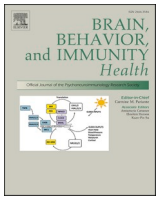
Brain, Behavior, & Immunity - Health 35 (2024) 100719

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Longitudinal associations between dimensions of maltreatment and internalizing symptoms in late adolescence: The role of inflammation during the COVID-19 pandemic

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ARTICLE INFO

Keywords:
Internalizing symptoms
Maltreatment
Adolescence
Inflammation

ABSTRACT

Childhood adversity and depression have been linked with heightened inflammation. However, few longitudinal studies examine how dimensions of maltreatment (i.e., abuse and neglect) differentially impact pathways to heightened inflammation and internalizing symptoms. The present study examined effects of abuse and neglect on (1) internalizing symptoms through inflammation, and (2) on inflammation through internalizing symptoms across 3 years of adolescence in the context of the COVID-19 pandemic. In a sample of 78 adolescents, significant indirect effects revealed that childhood abuse, not neglect, significantly predicted future internalizing symptoms, which predicted future heighted C-reactive protein (CRP). Using prospective longitudinal data, these findings emphasize the importance of examining distinct forms of maltreatment in understanding the developmental pathways connecting early adversity, internalizing symptoms, and inflammation.

1. Introduction

Data indicate that 40–50% of children in the U.S. will experience some form of adversity (Green et al., 2010), and children who experience early adversity are likely to experience problems with health-risk behaviors and both internalizing and externalizing psychopathology (Heleniak et al., 2016; Duffy et al., 2018; Miller and Cole, 2012). Although these associations are well established, neurobiological mechanisms linking maltreatment and psychopathology during adolescence are less known.

Social psychoneuroimmunology research highlights the role of social experiences in immune system changes (Muscatell, 2021), which suggests more extreme forms of social stress, such as maltreatment, may have a critical role in later immune system changes associated with health and well-being. Further, the Neuroimmune Network Hypothesis proposes that the biological embedding of early life adversity occurs through pro-inflammatory and hyper-responsive neural circuitry, resulting in a neuroimmune pathway to health consequences (Nusslock and Miller, 2016). Previous research emphasizes the role of cumulative childhood adversity such that early life stress promotes increases in circulating inflammatory factors in the body (Danese et al., 2008; Kautz et al., 2023). However, animal models suggest that subtypes of adversity may be associated with distinct underlying processes associated with elevated inflammation (Kuhlman et al., 2017). Specifically, theoretical models propose threat experiences may have stronger effects on biological markers, compared to other types of adversity (Colich et al., 2020). This model was supported by a recent empirical study reporting a stronger association between experiences of threat with heightened inflammation and depression trajectories, compared with other adverse experiences (Iob et al., 2022). The dimensional approach to childhood adversity proposes that dimensions of threat (i.e., harm or harm of threat such as abuse) or deprivation (i.e., absence of expected inputs from the environments such as neglect) may have different developmental mechanisms linking psychopathology (McLaughlin and Sheridan, 2016). However, research examining associations between these subtypes of maltreatment and psychopathology from the social psychoneuroimmunology perspective (Muscatell, 2021) is scarce. Understanding how specific dimensions of maltreatment may heighten risk for immune dysfunction and psychopathology is important for identifying those at risk to promote early intervention and prevent negative health

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https://doi.org/10.1016/j.bbih.2023.100719
Received 20 June 2023; Received in revised form 15 November 2023; Accepted 18 December 2023
Available online 21 December 2023

outcomes.

Early life adversity such as childhood maltreatment increases risk for development of depression and is one of the leading risk factors for depression (Pagliaccio and Barch, 2016). Depression has a relativity early onset with a peak period for onset during adolescence and a lifetime prevalence that rises to 25% by the end of adolescence (Kessler et al., 2001). Depression in adults has been consistently linked to inflammation (Leighton et al., 2018) and, in adolescents, a meta-analysis suggests that inflammatory biomarkers, such as C-reactive protein (CRP), were associated with both current and future depressive symptoms in clinical and non-clinical samples (Colasanto et al., 2020). Results of this meta-analysis suggest potential bidirectional associations between depression and inflammatory biomarkers in adolescents; however, previous cross-sectional research has found non-significant associations (D'Acunto et al., 2019). More longitudinal research clarifying the direction of these effects is needed. In a longitudinal study of high-risk (family history of depression) female adolescents, those with childhood adversity showed increases in inflammatory biomarkers (indicated by CRP) with the emergence of depression and their CRP levels remained higher even after depressive symptoms had decreased (Miller and Cole, 2012). This finding suggests co-development of depression and inflammatory biomarkers, yet the direction of the effects cannot be specified.

The current study examines longitudinal pathways from maltreatment on both inflammation and internalizing symptoms during late adolescence in the context of the COVID-19 pandemic. The COVID-19 pandemic was a period when social, personal, and financial stress were heightened, and those with experiences of childhood maltreatment may be particularly vulnerable to these effects. Using a community sample of adolescents, this current study aims to investigate 1) whether inflammation mediates the effects of prior experiences of abuse and neglect on internalizing symptoms one year later; and 2) whether internalizing symptoms mediates the effects of prior experiences of abuse and neglect on inflammation. Given prior research indicating sex differences in inflammation and depression levels (Breslau et al., 2017; Mac Giollabhui et al., 2021), we explored sex as a covariate in our models. This study clarifies longitudinal effects between inflammation and internalizing symptoms in adolescence and distinctive effects of threat vs. deprivation of adversity in the adversity-inflammation pathways.

2. Methods and materials

2.1. Participants

The current study included data collected as part of a larger longitudinal project that started before the COVID-19 pandemic. A community sample of adolescents (N = 78, 47% Female) participated in annual assessments across three years and were 18–19 years old at Time 1 (M = 18.83, SD = 0.60 for Time 1; M = 20.26, SD = 0.64 for Time 2; M = 21.22, SD = 0.64 for Time 3). About 77% of participants identified as White, 18% Black, 4% more than one race, and 1% other. Inclusion and exclusion criteria for the larger study can be viewed in previous publications (Kim-Spoon et al., 2021). Rate of participation was not significantly predicted by demographic backgrounds including sex, race (White vs. non-White), and family income (ps = .270 - 0.959). All procedures were approved by the institutional review board of the university and written informed consent was received from all participants.

2.2. Measures

2.2.1. Covariates

Body Mass Index (BMI) was collected via self-reported height and weight. BMI is consistently and robustly correlated with elevated levels of CRP (Horn et al., 2018) for a review on issues regarding reproducibility issues with CRP and depression). Additionally, we ran exploratory analyses examining sex as a covariate (coded 0 = male and 1 = female). See Appendix A in the supplemental data for additional information on testing covariates.

2.2.2. Maltreatment

Maltreatment was measured using the Maltreatment and Abuse Chronology of Exposure (MACE; Teicher and Parigger, 2015), which evaluates severity of exposure to types of maltreatment during each year of childhood (ages 1–18). Adolescents completed this questionnaire at Time 1 and Time 2 and were asked to retrospectively indicate ages at which they experienced events from 52 items each time. Teicher and Parigger (2015) reported acceptable test-retest reliability (r = 0.63 - 0.90). The test-retest reliability across time points (over one year) was acceptable for the current sample (r = 0.56-0.92). A maximum score was calculated between Time 1 and Time 2. Neglect included subscales of physical neglect (5 items) and emotional neglect (5 items). Abuse included subscales of physical abuse (6 items), sexual abuse (7 items), verbal abuse (4 items), and emotional abuse (6 items). See Appendix A in the supplemental data for more information.

2.2.3. Inflammation

Salivary cytokine levels were assessed at the Time 2 study visit during the day with two 2 mL vials and stored in a freezer at −20 °C until being assayed. Cytokine C-Reactive Protein (CRP) was selected a priori, and levels were determined using an the Salimetrics assay kit. Detection limits were 0.042 pg/mL for CRP. Intra-assay coefficient of variability was 3.2% and Inter-assay coefficient of variability was 2.6%. The average (SD) time of sampling was 3:12 p.m. (2.29 h). We did not find a significant correlation between time of day and salivary CRP levels (r = 0.14, p = .205). CRP was non-normally distributed, thus natural-log transformation was conducted and used in subsequent analyses.

2.2.4. Internalizing symptoms

Internalizing symptoms were assessed at the Time 1 and Time 3 study visit using the Adult Self-Report (ASR), internalizing subscale (Achenbach and Rescorla, 2001). Internalizing symptoms include withdrawn-depressed, anxious-depressed, and somatic complaints scales. Reliability was acceptable (α = 0.91 for Time 1 and α = 0.94 for Time 3), and was consistent with past studies (e.g., α = 0.93; Achenbach and Rescorla, 2001). See Appendix A in the supplemental data for more information.

2.3. Data analytic plan

The hypothesized models with direct and indirect effects were tested via Structural Equation Modeling (SEM) in M*plus* (Muthén and Muthén, 1998–2021). We used full information maximum likelihood (FIML; Arbuckle, 1996; Little and Rubin, 2003) estimation procedure to handle missing data, which allows all available data to be included regardless of the pattern of missingness (Schafer and Graham, 2002). BMI was included in all analyses as a covariate. Table 1 presents descriptive statistics and correlations among study variables.

3. Results

3.1. Inflammation as a mediator between maltreatment and internalizing symptoms

The baseline model fit was fully saturated (χ^2 = 0, df = 0, p = .000, RMSEA = 0.00, and CFI = 1.00). To evaluate the model fit, we removed the non-significant path from neglect to internalizing symptoms. The subsequent model fit the data well (χ^2 = 0, df = 1, p = .989, RMSEA = 0.00, and CFI = 1.00). As shown in Fig. 1A, there were significant direct effects from abuse to internalizing symptoms (b = 1.62, SE = 0.68, p = .017) and from CRP to internalizing symptoms (b = 6.47, SE = 2.31, p = .005), suggesting that experiences of abuse and higher CRP levels

Table 1
Descriptive statistics and bivariate correlations of the study variables.

	1	2	3	4	5	6	7
1. Sex	–						
2. BMI T1	.336**	–					
3. Abuse	.340**	.138	–				
4. Neglect	.230*	−.013	.526**	–			
5. CRP T2	.341**	.459**	.119	.067	–		
6. Depressive symptoms T1	.154	.193	.456**	.254*	.293*	–	
7. Depressive symptoms T3	.188	.075	.324**	.180	.301*	.716**	–
M	47% (F)	28.24	2.76	1.36	2.75	15.74	17.38
SD	–	7.83	2.41	1.65	0.64	10.68	13.22
Min	–	17.43	0.00	0.00	1.51	0.00	0.00
Max	–	52.51	8.75	6.00	3.63	43.00	59.00

Note. T1 = Time 1, T2 = Time 2, T3 = Time 3. F = Female.
*$p < .05$, **$p < .01$.

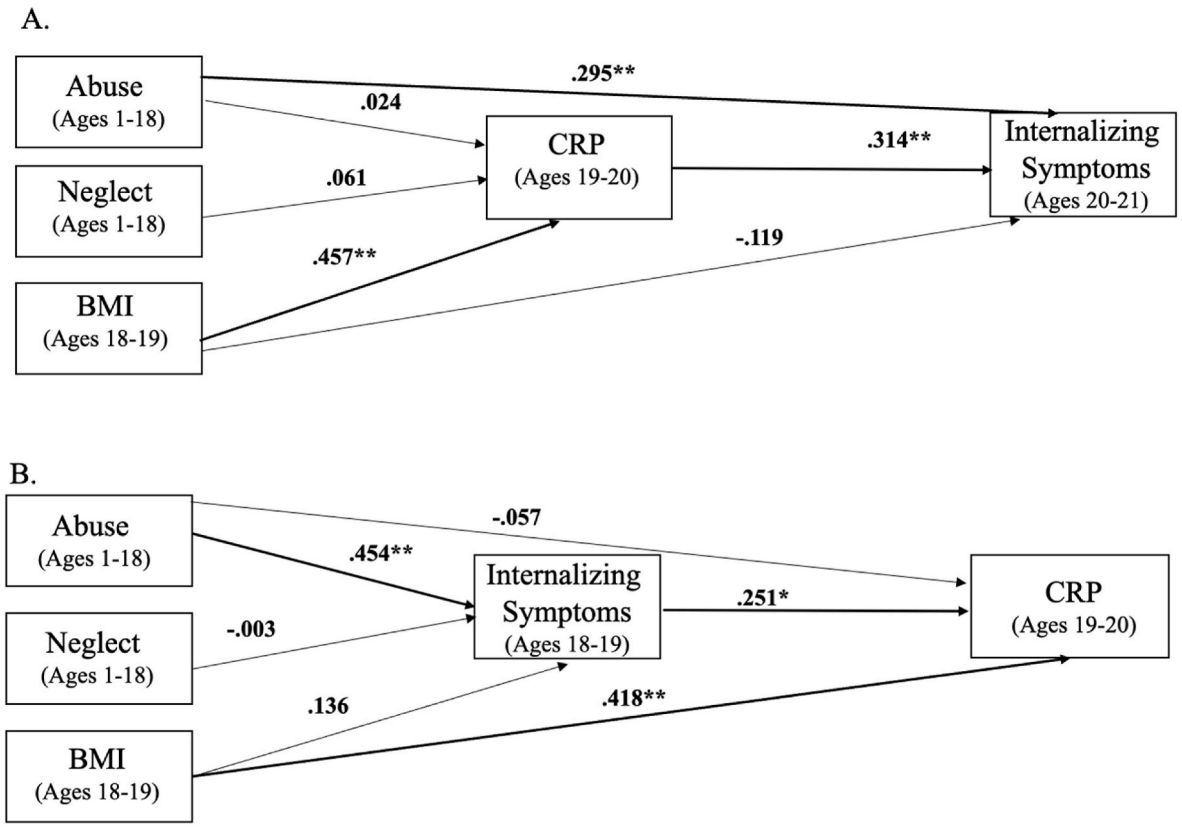

Fig. 1. Models Examining Developmental Pathways from Maltreatment to Internalizing Symptoms and Inflammation
Note. Standardized estimates (Betas) are presented. *$p < .05$, **$p < .01$.

predicted higher internalizing symptoms. There were no significant associations from childhood abuse or neglect to CRP. Indirect effects from childhood abuse to internalizing symptoms through CRP were not significant (95% CI: -0.484 to 0.492).

3.2. Internalizing symptoms as a mediator between maltreatment and inflammation

The baseline model fit was fully saturated ($\chi^2 = 0$, *df = 0*, $p = .000$, RMSEA = 0.00, and CFI = 1.00). To evaluate the model fit, we removed the non-significant path from neglect to CRP. The subsequent model fit the data well ($\chi^2 = 0.291$, *df = 1*, $p = .590$, RMSEA = 0.00, and CFI = 1.00). As shown in Fig. 1B, there was a significant direct effect from abuse to internalizing symptoms ($b = 2.03$, $SE = 0.60$, $p = .001$) and from internalizing symptoms to CRP ($b = 0.02$, $SE = 0.01$, $p = .027$). Indirect effects from abuse to higher CRP levels via higher internalizing symptoms were significant (95% CI: 0.002 to 0.070). The results suggest that experiences of abuse were related to higher internalizing symptoms which in turn were related to higher CRP levels. However, there was no significant association from childhood neglect to internalizing symptoms. When adding sex as a covariate to both models, significant paths remained the same and sex did not significantly predict internalizing symptoms or CRP in either model. See Appendix B in the supplemental data for more information.

4. Discussion

Adolescence is a developmental period characterized by pubertal onset, increased peer influence, the development of alterations to inflammatory pathways, and the peak period for the onset of internalizing disorders, such as depression (Kuhlman et al., 2017; Thapar et al., 2012). Although depression and inflammation have been consistently linked in

adults, literature on the direction of these associations are less clear in community samples of adolescents. Additionally, early adversity is one of the leading risk factors of the development of depression (Pagliaccio and Barch, 2016), and is associated with risk for heightened inflammation and dysregulated psychoneuroimmune functioning (Kuhlman et al., 2017). Using the social psychoneuroimmunology perspective, the current study utilized three time points of data to examine longitudinal pathways from childhood maltreatment between ages 1 and 18 to internalizing symptoms and inflammation during late adolescence. Additionally, inflammation was measured during the onset of COVID-19, which provides a stress context to understand immune functioning susceptibility after early adversity.

In our data, we found significant indirect effects of abuse on CRP during the pandemic via higher internalizing symptoms one year prior to the pandemic. This finding supports evidence in clinical samples of adolescents where participants had elevated CRP levels six months after a depressive episode (Miller and Cole, 2012). These findings are also in line with a more recent finding based on a community sample of adolescents, where higher depressive symptoms were associated with future, not concurrent, elevated interleukin-6 (IL-6) levels (Giollabhui et al., 2020). Importantly, our findings elucidate that internalizing symptoms mediated childhood abuse and future heightened CRP. Thus, early abuse, not neglect, may increase vulnerability to developing internalizing symptoms during adolescence that are related to elevated inflammation. This finding is important for early risk identification, as chronic inflammation has been associated with negative physical health consequences in adulthood, such as cardiovascular disease (Furman et al., 2019). In our sample, those adolescents with higher internalizing symptoms after abuse experiences are likely to be vulnerable to effects of environmental stress, such as stress generated by the COVID-19 pandemic.

In contrast, we did not find evidence for the indirect effects of maltreatment on internalizing symptoms via CRP. Instead, childhood abuse significantly predicted internalizing symptoms, and CRP significantly predicted future internalizing symptoms one year later. This finding is consistent with prior research showing threat experiences in childhood are associated with higher depressive symptoms (Chahal et al., 2022) and that inflammation is associated with increased depressive symptoms (Moriarity et al., 2019; Rengasamy et al., 2021). The lack of a significant direct association between childhood maltreatment and later inflammation in our findings is not consistent with prior psychoneuroimmunology research and the hypothesized biological embedding of adversity through inflammatory pathways (Muscatell, 2021; Nusslock and Miller, 2016). Our results should be replicated before making any conclusion regarding the null finding.

Some limitations of the current study should be noted. First, we were not able to explore possible sex differences in the associations among abuse/neglect, internalizing symptoms, and inflammation, due to our sample size. Although the hypothesized model was a relatively simple path model, the sample size was lower than what is recommended (i.e., $N = 78$ vs. $N = 95$ based on the 5:1 ratio of sample size to number of free parameters, according to Bentler and Chou, 1987). We present our findings as initial evidence for the direction of the longitudinal effects of abuse, internalizing symptoms, and inflammation. Future studies with bigger sample sizes should replicate our findings and fully explore possible sex differences. Second, CRP was only measured at one time point during late adolescence. More chronic levels of inflammation may be present at younger ages based on the timing of maltreatment. Future studies examining maltreatment with bidirectional associations of inflammation and depressive symptoms will benefit from modeling longitudinal repeated measures of both inflammation and depression. Lastly, we did transform the CRP variable to better address skewness of residuals, but it will be important for future research to consider using non-transformed CRP values as this could introduce bias to the results (Moriarity, 2022).

Despite the limitations, study strengths include utilizing a dimensional approach to examining adversity effects on development and examining bi-directional effects of internalizing symptoms and inflammation during late adolescence. Our findings also highlight the importance of examining abuse and neglect separately, as we found distinctive associations with abuse, not neglect. These results are consistent with theoretical models proposing threat experiences may have stronger effects on health, as abuse, not neglect, is associated with indices of accelerated aging (Colich et al., 2020). Finally, our study used three years of longitudinal data and inflammation during the first year of the COVID-19 pandemic when stress was heightened in multiple domains.

The current study broadens our understanding of how childhood abuse may increase risk for the development of internalizing symptoms related to future heighted inflammation. These findings emphasize the importance of examining distinct forms of maltreatment in understanding the longitudinal pathways connecting early adversity, internalizing symptoms, and inflammation. This research is an important step towards identifying adolescents with a history of abuse that may be particularly vulnerable to internalizing symptoms associated with heighted inflammation. Future work should focus on understanding mechanisms linking abuse and internalizing symptoms, as identifying youth at risk for depression related inflammation earlier in development may help to prevent depression onset and the progression of future physical health problems associated with chronic inflammation in adulthood.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This work was supported by the grants from the National Institute on Drug Abuse (R01 DA036017 to Jungmeen Kim-Spoon and Brooks Casas) and the Virginia Tech Institute for Society, Culture and Environment (ISCE). We thank the former and current members of the JK Lifespan Development Lab at Virginia Tech for their help with data collection. We are grateful to the adolescents and parents who participated in our study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100719.

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