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## Brain, Behavior, &amp; Immunity - Health

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## Full Length Article

## Childhood sexual abuse history amplifies the link between disease burden and inflammation among older adults with HIV

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## ARTICLE INFO

## Keywords:

HIV  
Inflammation  
Childhood trauma  
Early life stress  
Disease burden  
Chronic conditions

## ABSTRACT

As they age, people living with HIV (PLWH) experience greater rates of inflammation-related health conditions compared to their HIV-negative peers. Because early life adversity can exaggerate proinflammatory effects of later physiological challenges, inflammation may be higher among PLWH with these combined risks, which could inform intervention approaches to mitigate multimorbidity. In this cross-sectional analysis, we investigated individual and combined effects of childhood sexual abuse (CSA) history and physiological burden (Veterans Aging Cohort Study Index scores) on serum cytokine and C-reactive protein (CRP) levels among PLWH. Participants ( $n = 131$ ; age 54 and older) were patients at an outpatient HIV clinic who completed a psychosocial survey and biomedical research visit as part of a larger study. 93% were virally suppressed, and 40% reported experiencing sexual abuse in childhood. Composite cytokine levels (summarizing IL-6, TNF- $\alpha$ , IFN- $\gamma$ ), CRP, and disease burden did not differ significantly between those who had a history of CSA and those who did not. Participants with greater disease burden had higher composite cytokine levels ( $r = 0.29$ ,  $p = 0.001$ ). The disease burden by CSA interaction effect was a significant predictor of composite cytokine levels (but not CRP), and remained significant after controlling for age, sex, race, BMI, anti-inflammatory medication use, selective serotonin reuptake inhibitor use, depressive symptoms, and smoking status ( $F(1, 114) = 5.68$ ,  $p = 0.02$ ). In follow-up simple slopes analysis, greater disease burden was associated with higher cytokine levels among those with CSA history ( $b = 0.03$ ,  $SE = 0.008$ ,  $p < 0.001$ ), but not among those without CSA history. Further, in the context of greater disease burden, individuals with a CSA history tended to have higher cytokine levels than those without a CSA history ( $b = 0.38$ ,  $SE = 0.21$ ,  $p = 0.07$ ). These data suggest that the physiological sequelae of childhood trauma may persist into older age among those with HIV. Specifically, links between physiological burden and inflammation were stronger among survivors of CSA in this study. The combined presence of CSA history and higher disease burden may signal a greater need for and potential benefit from interventions to reduce inflammation, an area for future work.

## 1. Introduction

Although people living with HIV (PLWH) have experienced notable gains in health and lifespan with effective anti-retroviral therapy (ART) regimens, they continue to face substantial health disparities as they age

compared to their HIV-negative peers. PLWH develop cardiovascular disease, cancer, cognitive impairment, and frailty at higher rates than comparison groups without HIV (Pathai et al., 2014). These patterns are consequential, as the leading causes of death for PLWH have shifted to non-AIDS related chronic diseases, including non-HIV/AIDS defining

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Received 25 August 2021; Accepted 28 August 2021

Available online 31 August 2021

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cancers and cardiovascular disease (Smith et al., 2014). Accordingly, there is a growing need to determine underlying biopsychosocial mechanisms that drive the development of these comorbidities in PLWH.

Chronic inflammation underlies many of these adverse health outcomes (Furman et al., 2019), and PLWH have elevated inflammation levels (Peterson and Baker, 2019). Although consistent ART adherence and successful viral suppression can reduce inflammation (Castillo-Mancilla et al., 2020), persistent HIV infection still contributes to inflammatory processes via several pathways including low-level residual viral replication, co-infections (e.g., cytomegalovirus, Hepatitis C virus), and microbial translocation (Gabuzda et al., 2020). Among PLWH, those with higher inflammation levels experience poorer health than those with lower inflammation levels. For example, in an observational study of over 4,000 HIV-positive adults receiving ART, interleukin-6 (IL-6) levels at study entry were associated with risk for developing cardiovascular problems and non-AIDS defining cancers over time (Borges et al., 2016). A key priority to support successful aging in PLWH includes determining “for whom” higher inflammation levels are most likely, as well as ways to address them.

Early life stress (such as childhood trauma, abuse, and maltreatment) can have lasting effects on health into adulthood, including exacerbating inflammatory processes. According to the well-established Biological Embedding of Childhood Adversity model, early life stressors result in biological and behavioral changes that contribute to elevated inflammation levels, and subsequent excess morbidity and mortality risk (Miller et al., 2011). For example, experiencing childhood trauma can promote risk for depression and post-traumatic stress disorder (Danese and Lewis, 2017), both of which are linked to chronic inflammation (Kiecolt-Glaser et al., 2015; Michopoulos et al., 2017; Yang and Jiang, 2020). In a meta-analysis of 25 studies summarizing data from over 16,000 adults, childhood trauma history was associated with higher levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6, and C-reactive protein (CRP) (Baumeister et al., 2016). Compared to those without a childhood abuse history, healthy adults with a history of any type of childhood abuse had steeper rises in inflammation (as measured by a composite of IL-6, TNF- $\alpha$ , and IL-1 $\beta$  levels) over the course of approximately two years (Renna et al., 2021). Among older PLWH, those with more childhood adversities had greater allostatic load (defined by biomarkers of cardiovascular, metabolic, inflammatory, and hypothalamic-pituitary-adrenal [HPA] axis dysregulation) compared to those with fewer childhood adversities (Wallace et al., 2020). These patterns may be particularly relevant for PLWH, as this group appears to have greater rates of childhood adversity than those in the general population on average (Wallace et al., 2020).

Further, childhood trauma history may exacerbate the effect of later physiological insults on systemic inflammation. For example, experiencing adversity during early developmentally-critical periods can result in epigenetic programming that sensitizes inflammatory responses to future challenges (Miller et al., 2011). Dysregulated HPA axis function contributes to this pattern; childhood trauma is associated with hyperactive cortisol signaling and alterations in glucocorticoid receptor functioning (Danese and Lewis, 2017; Miller et al., 2011). Over time, these changes can reduce sensitivity to the glucocorticoid signaling that typically dampens inflammation, setting the stage for exaggerated or prolonged inflammatory responses. Across several studies in a recent meta-analysis, youth who experienced childhood adversity had larger ex vivo cytokine production in response to lipopolysaccharide than those who did not, though formal statistical comparison was not possible due to heterogeneity in study methods (Kuhlman et al., 2020). The ways in which childhood adversity interacts with later and more persistent physiological challenges, such as chronic disease burden, has been less explored. In a recent study, adults with major depressive disorder (MDD) who also had a childhood trauma history had higher IL-6 levels than comparison participants without these risks, whereas experiencing only MDD was not associated with higher inflammation (de Punder et al., 2018). In the context of chronic conditions, systemic inflammation functions as a general, broad response to physiological insults and

multi-system damage (Bennett et al., 2018), which could fuel multi-morbidity and disease progression, creating a vicious cycle. Taken together, it is possible that inflammation-promoting effects of childhood trauma may occur to a greater extent under conditions of heightened physiological burden.

In summary, childhood trauma exerts longstanding effects on inflammatory pathways into adulthood, and these patterns are especially relevant for PLWH. Further, the effects of childhood trauma on inflammation may accumulate in the context of higher disease burden. Accordingly, considering interactions between childhood trauma history and the severity of chronic conditions may provide unique insight in identifying those for whom inflammation is most notable. In this cross-sectional analysis, we investigated the individual and combined effects of childhood sexual trauma history (as measured by childhood sexual abuse, CSA) and disease burden (measured by the Veterans Aging Cohort Study index, VACS) on inflammation levels in older adults with HIV. Because data were drawn from a larger study on HIV and aging in which participants were asked to report their childhood sexual abuse history (but not other types of early life adversity), the current analysis focused on CSA history as opposed to broader measures of adverse childhood experiences. We hypothesized that CSA history and greater disease burden would be individually associated with higher inflammation levels, and that the links between disease burden and inflammation would vary according to CSA history.

## 2. Methods

### 2.1. Participants

Data for this cross-sectional analysis were drawn from a study of older PLWH recruited from the HIV clinics at New York-Presbyterian Hospital/Weill Cornell Medicine. This analysis included 131 participants who completed the psychosocial and biomedical study visits, had data available for childhood trauma and inflammation variables, and had CRP levels below 10 mg/L, a threshold indicating likely acute infection (Boylan and Ryff, 2013; Pearson et al., 2003; S. J. Wilson et al., 2018).

Participants were initially identified using an age-stratified random selection strategy as part of a larger multi-site survey study titled Research on Older Adults with HIV 2.0 (Erenrich et al., 2018). Next, a subset of these participants was invited to an additional biomedical study visit for additional health and aging assessments. Those invited were age 55 or older (to facilitate study of aging outcomes) English-speaking participants living with HIV. Exceptions were made to enroll two individuals who were age 54 and met the other inclusion criteria. The study procedures were approved by the Weill Cornell Medicine's Institutional Review Board (IRB# 1603017050). Participants provided informed consent, and received compensation for attending the study visits.

### 2.2. Procedures

At the survey visit, participants reported psychosocial information including sociodemographic factors, CSA history, depressive symptoms, and smoking status. Participants were instructed to arrive fasting for 8 h to the separate biomedical research visit at the Weill Cornell Clinical and Translational Science Center. Blood samples were drawn and processed, and serum was stored at  $-80^{\circ}\text{C}$  then later assayed for inflammatory markers.

### 2.3. Measures

#### 2.3.1. Inflammation biomarkers

Serum proinflammatory biomarker data for CRP and proinflammatory cytokines IL-6, TNF- $\alpha$ , and IFN- $\gamma$  were utilized for analysis. Electrochemiluminescence-based assays were performed according to Meso Scale Discovery (Rockville, MD) kit instructions (K151STG and K15052G respectively) using the MESO QuickPlex SQ120 Analyzer.

Assays were run in duplicate with quality controls, with 10% repeated for confirmation. The intra-assay coefficient of variation (CV) for CRP, IL-6, TNF- $\alpha$ , and IFN- $\gamma$  ranged from 2.4% to 6.4%, and inter-assay CVs ranged from 5.0% to 10.2%. The detection limits of CRP, IL-6, TNF- $\alpha$ , and IFN- $\gamma$  are 0.01 ng/ml, 0.10 pg/ml, 0.20 pg/ml, and 0.40 pg/mL, respectively.

### 2.3.2. Childhood sexual abuse history

Childhood sexual abuse history was indicated by participants' responses to two questions about sexual abuse before age 16 on the psychosocial survey. Using modified items based upon the Adverse Childhood Experiences International Questionnaire (World Health Organization, 2018), participants were asked whether they experienced (1) unwanted sexual touching or (2) unwanted attempted or actual intercourse, with response options "never," "once," "a few times," or "many times." For the purpose of analysis, we created a dichotomous variable to indicate the presence of a CSA history (any endorsement of either question) vs. no CSA history (responding "never" to both questions).

### 2.3.3. Disease burden

The Veterans Aging Cohort Study (VACS) index, a validated and widely-used measure of accumulated organ system injury among PLWH, was used to assess disease burden (Justice et al., 2012). VACS index scores were calculated using a standardized, publicly-available tool (VACS calculator, version 2: <https://vacs-apps2.med.yale.edu/calculator>) to compute scores based upon clinical data for each participant. The VACS index uses the following components to calculate scores: age, sex, race, CD4 count, HIV-1 RNA viral load, hemoglobin, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, and hepatitis C infection status. Clinical characteristics and laboratory data were obtained via chart review, using the closest clinical encounter to the time of the biomedical study visit.

### 2.3.4. Additional health-related variables and covariates

We considered covariates typically associated with inflammation levels, as well as those that could help to explain CSA's effects in adulthood (e.g., psychological symptoms and recent intimate partner violence). Body mass index (BMI) was calculated using height and weight measured at the biomedical visit. Smoking status was assessed via self-report on the psychosocial survey. Depressive symptoms were measured using the 10-item version of the Center for Epidemiological Studies Depression (CES-D-10) Scale (Andresen et al., 1994), with higher total scores indicating greater depressive symptoms. Posttraumatic stress disorder (PTSD) symptoms were measured using the 17-item PTSD Checklist – Civilian Version (PCL-C), with higher total scores indicating greater trauma symptoms (Weathers et al., 1994). To measure whether participants experienced intimate partner violence (IPV; e.g., assault, sexual coercion) in adulthood, we examined responses to 7 modified items based on the Revised Conflict Tactics Scale (Straus and Douglas, 2004) and coded a variable to index any vs. no reports of IPV. Menopausal status was assessed via women's responses to a self-report item assessing time since the last menstrual period; they were considered pre-menopausal if they reported a period in the last 1–3 months, peri-menopausal if they reported a period between 3 and 9 months ago, or post-menopausal if they reported >12 months since their last period. Medication lists were reconciled by research nurses at the study visit. Dichotomous variables were coded to indicate any vs. no regular use of systemic anti-inflammatory medications (immunosuppressants, systemic glucocorticoids, anti-gout medications, and statins; WHO ATC categories L04A, H02A, M04A, and C10AA respectively) and selective serotonin reuptake inhibitors (SSRIs; WHO ATC category N06AB) given meta-analytic findings demonstrating their association with lower inflammation levels (Wang et al., 2019). When relevant, in order to maximize the sample for adjusted analyses, we used medical chart data from the nearest clinical encounter for those with missing covariate data.

### 2.3.5. Statistical analysis

Inflammation data were examined for outliers, and each biomarker was winsorized to 3 standard deviations (SD) from the mean (Boylan and Ryff, 2013; Gouin et al., 2020) then log-transformed due to positive skew. Raw and winsorized, log-transformed values are presented in the Supplementary Material. Given moderate-to-strong correlations between IL-6, TNF- $\alpha$ , and IFN- $\gamma$  cytokine levels ( $r = 0.30$  to  $r = 0.59$ ), a composite score was computed (i.e., mean of standardized variables) in order to facilitate interpretation and limit the number of statistical comparisons. The composite of cytokine levels was computed by standardizing the log-transformed, winsorized variables to index z-scores for each cytokine, then averaging the standardized variables. CRP was examined separately, as correlations between CRP and cytokine levels were weaker and less consistent.

Analyses were conducted in SPSS, Version 24.0 (IBM Corp., Armonk, NY) using a two-tailed alpha level of 0.05 for statistical significance. Using Hayes' PROCESS macro for simple moderation analysis (version 3.4.1, model 1), separate linear regression models were used to test whether the CSA by disease burden interaction was a key predictor of inflammatory biomarker outcomes (composite cytokine levels and CRP levels). Adjusted models included age, sex, race, BMI, smoking status, anti-inflammatory medication use, SSRI medication use, and depressive symptoms, based on broader literature suggesting their consistent links with inflammation (Lu et al., 2019; S. J. Wilson et al., 2018). Ancillary analyses adjusted for PTSD symptom scores and experiencing IPV. Because depressive symptom scores and PTSD symptom scores were strongly correlated ( $r = 0.71$ ), these covariates were not included in the same model due to multicollinearity concerns; instead, a separate ancillary model substituted PTSD symptom scores for depressive symptoms as a covariate. Statistically-significant interaction effects ( $p < 0.05$ ) were probed using simple slopes analysis, by testing the conditional effect of VACS scores on inflammation for those with and without a CSA history, and the effect of CSA history at  $\pm 1$  SD VACS scores. The Johnson-Neyman method was used to identify the region of significance (i.e., VACS score above which the effect of CSA is statistically significant) (Hayes and Rockwood, 2017). Cases with missing data were excluded listwise from adjusted analyses.

## 3. Results

On average, participants were 61 years of age (SD = 5.88; range 54–78 years) and had been diagnosed with HIV 23 years ago (SD = 5.71; range 4–35 years). Participants most commonly represented in the sample were men (70%), non-smokers (84%), and virally suppressed (93% with HIV-1 viral load <200 copies/ml). Of the 40 women participants, 27 (67.5%) were post-menopausal, 2 (5%) were peri-menopausal, and menopausal status was missing for 11 participants (27.5%). Fifty-two participants (40%) reported experiencing childhood sexual abuse before age 16. Composite cytokine levels, CRP levels, and disease burden (as indicated by VACS index scores) did not differ significantly between those who had a history of CSA and those who did not ( $p$ -values for comparisons >0.18). Those with a CSA history had higher levels of PTSD symptoms than those without a CSA history ( $t(129) = 2.74$ ,  $p = 0.007$ ). Of the 122 participants who responded to items about IPV in adulthood, 20% reported experiencing IPV, and rates did not differ significantly by CSA history in this sample ( $p = 0.16$ ). Sociodemographic factors did not vary significantly according to childhood sexual abuse history (Table 1).

The mean VACS index score in this sample was 31 (SD = 16.24), corresponding to a 5-year mortality risk of approximately 13%. As expected, disease burden and inflammation levels were correlated such that participants with higher VACS index scores had higher composite cytokine levels ( $r = 0.29$ ,  $p = 0.001$ ) than those with lower VACS index scores. On the other hand, bivariate links between VACS index scores and CRP were not statistically significant.

In the unadjusted model examining interaction effects, the disease burden by CSA history interaction was a significant predictor of

**Table 1**  
Sample characteristics.

Characteristic	Overall sample (n = 131)	History of childhood sexual abuse (n = 52)	No history of childhood sexual abuse (n = 79)	p-value
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
Age (yrs)	61.23 (5.88)	60.38 (5.24)	61.78 (6.23)	0.18
Sex				
Female	40 (31%)	19 (37%)	21 (27%)	0.23
Male	91 (69%)	33 (63%)	58 (73%)	
Race				
Black	61 (48%)	23 (45%)	38 (50%)	0.33
White	42 (33%)	15 (29%)	27 (36%)	
Asian or Pacific Islander	1 (1%)	1 (2%)	0 (0%)	
Multiple or other races	23 (18%)	12 (24%)	11 (14%)	
Ethnicity				
Hispanic/Latino	37 (33%)	19 (41%)	18 (27%)	0.12
Non-Hispanic/Latino	75 (67%)	27 (59%)	48 (73%)	
Education level				
≤12 years	33 (26%)	9 (18%)	24 (31%)	0.09
>12 years	95 (74%)	42 (82%)	53 (69%)	
Viral load				
<200 copies/mL	122 (93%)	49 (94%)	73 (92%)	1.00
≥200 copies/mL	9 (7%)	3 (6%)	6 (8%)	
Time since HIV diagnosis (yrs)	23.40 (5.71)	22.73 (6.47)	23.85 (5.14)	0.28
VACS score	31.35 (16.24)	29.00 (14.82)	32.90 (17.03)	0.18
BMI (kg/m <sup>2</sup> )	27.78 (5.36)	28.53 (5.31)	27.28 (5.36)	0.19
Current tobacco use	21 (16%)	6 (12%)	15 (19%)	0.26
Anti-inflammatory use	67 (51%)	28 (54%)	39 (49%)	0.62
SSRI use	14 (11%)	4 (8%)	10 (13%)	0.56
Experienced intimate partner violence	24 (20%)	12 (26%)	12 (16%)	0.16
Depressive symptoms (CES-D-10)	9.67 (6.22)	10.43 (6.12)	9.18 (6.27)	0.26
PTSD symptoms (PCL-C)	33.82 (13.35)	37.65 (14.98)	31.29 (11.56)	0.007

Note: Data were missing for several participants for race (n = 4), ethnicity (n = 19), education (n = 3), CES-D-10 score (n = 2), and intimate partner violence (n = 9). % indicates percentage of those with available data for each variable. p-values reflect t-test, Chi-square, and Fisher's exact tests as appropriate for between-group differences based on childhood trauma history.

composite cytokine levels ( $F(1, 127) = 5.29, p = 0.02$ ), but not CRP levels ( $F(1, 127) = 1.42, p = 0.23$ ). In the adjusted model predicting composite cytokine levels, the interaction effect remained statistically-significant ( $F(1, 114) = 5.68, p = 0.02$ ) while controlling for age, sex, race, BMI, smoking status, anti-inflammatory medication use, SSRI use, and depressive symptoms (Table 2). The interaction was probed using simple slopes analysis to indicate the pattern of results, as shown in Fig. 1. Among those with a CSA history, greater disease burden was related to higher cytokine levels ( $b = 0.03, SE = 0.008, p < 0.001$ ); this link was not statistically significant among those without a CSA history ( $p = 0.29$ ). Furthermore, among those with greater disease burden (i.e., 1 SD above the mean, tested at VACS index score of 47.03), participants with a CSA history tended to have greater cytokine levels than those without a CSA history ( $b = 0.38, SE = 0.21, p = 0.07$ ). The Johnson-Neyman test results revealed that there was a significant effect of CSA history on composite

**Table 2**  
Linear regression models with key interaction (childhood sexual abuse history by disease burden) predicting cytokine levels.

Effect	Outcome: Composite cytokine levels				
	Estimate	SE	95% CI		p
			LL	UL	
<b>Unadjusted model</b>					
Disease burden (VACS Index score)	.008	.005	-.002	.02	.11
CSA history (yes)	.11	.13	-.16	.38	.42
Disease burden x CSA history	.02	.009	.003	.04	.02
<b>Adjusted model</b>					
Age (years)	-.003	.01	-.03	.02	.83
Sex (male)	.03	.15	-.28	.34	.83
Race (white)	-.005	.16	-.32	.31	.97
BMI (kg/m <sup>2</sup> )	.03	.01	-.0005	.05	.05
Current smoking (yes)	.22	.18	-.15	.58	.24
Anti-inflammatory use (yes)	.08	.14	-.20	.35	.59
SSRI use (yes)	-.44	.22	-.88	.003	.05
Depressive symptoms (CES-D-10 total)	.03	.01	.006	.05	.01
Disease burden (VACS Index score)	.007	.006	-.006	.02	.29
CSA history (yes)	.04	.14	-.24	.32	.76
Disease burden x CSA history	.02	.009	.004	.04	.02

Note: Composite cytokine levels summarize log-transformed IL-6, TNF-alpha, and IFN-gamma levels. SE = standard error; LL = lower limit; UL = upper limit; CSA = childhood sexual abuse.

cytokine levels at VACS index scores of 50.50 and above. In ancillary analyses, adjusting for PTSD symptoms (by substituting PCL-C scores for CES-D-10 scores in the model) and experiences of IPV (by adding them as a covariate) did not alter the pattern of results, such that the interaction effects and simple slopes remained significant predictors of composite cytokine levels.

#### 4. Discussion

In this cross-sectional analysis, we tested the effects of childhood sexual abuse history, disease burden, and their interaction on serum cytokine and CRP levels among PLWH (ages 54 and older) who were engaged in HIV care at a single outpatient program. Greater disease burden was associated with cytokine levels among survivors of CSA, but these links were weaker among those without a CSA history. At greater levels of disease burden, those who reported experiencing childhood sexual abuse had higher cytokine levels than those who did not experience childhood sexual abuse. These relationships were present when accounting for other key sociodemographic and health-related factors, including depressive symptoms, PTSD symptoms, and smoking status, which are common behavioral contributors to inflammation. On the other hand, these relationships were not observed for CRP. This study suggests that the link between disease burden and cytokine levels may be stronger among survivors of childhood sexual abuse. These findings imply that considering the interaction between psychosocial and physiological factors yields useful information about inflammatory processes in older PLWH, who experience elevated risk for developing health problems as they age.

Interestingly, the interaction between CSA and disease burden was a significant predictor of cytokine levels, but not CRP levels. Since CRP production is stimulated by IL-6, it is possible that downstream links with CRP are weaker. This follows a previously-noted pattern that cytokines such as IL-6 appear to be more responsive to psychosocial factors than CRP (Kiecolt-Glaser et al., 2015); similarly, we observed that cytokines were associated with depressive symptoms in this cohort, but CRP was not (Derry et al., 2021).

Consistent with well-established literature indicating that history of early life stress contributes to immune dysregulation across the lifespan, these data underscore that the physiological sequelae of childhood sexual abuse can persist into older age among PLWH. Further, in addition to robust links between childhood trauma and chronic disease onset (Felitti

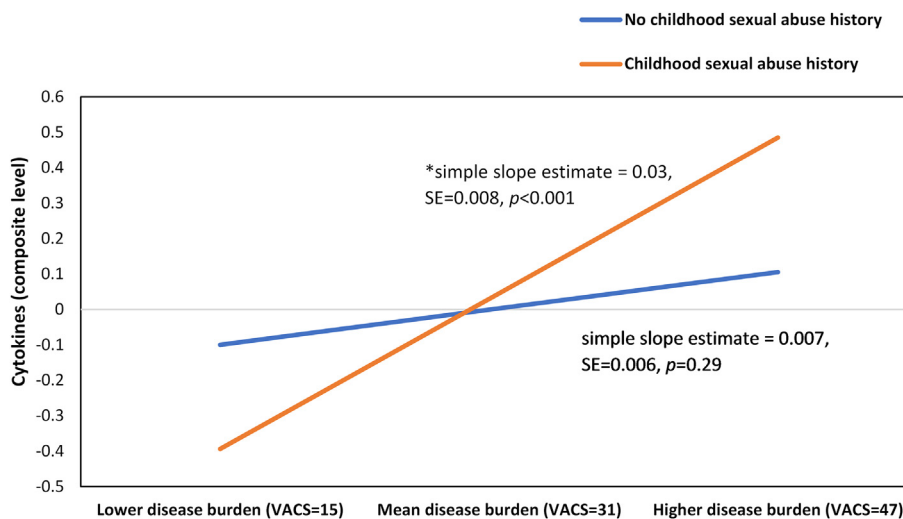


Fig. 1. Composite cytokine levels (IL-6, TNF- $\alpha$ , and IFN- $\gamma$ ) from the regression model examining the interaction between disease burden (VACS index scores) and childhood trauma history as the key predictor, adjusting for age, sex, race, BMI, smoking status, anti-inflammatory use, SSRI use, and depressive symptoms. \*indicates significant simple slope for the effect of VACS score predicting cytokine levels in the presence of childhood sexual abuse history (b = 0.03, SE = 0.008, 95% CI = 0.01 to 0.04,  $p < 0.001$ ).

et al., 1998), our findings are in line with work suggesting that childhood trauma history can influence immune function in the context of existing health conditions. For example, breast cancer survivors who experienced more childhood adversities had poorer cellular immune control over latent Epstein-Barr virus and cytomegalovirus than those who experienced fewer childhood adversities (Fagundes et al., 2013). This pattern may have downstream effects on inflammation, as viral reactivation (indexed by antibody titers) can prompt increases in CRP and IL-6 (Bennett et al., 2012). Among patients with metastatic lung cancer, those with a history of childhood adversity had higher levels of CRP, physical symptoms, and psychological distress compared to those without such a history (McFarland et al., 2020). Similarly, our findings among PLWH suggest that a history of CSA may alter inflammatory processes. In this study, while there were not significant overall differences in inflammation levels based on CSA history, the effect of CSA was observed in the context of greater physiological burden. These data support the possibility that a history of childhood sexual abuse may contribute to advanced aging mechanisms by exacerbating the physiological toll of chronic conditions, an area for future study.

There are several ways in which these findings can inform approaches to enhance health among PLWH. In future work, it may be useful to determine whether CSA history could guide the identification of subgroups to prioritize when studying and employing interventions. For example, approaches to mitigate chronic inflammation may be particularly needed in PLWH who have a history of childhood sexual abuse. In addition, inflammation-related interventions likely need to attend to both physiological and psychosocial factors as people age with HIV. Though existing approaches have focused primarily on pharmacological treatments (Kettelhut et al., 2020), including statin medications, integrating psychosocial approaches appears promising. In a study of adults participating in a lifestyle intervention, the relationship between adverse childhood experiences and inflammation was attenuated for those who had greater resilience resources, such as social engagement, meaning in life, and positive health behaviors like exercise (Gouin et al., 2017). In a recent meta-analysis of 56 randomized controlled trials across various disease conditions, psychosocial interventions (such as cognitive-behavioral therapy) reduced markers of harmful immune function (such as proinflammatory cytokines) by 18% relative to control groups (Shields et al., 2020). In fact, moderation analyses revealed that the immune benefits of psychosocial treatments were especially strong among PLWH and for reducing pro-inflammatory cytokines. Taken together, the presence of both a childhood trauma history and higher disease burden might signal a greater need for and potential benefit from interventions to reduce inflammation.

Of note, this study did not recruit individuals with respect to their

childhood abuse history. Still, a substantial portion (40%) reported a history of childhood sexual abuse. Unfortunately, other studies suggest that a notable portion of adults in the general population have experienced childhood abuse. Further, child abuse and neglect are associated with increased HIV risk behaviors in adulthood (Arriola et al., 2005; H. W. Wilson and Widom, 2011), and adverse childhood experiences may be more common among PLWH, though further study including formal statistical comparison is needed. For example, in the large Adverse Childhood Experiences study of patients enrolled in the Kaiser health plan, 22% reported experiencing childhood sexual abuse (Felitti et al., 1998). Data from the Behavioral Risk Factor Surveillance System, a nationally-representative telephone survey, reported 12% prevalence of childhood sexual abuse; women, those identifying as gay, lesbian, or bisexual, and those with lower socioeconomic status were more likely to report a childhood sexual abuse history than other groups (Merrick et al., 2018). In a study of PLWH receiving outpatient care, 25% experienced a history of childhood sexual abuse (Wallace et al., 2020). In line with broader literature suggesting variable yet high rates of traumatic experiences that impact health among PLWH, these patterns attest to the importance of a trauma-informed approach to HIV care (Brezing et al., 2015).

This study's strengths include the diverse sample of participants, with 48% identifying as Black and 33% identifying as Hispanic. The broad age range of the sample (54–78 years) and representation of women (31%) are also unique contributions to HIV research, which often focuses on younger, primarily male samples. In addition, the inclusion of relevant covariates, including depressive and PTSD symptoms, enhances the rigor and conclusions of our findings. Yet, the study's cross-sectional design precludes conclusions about whether these interaction effects persist or impact meaningful health outcomes over time, a primary limitation. It is also possible that additional, unexamined variables could contribute to or help to explain the observed patterns. For example, survivors of childhood sexual abuse may experience additional traumatic events at higher rates during adulthood (Arriola et al., 2005; Brennan-Ing et al., 2020), which could partially explain the patterns observed in the current study. We considered this possibility by accounting for intimate partner violence, which did not alter the pattern of results. However, in future studies that investigate the persistent effects of childhood adversity among older adults with HIV, it would be useful to assess recent stressful and/or traumatic events across other domains. In addition, this analysis included women, a group that is under-represented in HIV research. In a recent study of women without HIV, increases in inflammation during the menopausal transition were particularly pronounced among those with adverse childhood experiences (Metcalfe et al., 2021). While we did not investigate the influence of menopausal status on the results given

the small number of pre- and peri-menopausal women in the sample (respectively:  $n = 0$  and  $n = 2$ , 1.5% of sample), future work to investigate how menopausal transitions impact the relationship between childhood trauma and inflammation among women with HIV is warranted.

This study utilized retrospective reports of childhood sexual abuse; retrospective and prospective reports of child sexual abuse had 86% agreement in a recent meta-analysis (Baldwin et al., 2019). Yet, retrospective versus prospective methods identified different groups of individuals in the meta-analysis, so the pattern of results observed in our study may or may not apply when assessing child abuse prospectively. Broader measures of other types of childhood abuse or adversity, such as emotional abuse, physical abuse, or neglect, were not available in the larger study, which was not designed to address this specific research question. The two-item assessment of childhood sexual abuse available for analysis in this study was limited compared to other commonly-used measures, such as the inventory in the Adverse Childhood Experiences Study (Felitti et al., 1998) and the Childhood Trauma Questionnaire (Bernstein et al., 1994). As a result, it is possible that the frequency of childhood sexual abuse was underestimated in this study, and other types of traumatic events and adversities were not measured. Future work that includes more comprehensive assessment of different types of early life adversities is a needed step for understanding these patterns, as the effects of childhood adversity may vary across different types of abuse, trauma, and neglect (Renna et al., 2021).

In conclusion, this study of PLWH highlights that the combination of childhood sexual abuse and physiological burden may signal a subgroup of individuals who are particularly vulnerable to elevated inflammation. Specifically, in the context of similarly-high disease burden levels, those with a childhood sexual abuse history may experience greater inflammatory consequences than those without a childhood sexual abuse history. This suggests a need for future work to determine whether these patterns persist over time, contribute to adverse health outcomes (e.g., further multimorbidity, functional decline, and/or disease progression), and provide utility for identifying “for whom” and “how” to employ strategies that mitigate inflammation.

## Funding

Work on this study and manuscript was supported by funding from the American Psychological Foundation (Visionary Grant), the MAC AIDS Fund, the New York Community Trust, the National Cancer Institute (K99 CA245488), the National Institute of Allergy and Infectious Diseases (T32 AI007613), and the National Center For Advancing Translational Sciences (UL1TR000457). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

## Declaration of competing interest

Dr. Derry has an unrelated financial relationship (spouse employment) with Elanco. Dr. Glesby is a consultant to Sobi, ReAlta Life Sciences, Enzychem, and Regeneron and receives royalties from Springer and UpToDate. Dr. Glesby's institution has received research support from Gilead Sciences and Regeneron to support his work.

## Acknowledgements

The authors express appreciation to the participants in this study and to the staff at the Weill Cornell Clinical and Translational Science Center.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbih.2021.100342>.

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