panic. This finding provides a path toward synthesizing associations between various individual psychiatric diagnoses and inflammation (Duivis et al., 2013; Hoge et al., 2009; Michopoulos et al., 2017; Ogłodek et al., 2016; O'Donovan et al., 2010; Wagner et al., 2015). This is also thematically consistent with other studies of general health outcomes, which demonstrate stronger associations with broad internalizing than individual disorders (Eaton et al., 2013; Kim et al., 2021; van de Pavert, Sunderland, Luijten, Slade, & Teesson, 2017). By explicitly modeling comorbidities, our study demonstrates how transdiagnostic markers can help reveal stronger and more cohesive statistical associations with biological systems (DeYoung et al., 2023; Zald & Lahey, 2017).

There is value in considering why the moderation effect between ACEs and internalizing distress becomes non-significant after covarying for BMI. Elevated BMI is typically associated with higher adipose fatty tissue concentrations (de Heredia, Gómez-Martínez, & Marcos, 2012). Inflammatory markers such as IL-6 and CRP are synthesized in response to signaling molecules released through adipose tissue (Ouakinin, Barreira, & Gois, 2018). Moreover, research has established a bidirectional relationship between adipose tissue and clinical depression (Shelton & Miller, 2011). BMI may promote inflammation through similar underlying processes as internalizing psychopathology (e.g. activation of endocrine systems). Therefore, covarying for variables like BMI when predicting inflammation may remove meaningful variance (Slopen, Koenen, & Kubzansky, 2012). Notably, associations among internalizing conditions, inflammation, adverse childhood experiences, and BMI are frequently observed consistent with a shared pathophysiological process (Lamers, Milaneschi, de Jonge, Giltay, & Penninx, 2018). BMI may indirectly mediate the relationship between early adversity, adult internalizing, and adult inflammation (Palmos et al., 2019). Continuing examination of physiological contributors to chronic inflammation could improve our understanding of the underlying mechanistic pathways linking early adversity and internalizing distress.

This study has several limitations that point to important future directions of research. Although we used established methods for analyzing MIDUS inflammatory data (Elliot & Chapman, 2016; Friedman & Herd, 2010; Sheffler et al., 2019; Slopen et al., 2010), alternative approaches have been proposed. Representing inflammation as a latent construct involves measurement trade-offs. Aggregating multiple indicators together could mask genuine associations specific to particular inflammation indices (Moriarity & Alloy, 2021). It is also possible that replacing extreme inflammatory values removed some relevant information (Moriarity, 2022). Prior work has shown that baseline inflammation may lead to subsequent depressive symptoms (Valkanova, Ebmeier, & Allan, 2013), but the opposite has also been observed (Copeland, Shanahan, Worthman, Angold, & Costello, 2012; Glaus et al., 2014; Zainal & Newman, 2022). Due to the cross-sectional nature of the data, causality is difficult to determine, although the literature suggests some form of a bidirectional phenomenon. Recall of early adversity can be influenced by current distress (Martin-Wagar et al., 2024), which can result in substantially different associations between retrospective and prospective measures of ACEs (Colman et al., 2016; Hardt & Rutter, 2004). Studies of past adversity based solely on retrospective measures face challenges when trying to distinguish between current distress and ACEs. Race may also function as a proxy for adversity. Therefore, it is difficult to disentangle these relationships using cross-sectional designs. This was a motivating factor for using hierarchical models with and without covariates. Lastly, the CTQ, which contributed to our ACEs measure, has known limitations. These include a lack of cross-cultural considerations and variability in internal consistency across studies (Georgieva, Tomas, & Navarro-Pérez, 2021).

In conclusion, a latent factor reflecting past 12-month internalizing distress symptoms and trait neuroticism moderated the relationship between ACEs and midlife inflammation. Therefore, assessment of early adversity and internalizing distress in isolation appears to be insufficient – it was important to consider both together to capture the long-term inflammation effects more fully within the MIDUS sample. In addition, this transdiagnostic factor was a better predictor than disorder-specific facets of

depression, anxiety, and panic. Given the growing research base validating transdiagnostic approaches for studying health outcomes, clinicians should be encouraged to also incorporate transdiagnostic symptom measures in their practice (Ruggero et al., 2019). Such assessments may reveal opportunities for intervention, which could shape the long-term physical health trajectories of patients with ACEs.

References

Abela, J. R. Z., & Hankin, B. L. (2011). Rumination as a vulnerability factor to depression during the transition from early to middle adolescence: A multi-wave longitudinal study. *Journal of Abnormal Psychology*, 120(2), 259–271. https://doi.org/10.1037/a0022796

Appleton, A. A., Buka, S. L., Loucks, E. B., Gilman, S. E., & Kubzansky, L. D. (2013). Divergent associations of adaptive and maladaptive emotion regulation strategies with inflammation. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, 32(7), 748–756. https://doi.org/10.1037/a0030068

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Molecular Psychiatry*, 21(5), Article 5. https://doi.org/10.1038/mp.2015.67

Bentler, P. M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin*, 107, 238–246. https://doi.org/10.1037/0033-2909.107.2.238

Bernstein, D., & Fink, L. (1998) *Childhood trauma questionnaire: A retrospective self- report manual*. San Antonio: The Psychological Corporation.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., … Zule, W. (2003). Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abuse & Neglect*, 27(2), 169–190. https://doi.org/10.1016/s0145-2134(02)00541-0

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The bidirectional relationship of depression and inflammation: Double trouble. *Neuron*, 107(2), 234–256. https://doi.org/10.1016/j.neuron.2020.06.002

Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology*, 35(13), 2617–2623. https://doi.org/10.1038/npp.2010.159

Claridge, G., & Davis, C. (2001). What's the use of neuroticism? *Personality and Individual Differences*, 31(3), 383–400. https://doi.org/10.1016/S0191-8869(00)00144-6

Coelho, R., Viola, T. W., Walss-Bass, C., Brietzke, E., & Grassi-Oliveira, R. (2014). Childhood maltreatment and inflammatory markers: A systematic review. *Acta Psychiatrica Scandinavica*, 129(3), 180–192. https://doi.org/10.1111/acps.12217

Colman, I., Kingsbury, M., Garad, Y., Zeng, Y., Naicker, K., Patten, S., … Thompson, A. H. (2016). Consistency in adult reporting of adverse childhood experiences. *Psychological Medicine*, 46(3), 543–549. https://doi.org/10.1017/S0033291715002032

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A., & Costello, E. J. (2012). Cumulative depression episodes predicts later C-reactive protein levels: A prospective analysis. *Biological Psychiatry*, 71(1), 15–21. https://doi.org/10.1016/j.biopsych.2011.09.023

Costa, P. T., & McCrae, R. R. (1988). Personality in adulthood: A six-year longitudinal study of self-reports and spouse ratings on the NEO personality inventory. *Journal of Personality and Social Psychology*, 54(5), 853–863. https://doi.org/10.1037/0022-3514.54.5.853

Costello, H., Gould, R. L., Abrol, E., & Howard, R. (2019). Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. *BMJ Open*, 9(7), e027925. https://doi.org/10.1136/bmjopen-2018-027925

Danese, A., Moffitt, T. E., Pariante, C. M., Ambler, A., Poulton, R., & Caspi, A. (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of General Psychiatry*, 65(4), 409. https://doi.org/10.1001/archpsyc.65.4.409

Danesh, J., Kaptoge, S., Mann, A. G., Sarwar, N., Wood, A., Angleman, S. B., … Gudnason, V. (2008). Long-term interleukin-6 levels and subsequent risk of coronary heart disease: Two new prospective studies and a systematic review. *PLoS Medicine*, 5(4), e78. https://doi.org/10.1371/journal.pmed.0050078

de Heredia, F. P., Gómez-Martínez, S., & Marcos, A. (2012). Obesity, inflammation and the immune system. *Proceedings of the Nutrition Society*, 71(2), 332–338. https://doi.org/10.1017/S0029665112000092

DeYoung, C. G., Blain, S. D., Latzman, R. D., Grazioplene, R., Haltigan, J. D., Kotov, R., … Tobin, K. E. (2023). *The Hierarchical Taxonomy of Psychopathology (HiTOP) and the search for neurobiological substrates of mental illness: A review and roadmap for future research*. PsyArXiv. https://doi.org/10.31234/osf.io/yatw7

Duivis, H. E., Vogelzangs, N., Kupper, N., de Jonge, P., & Penninx, B. W. J. H. (2013). Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology*, 38(9), 1573–1585. https://doi.org/10.1016/j.psyneuen.2013.01.002

Eaton, N. R., Krueger, R. F., & Oltmanns, T. F. (2011). Aging and the structure and long-term stability of the internalizing spectrum of personality and psychopathology. *Psychology and Aging*, 26(4), 987–993. https://doi.org/10.1037/a0024406

Eaton, N. R., Krueger, R. F., Keyes, K. M., Wall, M., Hasin, D. S., Markon, K. E., … Grant, B. F. (2013). The structure and predictive validity of the internalizing disorders. *Journal of Abnormal Psychology*, 122(1), 86–92. https://doi.org/10.1037/a0029598

Ehlers, A., & Steil, R. (1995). Maintenance of intrusive memories in post-traumatic stress disorder: A cognitive approach. *Behavioural and Cognitive Psychotherapy*, 23(3), 217–249. https://doi.org/10.1017/S135246580001585X

Elliot, A. J., & Chapman, B. P. (2016). Socioeconomic status, psychological resources, and inflammatory markers: Results from the MIDUS study. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, 35(11), 1205–1213. https://doi.org/10.1037/hea0000392

Elliot, A. J., Turiano, N. A., & Chapman, B. P. (2017). Socioeconomic Status interacts with conscientiousness and neuroticism to predict circulating concentrations of inflammatory markers. *Annals of Behavioral Medicine*, 51(2), 240–250. https://doi.org/10.1007/s12160-016-9847-z

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., … Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) study. *American Journal of Preventive Medicine*, 14, 245–258. https://doi.org/10.1016/S0749-3797(98)00017-8

Friedman, E. M., & Herd, P. (2010). Income, education, and inflammation: Differential associations in a national probability sample (The MIDUS Study). *Psychosomatic Medicine*, 72(3), 290–300. https://doi.org/10.1097/PSY.0b013e3181cfe4c2

Georgieva, S., Tomas, J. M., & Navarro-Pérez, J. J. (2021). Systematic review and critical appraisal of Childhood Trauma Questionnaire – Short Form (CTQ-SF). *Child Abuse & Neglect*, *120*, 105223. https://doi.org/10.1016/j.chiabu.2021.105223

Gill, H., El-Halabi, S., Majeed, A., Gill, B., Lui, L. M. W., Mansur, R. B., … Rosenblat, J. D. (2020). The association between adverse childhood experiences and inflammation in patients with major depressive disorder: A systematic review. *Journal of Affective Disorders*, *272*, 1–7. https://doi.org/10.1016/j.jad.2020.03.145

Glaus, J., Vandeleur, C. L., von Känel, R., Lasserre, A. M., Strippoli, M.-P. F., Gholam-Rezaee, M., … Preisig, M. (2014). Associations between mood, anxiety or substance use disorders and inflammatory markers after adjustment for multiple covariates in a population-based study. *Journal of Psychiatric Research*, *58*, 36–45. https://doi.org/10.1016/j.jpsychires.2014.07.012

Gonçalves, R. B., Coletta, R. D., Silvério, K. G., Benevides, L., Casati, M. Z., da Silva, J. S., & Nociti, F. H. (2011). Impact of smoking on inflammation: Overview of molecular mechanisms. *Inflammation Research*, *60*(5), 409–424. https://doi.org/10.1007/s00011-011-0308-7

Gouin, J.-P., Caldwell, W., Woods, R., & Malarkey, W. B. (2017). Resilience resources moderate the association of adverse childhood experiences with adulthood inflammation. *Annals of Behavioral Medicine*, *51*(5), 782–786. https://doi.org/10.1007/s12160-017-9891-3

Griffith, J. W., Zinbarg, R. E., Craske, M. G., Mineka, S., Rose, R. D., Waters, A. M., & Sutton, J. M. (2010). Neuroticism as a common dimension in the internalizing disorders. *Psychological Medicine*, *40*(7), 1125–1136. https://doi.org/10.1017/S0033291709991449

Hankin, B. L., Abramson, L. Y., & Siler, M. (2001). A prospective test of the hopelessness theory of depression in adolescence. *Cognitive Therapy and Research*, *25*(5), 607–632. https://doi.org/10.1023/A:1005561616506

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: Review of the evidence. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *45*(2), 260–273. https://doi.org/10.1111/j.1469-7610.2004.00218.x

Hilsman, R., & Garber, J. (1995). A test of the cognitive diathesis-stress model of depression in children: Academic stressors, attributional style, perceived competence, and control. *Journal of Personality and Social Psychology*, *69*(2), 370–380. https://doi.org/10.1037/0022-3514.69.2.370

Hoge, E. A., Brandstetter, K., Moshier, S., Pollack, M. H., Wong, K. K., & Simon, N. M. (2009). Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depression and Anxiety*, *26*(5), 447–455. https://doi.org/10.1002/da.20564

Hostinar, C. E., & Miller, G. E. (2019). Protective factors for youth confronting economic hardship: Current challenges and future avenues in resilience research. *American Psychologist*, *74*, 641–652. https://doi.org/10.1037/amp0000520

Hostinar, C. E., Lachman, M. E., Mroczek, D. K., Seeman, T. E., & Miller, G. E. (2015). Additive contributions of childhood adversity and recent stressors to inflammation at midlife: Findings from the MIDUS study. *Developmental Psychology*, *51*(11), 1630–1644. https://doi.org/10.1037/dev0000049

Imhof, A., Froehlich, M., Brenner, H., Boeing, H., Pepys, M. B., & Koenig, W. (2001). Effect of alcohol consumption on systemic markers of inflammation. *The Lancet*, *357*(9258), 763–767. https://doi.org/10.1016/S0140-6736(00)04170-2

Jones, E. J., Marsland, A. L., & Gianaros, P. J. (2023). Do trait-level emotion regulation strategies moderate associations between retrospective reports of childhood trauma and prospective changes in systemic inflammation? *Stress and Health*, *39*(3), 525–538. https://doi.org/10.1002/smi.3205

Kerr, D. M., McDonald, J., & Minnis, H. (2021). The association of child maltreatment and systemic inflammation in adulthood: A systematic review. *PLOS ONE*, *16*(4), e0243685. https://doi.org/10.1371/journal.pone.0243685

Kessler, R. C., Andrews, G., Mroczek, D., Ustun, B., & Wittchen, H.-U. (1998). The world health organization Composite International Diagnostic Interview short-form (CIDI-SF). *International Journal of Methods in Psychiatric Research*, *7*(4), 171–185. https://doi.org/10.1002/mpr.47

Kim, H., Turiano, N. A., Forbes, M. K., Kotov, R., Krueger, R. F., Eaton, N. R., & HiTOP Utility Workgroup. (2021). Internalizing psychopathology and all-cause mortality: A comparison of transdiagnostic vs. Diagnosis-based risk prediction. *World Psychiatry*, *20*(2), 276–282. https://doi.org/10.1002/wps.20859

Krueger, R. F. (1999). The structure of common mental disorders. *Archives of General Psychiatry*, *56*(10), 921–926. https://doi.org/10.1001/archpsyc.56.10.921

Lacey, R. E., Pinto Pereira, S. M., Li, L., & Danese, A. (2020). Adverse childhood experiences and adult inflammation: Single adversity, cumulative risk and latent class approaches. *Brain, Behavior, and Immunity*, *87*, 820–830. https://doi.org/10.1016/j.bbi.2020.03.017

Lamers, F., Milaneschi, Y., de Jonge, P., Giltay, E. J., & Penninx, B. W. J. H. (2018). Metabolic and inflammatory markers: Associations with individual depressive symptoms. *Psychological Medicine*, *48*(7), 1102–1110. https://doi.org/10.1017/S0033291717002483

Liu, Y.-Z., Wang, Y.-X., & Jiang, C.-L. (2017). Inflammation: The common pathway of stress-related diseases. *Frontiers in Human Neuroscience*, *11*, 316. https://doi.org/10.3389/fnhum.2017.00316

Luchetti, M., Barkley, J. M., Stephan, Y., Terracciano, A., & Sutin, A. R. (2014). Five-factor model personality traits and inflammatory markers: New data and a meta-analysis. *Psychoneuroendocrinology*, *50*, 181–193. https://doi.org/10.1016/j.psyneuen.2014.08.014

Luthar, S. S., Cicchetti, D., & Becker, B. (2000). The construct of resilience: A critical evaluation and guidelines for future work. *Child Development*, *71*(3), 543–562.

Martin-Wagar, C. A., Marquardt, C. A., Liu, Y., Arbisi, P. A., Erbes, C. R., & Polusny, M. A. (2024). Inconsistent reporting of adverse life events is predicted by current internalizing distress among military service members. *Military Medicine*, *189*(1-2), 337–344. https://doi.org/10.1093/milmed/usac167

Masten, A. S., Hubbard, J. J., Gest, S. D., Tellegen, A., Garmezy, N., & Ramirez, M. (1999). Competence in the context of adversity: Pathways to resilience and maladaptation from childhood to late adolescence. *Development and Psychopathology*, *11*(1), 143–169. https://doi.org/10.1017/s0954579499001996

Mersky, J. P., Topitzes, J., & Reynolds, A. J. (2013). Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: A cohort study of an urban, minority sample in the U.S. *Child Abuse & Neglect*, *37*(11), 917–925. https://doi.org/10.1016/j.chiabu.2013.07.011

Metsios, G. S., Moe, R. H., & Kitas, G. D. (2020). Exercise and inflammation. *Best Practice & Research Clinical Rheumatology*, *34*(2), 101504. https://doi.org/10.1016/j.berh.2020.101504

Michopoulos, V., Powers, A., Gillespie, C. F., Ressler, K. J., & Jovanovic, T. (2017). Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and Beyond. *Neuropsychopharmacology*, *42*(1), 254–270. https://doi.org/10.1038/npp.2016.146

Miller, G. E., & Cole, S. W. (2012). Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biological Psychiatry*, *72*(1), 34–40. https://doi.org/10.1016/j.biopsych.2012.02.034

Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*, *137*(6), 959–997. https://doi.org/10.1037/a0024768

Moriarity, D. P. (2022). A primer on common analytic concerns in psychoneuroimmunology: Alternatives and paths forward. *Brain, Behavior, and Immunity*, *102*, 338–340. https://doi.org/10.1016/j.bbi.2022.03.007

Moriarity, D. P., & Alloy, L. B. (2020). Beyond diagnoses and total symptom scores: Diversifying the level of analysis in psychoneuroimmunology research. *Brain, Behavior, and Immunity*, *89*, 1–2. https://doi.org/10.1016/j.bbi.2020.07.002

Moriarity, D. P., & Alloy, L. B. (2021). Back to basics: The importance of measurement properties in biological psychiatry. *Neuroscience & Biobehavioral Reviews*, *123*, 72–82. https://doi.org/10.1016/j.neubiorev.2021.01.008

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry*, *169*(2), 141–151. https://doi.org/10.1176/appi.ajp.2011.11020335

Nowakowski, A. C. H., & Sumerau, J. E. (2015). Swell foundations: Fundamental social causes and chronic inflammation. *Sociological Spectrum*, *35*(2), 161–178. https://doi.org/10.1080/02732173.2014.1000554

O'Donovan, A., Hughes, B. M., Slavich, G. M., Lynch, L., Cronin, M.-T., O'Farrelly, C., & Malone, K. M. (2010). Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion–biology relationships. *Brain, Behavior, and Immunity*, 24(7), 1074–1077. https://doi.org/10.1016/j.bbi.2010.03.003

Ogłodek, E. A., Szota, A. M., Just, M. J., Szromek, A. R., & Araszkiewicz, A. (2016). A study of chemokines, chemokine receptors and interleukin-6 in patients with panic disorder, personality disorders and their co-morbidity. *Pharmacological Reports: PR*, 68(4), 756–763. https://doi.org/10.1016/j.pharep.2016.03.017

Oh, D. L., Jerman, P., Silvério Marques, S., Koita, K., Purewal Boparai, S. K., Burke Harris, N., & Bucci, M. (2018). Systematic review of pediatric health outcomes associated with childhood adversity. *BMC Pediatrics*, 18(1), 83. https://doi.org/10.1186/s12887-018-1037-7

Ormel, J., & Wohlfarth, T. (1991). How neuroticism, long-term difficulties, and life situation change influence psychological distress: A longitudinal model. *Journal of Personality and Social Psychology*, 60(5), 744–755. https://doi.org/10.1037/0022-3514.60.5.744

Ouakinin, S. R. S., Barreira, D. P., & Gois, C. J. (2018). Depression and obesity: Integrating the role of stress, neuroendocrine dysfunction and inflammatory pathways. *Frontiers in Endocrinology*, 9, 431. https://doi.org/10.3389/fendo.2018.00431

Pahwa, R., Goyal, A., & Jialal, I. (2023). Chronic inflammation. In *Statpearls*. Treasure Island, FL: StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK493173/

Palmos, A. B., Watson, S., Hughes, T., Finkelmeyer, A., McAllister-Williams, R. H., Ferrier, N., … Powell, T. R. (2019). Associations between childhood maltreatment and inflammatory markers. *BJPsych Open*, 5(1), e3. https://doi.org/10.1192/bjo.2018.80

Rodríguez-Hernández, H., Simental-Mendía, L. E., Rodríguez-Ramírez, G., & Reyes-Romero, M. A. (2013). Obesity and inflammation: Epidemiology, risk factors, and markers of inflammation. *International Journal of Endocrinology*, 2013, e678159. https://doi.org/10.1155/2013/678159

Rosseel, Y. (2012). . Lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, 48, 1–36. https://doi.org/10.18637/jss.v048.i02

Ruggero, C. J., Kotov, R., Hopwood, C. J., First, M., Clark, L. A., Skodol, A. E., … … Zimmermann, J. (2019). Integrating the Hierarchical Taxonomy of Psychopathology (HiTOP) into clinical practice. *Journal of Consulting and Clinical Psychology*, 87(12), 1069–1084. https://doi.org/10.1037/ccp0000452

Ryff, C. D., Almeida, D. M., Ayanian, J. Z., Carr, D. S., Cleary, P. D., Coe, C., … Williams, D. R. (2007). *Midlife in the United States* (*MIDUS* 2), 2004–2006: Version 8 (Version v8) [Dataset]. ICPSR – Interuniversity Consortium for Political and Social Research. https://doi.org/10.3886/ICPSR04652.V8

Sheffler, J. L., Piazza, J. R., Quinn, J. M., Sachs-Ericsson, N. J., & Stanley, I. H. (2019). Adverse childhood experiences and coping strategies: Identifying pathways to resiliency in adulthood. Anxiety, Stress & Coping, 32(5), 594–609. https://doi.org/10.1080/10615806.2019.1638699

Shelton, R. C., & Miller, A. H. (2011). Inflammation in depression: Is adiposity a cause? *Dialogues in Clinical Neuroscience*, 13(1), 41–53. https://doi.org/10.31887/DCNS.2011.13.1/rshelton

Slopen, N., Lewis, T. T., Gruenewald, T. L., Mujahid, M. S., Ryff, C. D., Albert, M. A., & Williams, D. R. (2010). Early life adversity and inflammation in African Americans and whites in the midlife in the United states survey. *Psychosomatic Medicine*, 72(7), 694. https://doi.org/10.1097/PSY.0b013e3181e9c16f

Slopen, N., Koenen, K. C., & Kubzansky, L. D. (2012). Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: A systematic review. *Brain, Behavior, and Immunity*, 26(2), 239–250. https://doi.org/10.1016/j.bbi.2011.11.003

Steiger, J. H. (1990). Structural model evaluation and modification: An interval estimation approach. *Multivariate Behavioral Research*, 25(2), 173–180. https://doi.org/10.1207/s15327906mbr2502_4

Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*, 21(7), 901–912. https://doi.org/10.1016/j.bbi.2007.03.011

Straka, K., Tran, M.-L., Millwood, S., Swanson, J., & Kuhlman, K. R. (2021). Aging as a context for the role of inflammation in depressive symptoms. *Frontiers in Psychiatry*, 11,605347. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.605347

Theuma, P., & Fonseca, V. A. (2003). Inflammation and emerging risk factors in diabetes mellitus and atherosclerosis. *Current Diabetes Reports*, 3(3), 248–254. https://doi.org/10.1007/s11892-003-0072-3

Thylur, D. S., & Goldsmith, D. R. (2022). Brick by brick: Building a transdiagnostic understanding of inflammation in psychiatry. *Harvard Review of Psychiatry*, 30(1), 40–53. https://doi.org/10.1097/HRP.0000000000000326

Tierney, N. J., & Cook, D. H. (2020). *Expanding tidy data principles to facilitate missing data exploration, visualization and assessment of imputations* (arXiv:1809.02264). arXiv. http://arxiv.org/abs/1809.02264

Tursich, M., Neufeld, R. W. J., Frewen, P. A., Harricharan, S., Kibler, J. L., Rhind, S. G., & Lanius, R. A. (2014). Association of trauma exposure with proinflammatory activity: A transdiagnostic meta-analysis. *Translational Psychiatry*, 4(7), Article 7. https://doi.org/10.1038/tp.2014.56

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders*, 150(3), 736–744. https://doi.org/10.1016/j.jad.2013.06.004

van de Pavert, I., Sunderland, M., Luijten, M., Slade, T., & Teesson, M. (2017). The general relationship between internalizing psychopathology and chronic physical health conditions: A population-based study. *Social Psychiatry and Psychiatric Epidemiology*, 52(10), 1257–1265. https://doi.org/10.1007/s00127-017-1422-9

Wagner, E.-Y. N., Wagner, J. T., Glaus, J., Vandeleur, C. L., Castelao, E., Strippoli, M.-P. F., … von Känel, R. (2015). Evidence for chronic low-grade systemic inflammation in individuals with agoraphobia from a population-based prospective study. *PLOS ONE*, 10(4), e0123757. https://doi.org/10.1371/journal.pone.0123757

Walsh, D., McCartney, G., Smith, M., & Armour, G. (2019). Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): A systematic review. *Journal of Epidemiology and Community Health*, 73(12), 1087–1093. https://doi.org/10.1136/jech-2019-212738

Wang, X., Lin, J., Liu, Q., Lv, X., Wang, G., Wei, J., … Si, T. (2022). Major depressive disorder comorbid with general anxiety disorder: Associations among neuroticism, adult stress, and the inflammatory index. *Journal of Psychiatric Research*, 148, 307–314. https://doi.org/10.1016/j.jpsychires.2022.02.013

Winter, T., Riordan, B. C., Conner, T. S., & Jose, P. (2021). Methodological and conceptual complexities of assessing relationships between single-occasion CRP inflammation and daily affect. *Brain, Behavior. & Immunity – Health*, 14, 100240. https://doi.org/10.1016/j.bbih.2021.100240

Zainal, N. H., & Newman, M. G. (2022). Depression and worry symptoms predict future executive functioning impairment via inflammation. *Psychological Medicine*, 52(15), 3625–3635. https://doi.org/10.1017/S0033291721000398

Zald, D. H., & Lahey, B. B. (2017). Implications of the hierarchical structure of psychopathology for psychiatric neuroimaging. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2(4), 310–317. https://doi.org/10.1016/j.bpsc.2017.02.003