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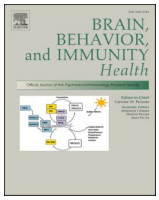

# Examining the relationships between adverse childhood experiences (ACEs), cortisol, and inflammation among young adults☆

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ABSTRACT

Adverse childhood experiences (ACEs) are associated with dysregulation of inflammation and cortisol. The objectives of this study were to use principal component analysis to explore the inflammatory biomarker data to create inflammation composite variables; to examine the relationship between these composite measures of inflammation with ACEs and cortisol; and to assess whether these relationships were moderated by sex. The analysis included 232 young adults from the Niagara Longitudinal Heart Study (NLHS). After adjusting for covariates, higher exposure to ACEs significantly predicted higher low-grade inflammation. These results further support the use of multiple biomarkers to understand the complex relationships among ACEs, cortisol, and inflammation, which should be further examined in longitudinal studies to study biomarker trajectories.

## 1. Background

Adverse childhood experiences (ACEs) are defined as traumatic events that occur before the age of 18 years that can have major consequences for behavioral and physiological development affecting one's life-course health trajectory. ACEs can include maltreatment and severe household dysfunctions as well as other events such as severe bullying, natural disasters, and extreme poverty. In turn, these traumatic experiences elicit physiological stress responses that prepare the body for danger, conditioning it into a fight, flight, or freeze mode (Gray and McNaughton, 2003). Exposure to stress over time can wear homeostatic mechanisms and contribute to longer-term, maladaptive physiological changes sometimes referred to as allostatic load and, in the extreme case, allostatic overload (McEwen, 1998). Immune (Miller et al., 2011) and cortisol (Hertzman, 2012) dysfunction as a result of ACEs exposure are increasingly acknowledged for their role in pathology of later physical (Giovannini et al., 2011; Lainampetch et al., 2019) and mental health diseases (Slavich and Irwin, 2014; Hori and Kim, 2019).

### 1.1. The association between ACEs and inflammatory biomarkers

Chronic inflammation has been established as an overlying mechanism in which the immune system contributes to the development of later disease (Nathan and Ding, 2010). Cytokines and other molecules that coordinate inflammatory processes are often used as biomarkers to assess levels of inflammation. Detected cytokines and other molecules often vary in concentration and certain patterns may indicate a specific inflammatory state.

Exposure to ACEs have been linked to inflammation in childhood, adolescence, and across adulthood. For example, the Avon Longitudinal Study of Parents and Children examined ACEs prior to 9 years of age (Slopen et al., 2013). Adversities that occurred between the ages of 6–8 years were associated with higher levels of C-Reactive Protein (CRP) and Interleukin-6 (IL-6) at 10 years. In addition, ACEs prior to 9 years were associated with higher levels of CRP at age 15 after adjusting for Body Mass Index (BMI), depression, and smoking status.

Exposure to ACEs have also been associated with inflammation

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among adolescents and young and middle-aged adults. The Family and Community Health Study examined ACEs from ages 12–25 years over 7 waves of data in males and females, with inflammatory data collected at the 7th wave (Simons et al., 2019). Harsh parenting was associated with inflammation after adjusting for smoking, education, sex, and other covariates. The Nurses' Health Study II that examined 702 women aged 25–42 identified elevated levels of CRP and IL-6 among women who reported sexual abuse after adjusting for age and adiposity (Bertone-Johnson et al., 2012). Another study that examined 141 women between the ages of 18–50 also found that those with higher ACE exposures had elevated levels of high sensitivity-CRP, IL-6, and Tumour Necrosis Factor α (TNFα) after adjusting age, education, smoking, and other covariates (Tietjen et al., 2012). Furthermore, the Dunedin Multidisciplinary Health and Development Study found that childhood maltreatment predicted higher levels of CRP 20 years later in male and female adults aged 32 years (Del Giudice and Gangestad, 2018).

Finally, childhood exposures to adverse experiences have also been shown to be associated with inflammation in later adulthood. The 1958 British Cohort examined ACEs between the ages 0–45 years over 7 waves of data in males and females with inflammatory data collected at ages 44–45 (Chen & Lacey, 2018). ACEs were associated with elevated adult inflammation and that socioeconomic, psychological distress, and behavioral factors particularly explained this association.

A number of meta-analyses have also been conducted examining how ACEs influence inflammation. One meta-analysis identified that CRP, IL-6, fibrinogen, and TNFα were the most widely reported biomarkers in ACEs research with CRP having the most robust findings (Coelho et al., 2014). Another systematic review identified that CRP, IL-6, and TNFα were the most widely reported biomarkers in childhood maltreatment research (Kerr et al., 2021). These three biomarkers represent low grade chronic inflammation (Miller et al., 2011) that are not only associated with an increased risk of developing later physical health disorders including cardiovascular disease (CVD) (Giovannini et al., 2011) and diabetes (Lainampetch et al., 2019), but also mental health disorders such as a major depressive disorder (Slavich and Irwin, 2014) and post-traumatic disorder (Hori and Kim, 2019).

### 1.2. ACEs and other biomarkers of interest

Since CRP, IL-6, and TNFα exert biological effects due to a larger network of immunologic molecules/proteins, other biomarkers are likely linked to the development of these physical and mental pathologies. Specifically, soluble Interleukin-6 receptor α (sIL-6Rα), glycoprotein 130 (gp130), soluble tumour necrosis factor receptor 1 (sTNFr1), soluble tumour necrosis factor receptor 2 (sTNFr2), and another cytokine, interferon gamma (IFNγ), are closely orbiting inflammatory components that are less examined (Coelho et al., 2014; Kerr et al., 2021) but may be important when investigating inflammation among those with a history of ACEs (Del Giudice and Gangestad, 2018). For instance, IL-6 exerts a biological effect by binding to sIL-6Rα to form a complex, which then binds to gp130 to drive transcription of pro-inflammatory genes in immune cells (Luo and Zheng, 2016). Therefore, these soluble receptors are crucial for IL-6 to exert the signals needed for immune cells to be pro-inflammatory. Similarly, TNFα also exerts a biological effect through binding to soluble receptors sTNFr1 and sTNFr2 (Cabal-Hierro and Lazo, 2012). IFNγ is another critical cytokine of interest as it mediates IL-6 and TNFα production in the context of psychological stress (Kim and Maes, 2003). Type 1 T-helper cells (Th1) secrete IFNγ which steer macrophages into IL-6 and TNFα production to sustain inflammation (Romagnani, 2000; Schroder et al., 2004). Some studies indicate that these additional biomarkers of interest are also linked to risk factors associated with ACE-related diseases. One study examining vascular health in women without CVD found that alterations in levels of soluble receptors sIL-6Rα and sTNFr1, but not the cytokines IL-6 and TNFα, were associated with cardiovascular risk factors (Cortez-Cooper et al., 2013). Similarly, adults aged over 60 years with more than 2 risk factors for CVD, compared to those less than 2, had more prevalent IFNγ producing T cell subsets and that they produced higher levels of IFNγ (Phoksawat et al., 2020). As those with a history of ACEs have increased risk for CVD, these findings demonstrate the importance of examining the soluble receptors in addition to CRP, IL-6, and TNFα, to better understand if these biomarkers are related and to understand their trajectory for later disease.

### 1.3. The association between ACEs and alterations in cortisol levels across age and sex

Cortisol is a hormone best known for its metabolic effects and as a product of the hypothalamic-pituitary-adrenocortical (HPA) axis (Russell and Lightman, 2019). Stresses that elevate cortisol levels over long periods of time can lead to a dysfunctional HPA axis resulting in altered cortisol levels throughout life. The relationship between ACEs and cortisol levels is complex. Current findings in the literature suggest that ACEs exposure lead to higher levels of basal cortisol levels during childhood until late adolescence/early adulthood but lower levels than typical when measured in mid to older adults (Miller et al., 2007). There are various approaches to measure cortisol including hair, saliva, urine, and blood. Acute measures of cortisol resulting from stress can be measured through saliva, urine, or blood which captures cortisol levels and changes in cortisol over a day (Meyer et al., 2014). These acute measures are often taken multiple times per day to account for the circadian rhythm variation of cortisol. Hair cortisol is known to be more reliable at assessing chronic stress compared to salivary, urinary, or blood and has been validated against the averages of multiple daily saliva (Xie et al., 2011) and urine measures (Sauvé et al., 2007). By collecting 3 centimeters (cm) of hair closest to the scalp, chronic cortisol levels spanning approximately the previous three months are captured (Meyer et al., 2014).

Both chronic and acute readings of cortisol have been associated with ACEs. For example, in the Cicchetti and Rogosch (2001) study, boys and girls aged 9.3 years on average with a history of both physical and sexual abuse had elevated salivary cortisol levels. Another study had similar findings where serum cortisol was significantly higher among female children with an average age of 13.4 years who were sexual abused (Simsek et al., 2016). Consistent with acute measures of cortisol among children, a study by Simmons et al. (2016) examining hair cortisol found that boys and girls with an average age of 9.5 years who had higher life-time exposure to a full array of ACEs including maltreatment (but excluding sexual abuse), severe household dysfunction, and other events were associated with elevated levels of chronic cortisol.

In contrast to the elevated levels of cortisol surrounding ACEs among children, studies that examined samples of older adults with past childhood traumatic experiences found that cortisol levels were lower than typical (Steudte et al., 2013; Hinkelmann et al., 2013; Yehuda et al., 1995). Further, the combination of past trauma and chronic cortisol levels below normal among adults were also associated with neuropsychiatric disorders such as post-traumatic stress disorder (PTSD) (Yehuda and Seckl, 2011). One study that examined a sample of middle-aged adults between the ages of 37–42 years who were mostly female, found that traumatized individuals (including but not exclusively limited to exposure to ACEs) with PTSD had lower levels of hair cortisol compared to non-PTSD and non-traumatized comparison groups (Steudte et al., 2013). Another study that examined males and females aged 41.7 years on average found associations between history of maltreatment and lower hair and salivary cortisol (Hinkelmann et al., 2013). Even among older adults between the ages of 56–72 years who were holocaust survivors, those also with a history of traumatic experiences and with PTSD had lower urinary cortisol compared to the non-PTSD survivors and non-traumatized comparison groups (Yehuda et al., 1995).

Interestingly, this difference in elevated cortisol levels among

children and lowered cortisol among adults who had past exposure to ACEs or other trauma was captured in a longitudinal study by Trickett et al. (2010) which examined cortisol trajectories over time from childhood and into adulthood among females who were sexually abused during childhood. They found significantly higher cortisol levels among the sexually abuse females throughout childhood which plateaued before age 20 but then significantly declined and was then lower compared to controls by young adulthood (Trickett et al., 2010). Importantly, cortisol levels among children and adults and the potential inflection point identified by Trickett et al. (2010) may also differ by sex. Several studies identified sex differences in which males had significantly higher levels of hair cortisol than females in childhood and in old age but did not specifically examine whether these differences were due to a differential response to exposure to ACEs or trauma among males and females (i.e., statistical moderation) (Simmons et al., 2016; Bossé et al., 2018). Moreover, there are no current studies that identify an inflection point where higher-than-normal cortisol levels transition to lower-than-normal levels and whether this inflection point differs between males and females.

### *1.4. Examining associations between inflammation and cortisol levels with ACEs*

The relationship between cortisol and inflammation is complex. Cortisol is a potent anti-inflammatory molecule that acts by binding to glucocorticoid receptors. Importantly, cortisol can modulate genes that are known to repress the critical pro-inflammatory transcription factors including NF-κB, among others (Webster et al., 2002). Activation of the HPA axis is also, in part, regulated by cytokines (Webster et al., 2002). Therefore, studies examining both inflammation and cortisol in relation to ACEs are needed to better understand biomarker trajectories between different arms of the stress response system.

One study, using data from the MIDUS II Biomarker Study (National Survey of Midlife Development in the United States), examined a cumulative measure of ACEs in relation to allostatic load using a composite measure of biological risk across seven systems that included HPA activity (including night-time urinary cortisol level) and inflammation (including CRP, IL-6, and other biomarkers) (Friedman et al., 2015). Among older adults, adjusting for educational attainment, social relationships, and health behaviors, they found that early life adversity predicted allostatic load and that the most dysfunctional subscales of the seven systems used to make up allostatic load were inflammation and cardiovascular function, followed by lipid metabolism. A second study also using data from the MIDUS II study examined contributions of ACEs and recent life events on inflammation at mid-life. ACEs were independently associated with higher levels of inflammation (composed of CRP, IL-6, and other biomarkers) in fully adjusted regression models that accounted for recent life events (Hostinar et al., 2015).

At older ages, these two studies using the MIDUS II data differed in direction of the effect of cortisol with ACEs. The study by Hostinar et al. (2015) found a significant negative correlation between ACEs and cortisol whereas the study by Friedman et al. (2015) reported a beta coefficient that was positive in the regression model. In addition, the study by Friedman et al. (2015) did not identify any sex-specific effects, whereas the study by Hostinar et al. (2015) found that being female was associated with exposure to a significantly greater types of ACEs and higher levels of both inflammation and cortisol. Based on this review, the relationship between inflammation and cortisol levels in relation to ACEs, when examined altogether, remains unclear.

Based on these findings, the current study examines the relationship between ACEs, chronic cortisol, and inflammation among young adults. The first objective of the study is to assess how various inflammatory biomarkers are related to each other to assess whether it is possible to create inflammation composite scales. This is accomplished by using principal component analysis (PCA) with the inflammatory biomarker data. This allows for the examination of how various inflammatory markers are associated and how these combinations of biomarkers operate. The second objective was to investigate the effect of ACEs on hair cortisol and these composite scales of inflammation. Given the consistent findings linking ACEs with inflammation reviewed above, those with higher exposure to ACEs are expected to have higher levels of inflammation. Those with higher exposure ACEs are also expected to have altered cortisol. Given the conflicting findings between ACEs and cortisol above, the direction in which ACEs predict cortisol may differ between males and females. As such, the third objective was to investigate whether the relationships between ACEs, inflammation, and cortisol were similar across males and females. Due to earlier pubertal maturity in females, the long-term, low levels of cortisol seen in adults may be seen in females at an earlier age compared to males. This corresponds to higher levels of inflammation but lower levels of cortisol in females compared to males.

## 2. Methods

### *2.1. Data collection*

The data for the study included a total of 326 young adults from the Niagara Longitudinal Heart Study (NLHS). The NLHS recruited and collected data from three previously conducted research projects from the Niagara region, Canada, from 2007 to 2012. The published NLHS study protocol by Wade et al. (2019) contains more detailed information of the study samples from these three previous projects. Out of the total sample, 232 participants had complete data on ACEs, chronic cortisol, and inflammatory biomarkers with 231 of these participants also having full covariate data. The high loss of sample participants in the dataset was due to 44% of males with missing cortisol due to their scalp hair being too short to provide a sample (Table a1 in Appendix). Participants were recruited using contact information from the three baseline studies over phone and social media. Data and tissue collection took place at the Human Hemodynamics Laboratory at Brock University. If the participant reported being recently sick or identified any recent antibiotic use, the appointment was rescheduled. Participants were also asked to fast, to avoid caffeine and alcohol for 4 h, and to avoid rigorous physical activity for 12 h prior to testing. The entire data collection procedure took between 3 ½ and 4 h to complete. After all anthropometric measurements and cardiovascular assessments were completed, a scalp hair sample was collected followed by blood collection from a licenced phlebotomist through the antecubital fossa prior to processing and analysis at the Inflammation & Immunity Laboratory, Brock University. Participants were then given a short break and a snack and beverage to reduce fatigue prior to completing a self-report questionnaire that contained the ACEs inventory and other measures used in the analysis. At the end of the lab visit participants were given a $100 (CDN) honorarium as compensation for participation and travel costs. In depth description of other procedures during data collection in the laboratory are published elsewhere (Wade et al., 2019). The study protocol was approved by the university research ethics board and all participants provided written informed consent (18–288 – WADE).

### *2.2. Measures*

#### *2.2.1. Chronic cortisol levels*

Chronic cortisol levels were measured through the scalp hair (Meyer et al., 2014). Estimating a growth rate of about 1 cm per month, 3 cm of harvested hair closest to the scalp was used for analysis providing a measure of 3-month chronic cortisol (Meyer et al., 2014). Each hair sample was minced with surgical grade scissors followed by three extraction steps. The residue from the extractions was mixed with 0.25 mL of a phosphate buffered saline solution to create a solution used in the salivary Cortisol ELISA kit (SLV-2930R, DRG International, Inc. Springfield, NJ) which was employed according to the manufacturer's recommended guidelines. The assay had a sensitivity of 0.09 ng/mL,

intra-assay coefficient of variation (CV) of 7.25%, and inter-assay CV of 6.22%.

#### 2.2.2. Inflammatory biomarkers

Inflammation was assessed at the protein level by quantifying concentrations of key inflammatory biomarkers in blood serum. Blood samples were collected and processed by centrifugation using a gold-cap blood collection tube (CABD367986L, VWR, Wayne, PA). The isolated sera were aliquoted to single-use volumes and stored at −80 °C until further analysis. Inflammatory biomarkers were measured on a MagPix Luminex platform using the magnetic bead-based multiplexing antibody assay (CAT # 171-AL001M, Bio-Rad, Hercules, California, USA) with an intra-assay CV of 5.18% and inter-assay CV of 3.56%. CRP levels were measured using the Quantikine CRP Immunoassay ELISA kit (DCRP00, R&D Systems, 614 McKinley Place NE Minneapolis, MN 55413). The assay had a sensitivity of 0.022 ng/mL, an intra-assay CV of 5.84%, and inter-assay CV of 14.59%.

#### 2.2.3. ACEs

The Childhood Trust Events Survey (CTES 2.0) was used to collect information on ACEs including maltreatment and household dysfunction adapted from the original Kaiser ACEs Study by Felitti et al. (1998) for use among children and adolescents (Childhood Trust, 2017). The CTES is a 26-item inventory that screens for exposure to traumatic childhood events occurring prior to the age of 18 years. For comparability, we included 14 items of the CTES that mirrored the 8 ACE domains identified in the original ACE study. These items focused on experiencing childhood maltreatment, including sexual (2 items), physical (1 item), and emotional abuse (2 items), and severe household dysfunction, including witnessing domestic violence (2 items), having someone in the household suffering from serious mental illness or suicidal ideation (2 items), neglect due to a family member being addicted to drugs or alcohol (2 items), or being incarcerated (1 item), and an unexpected separation from a parent or death of a family member (2 items). Any positive response on an item resulted in a positive coding for the specific domain.

#### 2.2.4. Covariates

This study included several covariates identified in previous literature as having potential links to chronic cortisol and inflammation. Consumption of non-steroidal anti-inflammatory drug (NSAID) exerts anti-inflammatory properties through inhibiting pro-inflammatory enzyme cyclooxygenase (Ong et al., 2007). As such, over-the-counter NSAID use included reported use of aspirin or ibuprofen over the past month for everyday or on most days and was coded dichotomously to indicate yes versus no. Usage of prescription medications including inhaled asthma medications including $\beta_2$ agonists, insulin, and hydrocortisone also have systemic anti-inflammatory effects (Karthikeyan et al., 2014; Sun et al., 2014; Barnes, 2006). As such, the usage of one or more of hydrocortisone, insulin, or asthma medications within the past month indicated prescription medication usage and was coded dichotomously to capture use versus non-use. Two dichotomous variables were constructed to identify smoking status comparing regular smokers and occasional smokers to non-smokers as the reference group. The 14-item Perceived Stress Scale (PSS) (Cohen et al., 1983) was used to capture perceptions of stress occurring within the last month. Some research suggests that a history of ACEs increases future sensitivity to stressful events which may impact measures of chronic hair cortisol and current levels of inflammatory biomarkers (Stowell et al., 2001). Scores for the PSS were summed and was included as a continuous variable. As individuals with a history of 4 or more ACEs exposures have a 1.5 times increased risk of being obese (BMI >35) (Felitti et al., 1998), BMI was included as a continuous variable using measures of height and weight. Finally, ACEs exposure is also associated with lower educational attainment (Merrick et al., 2018). As such, education was captured in an ordinal scale with least education starting from grade 9, grade 10, grade 11, grade 12, high school graduate, partial college or specialized training, standard college or university (undergraduate degree), to highest education, a graduate or professional training (graduate degree).

### 2.3. Data analysis

Cortisol and inflammatory biomarker data underwent data manipulation in preparation for the full analysis. Consistent with previous research methodology that controlled for outlier data, upper and lower cortisol and inflammatory biomarker outliers below the 1% and above the 99% of the distribution were Winsorized to the values at 1% and 99% respectively (Slopen et al., 2013; Hostinar et al., 2015; Bossé et al., 2018). Cortisol and inflammatory biomarker data underwent Box-Cox transformation to satisfy normality requirements prior to PCA and regression analysis (Table a2 in Appendix).

PCA with promax rotation was conducted to identify principal components that account for most of the variance in the inflammatory biomarker data. A parallel simulation analysis (using 1000 simulated iterations) and assessment of eigenvalues of the correlation matrix were used to identify the number of components to retain. The inflammation composite variables were created by extracting the component scores from the PCA.

The full analysis examining the relationships between ACEs, cortisol, and composite measures of inflammation proceeded in a series of steps. First, an attrition analysis examined potential for bias in deleting cases with missing data This analysis focused principally on chronic cortisol as many males did not have long enough scalp hair to provide a sample. Second, a correlation analysis was conducted across all variables included in the analysis. Third, hierarchical regression equations were examined to estimate associations between ACEs, inflammation, and cortisol while controlling for covariates to examine independent effects as well as interactions between ACEs x sex.

Finally, to further assess potential bias due to missing cortisol data resulting from an inability to get hair samples, the hierarchical regression equations listed above were repeated to include a set of conditionally relevant variables to allow participants with no data on cortisol to be retained in the full analysis rather than be excluded by the list wise deletion technique used in most regression algorithms. This technique creates two variables: 1) a dichotomous variable to code those with and without cortisol data, and 2) a variable measuring cortisol levels that is centered around its mean score so that the mean score equalled zero that is then multiplied by the dichotomous variable. This allows those with missing data on cortisol to be included in the analysis to test whether there is a mean difference between those with and without cortisol on inflammation while simultaneously testing whether differences in cortisol are related to differences in inflammation (see Cohen for details on this regression technique (Cohen, 2003)). All statistical analyses were performed on Statistical Analysis Software version 9.4.

## 3. Results

232 participants that had available ACEs, inflammation, and cortisol data were included in the full analysis. Analyses including covariate data included 231 participants as only 1 participant had missing covariate data. Most lost cases were due to missing cortisol data. In fact, 44% of males were removed from the analysis compared to only 7% of females as they did not have sufficient scalp hair to obtain a hair cortisol sample (Table a1 in Appendix). The average age of the final sample was 22.4 (SD = 1.9) years, with 50% of participants are between 21 and 24 years. Males represented 34.48% of the entire sample. An attrition analysis revealed that these missing cases were significantly more likely to report lower NSAID's use, perceived stress, and mean ACEs scores but higher CRP levels, and were more likely to report being a daily smoker (Table a1 in Appendix).

### 3.1. Assessing factor retention

Initial assessment of eigenvalues of the correlation matrix indicated that only the first three principal components should be retained (Fig. 1). The first three principal components accounted for 77% of the total variance within the biomarker data (Table 1) (also see Table 2).

### 3.2. Creating inflammation composite variables using PCA

PCA was applied to identify common components that accounted for most of the variance in the inflammatory biomarker data. A component loading 0.60 or above was considered strong and was the threshold used to determine if a biomarker loaded into the component. The first composite variable included sTNFr1, sTNFr2, and IFNγ. The second composite variable included sIL-6Rα and gp130. The third composite variable included CRP, IL-6, and TNFα (Table 2).

### 3.3. Correlation analysis

ACEs were positively correlated with low-grade inflammation, age, sex, NSAID's use, daily smoking, perceived stress, and BMI. Cortisol was positively correlated with prescription medication usage. Low-grade inflammation was positively correlated with age, NSAID's use, daily smoking, and PSS while BMI was negatively correlated with males compared to females. Soluble TNF receptors were positively correlated with soluble IL-6 receptors, low-grade inflammation, and BMI were negatively correlated with males compared to females. Soluble IL-6 receptors were positively correlated with males compared to females and negatively correlated to NSAID's use. Males were positively correlated with daily smoking but negatively correlated with perceived stress compared to females (Table 3).

### 3.4. Regression analysis

The regression analyses examining hair cortisol found that ACEs did not predict hair cortisol levels (Table a3, model 1 in Appendix). Being male significantly predicted higher hair cortisol levels while NSAID's use significantly predicted lower hair cortisol levels (Table a3, model 1 in Appendix). Further analysis that included the ACEs x sex interaction variable was not significant in predicting hair cortisol (Table a3, model 2 in Appendix).

The following hierarchical regressions examined associations between ACEs and the three composite measures of inflammation (soluble TNF receptors/IFNγ, soluble IL-6 receptors, and low-grade inflammation). Low-grade inflammation including IL-6, TNFα, and CRP have been established as the primary focus in most ACEs research on inflammation. Soluble IL-6 receptors included the soluble receptors critical for IL-6 signalling. Similarly, Soluble TNF receptors/IFNγ contained soluble receptors critical for TNFα signalling in addition to IFNγ, an important cytokine in the context of psychological stress. Higher exposure to ACEs significantly predicted higher low-grade inflammation levels (Table 4, Model 1) but did not significantly predict either of the soluble receptor composite measures (Table a4, Table a5). In fact, the fully adjusted models explained 31% of the variance of low grade inflammation but only 6%–8% of the variance of both soluble receptor composite measures. Being female, a daily smoker, and having a higher BMI also significantly predicted higher low-grade inflammation levels (Table 4, Model 1). There was no evidence of a sex interaction on the relationship between ACEs and any of the inflammation composite variables (Table 4, Table a4, Table a5). Lastly, being male was significantly associated with lower soluble TNF receptor levels while BMI was significantly associated with higher soluble TNF receptor levels (Table a4, Model 1 in Appendix).

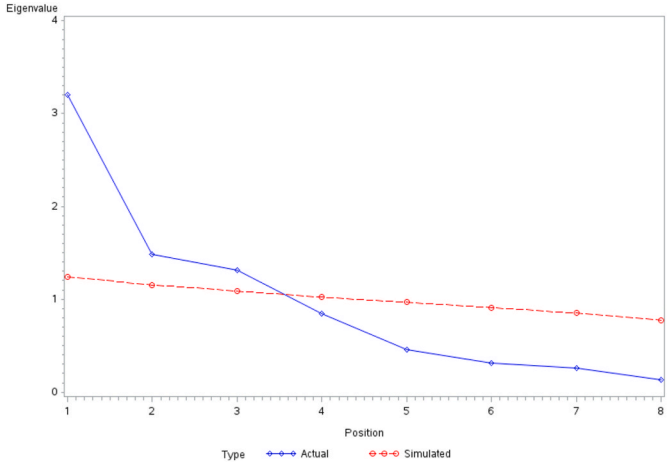



**Fig. 1.** Actual eigenvalues by median simulated eigenvalues indicate 3 components to retain.

**Table 1**
Percent of variance explained by each factor.

| Factor | Eigenvalue | Proportion Percent | Cumulative Percent |
|---|---|---|---|
| 1 | 3.51 | 0.44 | 0.44 |
| 2 | 1.53 | 0.19 | 0.63 |
| 3 | 1.08 | 0.14 | 0.77 |
| 4 | 0.82 | 0.10 | 0.87 |
| 5 | 0.42 | 0.05 | 0.92 |
| 6 | 0.28 | 0.03 | 0.95 |
| 7 | 0.25 | 0.03 | 0.99 |
| 8 | 0.11 | 0.01 | 1.00 |

**Table 2**
Factor loadings from principal component analysis with promax rotation.

| | Factor 1 | Factor 2 | Factor 3 |
|---|---|---|---|
| [1]CRP | −0.23 | 0.02 | **0.86** |
| [2]IL-6 | 0.36 | −0.14 | **0.71** |
| [3]sIL-6Rα | 0.20 | **0.83** | −0.02 |
| [4]gp130 | −0.12 | **0.95** | 0.05 |
| [5]TNFα | 0.18 | 0.21 | **0.60** |
| [6]sTNFr1 | **0.90** | −0.10 | 0.03 |
| [7]sTNFr2 | **0.95** | −0.02 | 0.01 |
| [8]IFNγ | **0.81** | 0.21 | −0.09 |

[1] C-Reactive Protein.
[2] Interleukin-6.
[3] Tumour Necrosis Factor α
[4] Interleukin-6 receptor α
[5] Glycoprotein 130.
[6] Soluble tumour necrosis factor receptor 1.
[7] Soluble tumour necrosis factor receptor 2.
[8] Interferon gamma.

### 3.5. Conditionally relevant variables analysis

Further to the attrition analysis above, we assessed the effect of losing so many males due to missing cortisol data. This final analysis included both those with and without data on cortisol using conditionally relevant variables. This procedure examined all cases that included both ACEs and blood samples to measure inflammation even though they were missing data on cortisol. The results were consistent with the regression analyses above indicating that these missing cases did not have an appreciable effect on the relationship between ACEs and the three composite measures of inflammation (Table a6)

**Table 3**
Correlation matrix of all variables (n = 232).

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1. [1]ACEs** | – | | | | | | | | | | | | | |
| **2. Cortisol** | −0.05 | – | | | | | | | | | | | | |
| **3. [2]Soluble TNF receptors/IFNγ** | 0.05 | −0.03 | – | | | | | | | | | | | |
| **4. [2]Soluble IL-6 receptors** | 0.01 | 0.05 | **0.32** | - | | | | | | | | | | |
| **5. [4]Low-grade inflammation** | **0.30** | −0.03 | **0.42** | 0.12 | - | | | | | | | | | |
| **6. Age** | **0.15** | 0.02 | −0.09 | −0.07 | **0.21** | – | | | | | | | | |
| **7. [5]Sex (male)** | **−0.16** | 0.07 | **−0.18** | **0.18** | **−0.19** | −0.04 | - | | | | | | | |
| **8. [6]NSAIDs** | **0.15** | 0.01 | 0.11 | **−0.14** | **0.18** | 0.04 | −0.11 | - | | | | | | |
| **9. [7]Presc. Med.** | 0.11 | 0.12 | −0.04 | −0.06 | 0.01 | 0.04 | −0.10 | 0.06 | - | | | | | |
| **10. [8]Daily smoker** | **0.24** | 0.02 | 0.04 | 0.09 | **0.19** | **0.15** | **0.14** | 0.02 | −0.06 | – | | | | |
| **11. [9]Occasional smoker** | 0.07 | −0.02 | 0.01 | 0.03 | 0.02 | 0.10 | 0.12 | 0.12 | −0.06 | −0.06 | – | | | |
| **12. [10]PSS.** | **0.30** | −0.05 | 0.05 | −0.06 | **0.16** | 0.06 | **−0.17** | 0.10 | 0.09 | 0.11 | −0.01 | – | | |
| **13. Body mass index** | **0.14** | −0.09 | **0.16** | −0.02 | **0.44** | 0.05 | −0.04 | **0.14** | −0.01 | 0.01 | **0.14** | 0.05 | – | |
| **14. [11]Education** | 0.01 | 0.01 | 0.02 | −0.04 | 0.10 | **0.42** | −0.09 | −0.07 | −0.01 | 0.01 | 0.01 | −0.10 | 0.06 | – |
| **Mean (Percentage)** | 2.46 | 39.28 | −0.12 | 0.02 | −0.01 | 22.39 | (34.49) | (41.38) | (5.60) | (5.63) | (5.19) | 24.63 | 25.80 | 6.06 |
| **SD** | 2.14 | 78.03 | 1.01 | 1.03 | 1.02 | 1.91 | – | – | – | – | – | 6.36 | 6.20 | 1.17 |

Bolded values $p < 0.05$, two tailed.
[1] Adverse childhod experiences (ACEs).
[2] Soluble TNF receptors/IFNγ – includes Soluble tumour necrosis factor receptor 1 (sTNFr1), Soluble tumour necrosis factor receptor 2 (sTNFr2) and Interferon gamma (IFNγ).
[3] Soluble IL-6 receptors – includes Interleukin-6 receptor α (sIL-6Rα), Glycoprotein 130 (gp130).
[4] Low-grade inflammation – includes C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumour Necrosis Factor α (TNFα).
[5] Reference category is female.
[6] Nonsteroidal anti-inflammatory drug (NSAID) – includes aspirin or ibuprofen.
[7] Prescription medication usage (Presc. Med.) – includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[8] Reported daily smoker – reference category is occasional smoker and non-smoker.
[9] Reported occasional smoker – reference category is daily smoker and non-smoker.
[10] Perceived stress scale (PSS).
[11] N = 231.

**Table 4**
OLS regression of low-grade inflammation on ACEs score controlling for covariates, cortisol, and ACEs x Sex (n = 231).

| | Model 1 | | | | Model 2 | | | | Model 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | b | p-value | 95% CI | | b | p-value | 95% CI | | b | p-value | 95% CI | |
| **ACEs[1]** | **0.07** | **0.02** | **0.01** | **0.13** | **0.07** | **0.02** | **0.01** | **0.13** | **0.06** | **0.02** | **0.01** | **0.13** |
| **Sex (male)[2]** | **−0.33** | **0.01** | **−0.59** | **−0.08** | **−0.33** | **0.01** | **−0.59** | **−0.08** | **−0.41** | **0.02** | **−0.77** | **−0.05** |
| **NSAIDs usage[3]** | 0.17 | 0.16 | −0.07 | 0.41 | 0.17 | 0.17 | −0.07 | 0.40 | 0.17 | 0.16 | −0.07 | 0.41 |
| **Presc. Med.[4]** | −0.09 | 0.73 | −0.58 | 0.41 | −0.10 | 0.70 | −0.60 | 0.40 | −0.09 | 0.74 | −0.59 | 0.42 |
| **Daily smoker[5]** | **0.72** | **0.01** | **0.20** | **1.24** | **0.72** | **0.01** | **0.19** | **1.24** | **0.69** | **0.01** | **0.16** | **1.22** |
| **Occasional smoker[6]** | −0.13 | 0.62 | −0.66 | 0.39 | −0.13 | 0.62 | −0.66 | 0.39 | −0.16 | 0.55 | −0.70 | 0.37 |
| **PSS[7]** | 0.01 | 0.41 | −0.01 | 0.03 | 0.01 | 0.40 | −0.01 | 0.03 | 0.01 | 0.39 | −0.01 | 0.03 |
| **Body mass index** | **0.07** | **0.01** | **0.05** | **0.08** | **0.07** | **0.01** | **0.05** | **0.08** | **0.07** | **0.01** | **0.05** | **0.08** |
| **Education** | 0.07 | 0.18 | −0.03 | 0.17 | 0.07 | 0.18 | −0.03 | 0.16 | 0.07 | 0.17 | −0.03 | 0.17 |
| **Cortisol** | | | | | 0.01 | 0.70 | −0.01 | 0.01 | 0.01 | 0.73 | −0.01 | 0.01 |
| **ACEs x Sex** | | | | | | | | | 0.04 | 0.55 | −0.09 | 0.16 |
| **Intercept** | −2.47 | 0.01 | −3.38 | −1.55 | −2.49 | 0.01 | −3.41 | −1.56 | −2.47 | 0.01 | −3.40 | −1.55 |
| **R-square** | 0.31 | | | | 0.31 | | | | 0.31 | | | |

*$p < 0.05$, two tailed.
[1] Adverse childhood experiences (ACEs).
[2] Reference category is female.
[3] Nonsteroidal anti-inflammatory drug (NSAID) – includes aspirin or ibuprofen.
[4] Prescription medication usage (Presc. Med.) – includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[5] Reported daily smoker – reference category is occasional smoker and non-smoker.
[6] Reported occasional smoker – reference category is daily smoker and non-smoker.
[7] Perceived stress scale (PSS).

## 4. Discussion

This study addresses a notable gap in the literature examining the relationships between ACEs and both inflammation and chronic cortisol among young adults in their early twenties. This study captured a broad range of adversities including both childhood maltreatment and severe household dysfunction. From the full dataset, the average ACEs score among individuals was close to 3 ACEs exposures, with over 80% of the full dataset to have reported exposure to at least 1 ACEs. This is somewhat higher than recent longitudinal estimates based on over 40,000 participants from the Canadian Longitudinal Study on Aging where 61.6% of participants reported exposure to at least 1 ACEs (Joshi et al., 2021). The higher exposure to ACEs in the current study reported could be due to variations in the types of ACEs captured as well as the different ages of the sample affecting recall to childhood events.

In fully adjusted models, the analysis found that higher ACEs was associated with low-grade inflammation but not with hair cortisol. PCA was applied to explore the inter-relatedness among multiple biomarkers to create composite inflammation variables that were then examined with ACEs and cortisol. These composite measures were built because

analyses that place individual biomarkers as the outcome variable in regression models present certain challenges. Specifically, studies that only examine CRP and IL-6 have reduced interpretability as these cytokines are involved in many inflammatory processes such that they are considered unambiguous biomarkers unless examined with other markers in the same analysis (Del Giudice and Gangestad, 2018). Furthermore, studies that include many biomarkers using individual regression models for each biomarker increases type 1 error in the analysis and the need to consider corrections for multiple tests (see Streiner, 2015). The PCA used in this analysis not only reduced the number of models but also provided context as to which biomarkers were related to one another. This data driven approach aligned with the biological plausibility of CRP, IL-6, and TNFα forming a composite component in which elevation of these three biomarkers are indicative of low-grade inflammation. Soluble IL-6 and TNFα receptors loaded into separate components which was expected as inflammatory states could contain higher sIL-6Rα and low gp130 in cases of pro-inflammatory states and low sIL-6Rα and high gp130 in cases of anti-inflammatory states (Del Giudice and Gangestad, 2018). IFNγ loading with the soluble TNF receptors was unexpected given that this cytokine plays a role in reactions to acute psychological-based stressors and is linked to elevated TNFα levels (Kim and Maes, 2003). More investigation is needed to understand long-term patterns of IFNγ and how this cytokine interacts with other biomarkers of interest.

The normality assumptions for the inflammation composite variables used as outcome variables was met only with the low-grade inflammation composite. Soluble IL-6 and TNFα composites approximated normality but were significantly skewed in the Anderson-Darling normality test. Furthermore, prior to PCA, the majority of the individually transformed inflammatory biomarkers also showed a significant skewness from a normal distribution based on the Anderson-Darling normality test.

ACEs was not associated with hair cortisol. This finding was unexpected as the study by Trickett et al. (2010) found that females with a history of sexual abuse had lower than typical cortisol levels. This difference could be due the inclusion of physical and emotional maltreatment, and household dysfunction in the measure of ACEs, as opposed to strictly examining those with sexually abused females (Trickett et al., 2010). However, the ACEs x sex interaction was a nonsignificant predictor of hair cortisol levels. This finding was unexpected as it was hypothesized that at higher exposure to ACEs and at earlier pubertal maturation, females would trend towards lower cortisol levels compared to similar aged males which would trend towards higher hair cortisol in this age group. The imbalance of male versus female participants in the final dataset could have affected this analysis and hinder the opposite directional effect between the sexes.

As predicted, ACEs was associated with low-grade inflammation. This finding is consistent with the majority of previous literature identifying a significant association between ACEs and CRP, IL-6, and TNFα individually across young and older samples. The direction of this association is consistent with the reviewed literature where higher exposure to ACEs predicted higher levels of CRP, IL-6, and TNFα. Several covariates included in the multiple regression analysis were also associated with the composite measures of low-grade inflammation and soluble receptors. Higher BMI significantly predicted both higher levels of soluble TNF receptors and low-grade inflammation. In other studies, BMI was also found to be associated with ACEs (Aas, 2017) and is a strong predictor of low-grade inflammation (Park et al., 2005), thus, the relationship between ACEs and low-grade inflammation could be partially mediated through BMI. In one study, higher levels of ACEs predicted higher CRP levels initially but disappeared after the inclusion of BMI in the regression model (Aas, 2017), suggesting that the effect of current BMI may be one mechanism linking ACEs to inflammation. Moreover, being male significantly predicted lower soluble TNF receptors/IFNγ and low-grade inflammation but higher soluble IL-6 receptors suggesting that ACEs may affect individuals differently based on their sex across inflammatory biomarkers, at least among this age cohort.

While this study adds to the current body of literature examining the relationship between exposure to child adversity and subsequent levels of hair cortisol and inflammation, there are notable limitations. First, the final dataset was substantially and disproportionately reduced as many males did not have hair long enough to provide a sample for cortisol analysis. Unfortunately, current hair styles and fashion had an impact on sample collection. However, the attrition analysis and conditionally relevant variable analysis lends support to the findings and suggests that differences on the effect between ACEs on measures of inflammation due to missing hair cortisol were minimal. Second, information collected on ACEs was done retrospectively after age 18 for all participants. However, as these data were collected during young adulthood, it is less likely to be prone to memory and recall issues than studies that examine middle and older-aged adults. Finally, this cross-sectional study was unable to ascertain if the link between ACEs to low-grade inflammation is chronic/long-term and was limited in its ability to examine potential mediation between ACEs and low-grade inflammation through BMI. Notwithstanding these limitations, this study was able to examine a broad array of inflammatory biomarkers—beyond most previous work—to identify if any are associated with ACEs. Based on the current literature search gp130, sTNFr1, and sTNFr2 were examined in only two prior ACEs studies (Bertone-Johnson et al., 2012, Aas, 2017), and IFNγ in one ACEs study (Lopes et al., 2012). As such, further investigation of soluble TNF and IL-6 receptors and other biomarkers are needed to better understand associations between inflammation and ACEs exposure.

To conclude, this study adds further evidence to the relationship between ACEs and inflammation among young adults while also considering hair cortisol levels. This study was also the first to examine a broadened scope of the typical biomarkers used in the composition of inflammation in relation to ACEs. Consistent with current ACEs literature, higher exposure to ACEs were found to be associated with higher levels of low-grade inflammation. More studies are required to examine if soluble TNF and IL-6 receptors are related to ACEs across the lifespan. Therefore, future research on different age cohorts and longitudinally across the life-course would help identify the presence, direction, and amount of change in biomarker trajectory over time.

## 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.

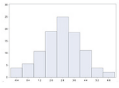
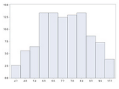
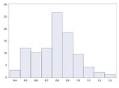
## Appendix

**Table a1**
Attrition Analysis

| | Total (n = 306) | Cortisol (232) | Without cortisol (74) | t, χ2 | df | p-value |
|---|---|---|---|---|---|---|
| **Sex (n,%)** | | | | | | |
| **Male** | 143 | 80 (55.94) | 63 (44.05) | 57.82 | 1 | **0.01*** |
| **Female** | 163 | 152 (93.25) | 11 (6.75) | | | |
| **Age (mean, SD)** | 22.48 (1.80) | 22.39 (1.91) | 22.74 (1.40) | 1.71 | 166.1 | 0.09 |
| **[1]NSAID usage (n, %)** | | | | | | |
| **Yes** | 117 | 96 (82.05) | 21 (17.95) | 4.02 | 1 | **0.05*** |
| **No** | 189 | 136 (71.96) | 53 (28.04) | | | |
| **[2]Presc. Med. (n, %)** | | | | | | |
| **Yes** | 16 | 13 (81.25) | 3 (18.75) | 0.27 | 1 | 0.60 |
| **No** | 290 | 219 (69.07) | 71 (30.93) | | | |
| **[3]Smoking (n, %)** | | | | | | |
| **Daily smoker** | 20 | 13 (65.00) | 7 (35.00) | 7.87 | 2 | **0.02*** |
| **Occasional smoker** | 22 | 12 (54.55) | 10 (45.45) | | | |
| **Non smoker** | 262 | 206 (78.63) | 56 (21.37) | | | |
| **[4]PSS (mean, SD)** | 24.00 (6.36) | 24.63 (6.36) | 22.01 (6.00) | −3.12 | 304 | **0.01*** |
| **Body mass index** | 25.89 (6.37) | 25.80 (6.20) | 26.17 (6.92) | 0.43 | 304 | 0.67 |
| **Education** | 6.02 (1.17) | 6.06 (1.17) | 5.89 (1.16) | −1.11 | 303 | 0.27 |
| **[5]ACEs** | | | | | | |
| **0** | 58 | 39 | 19 | 3.44 | 8 | 0.90 |
| **1** | 78 | 60 | 18 | | | |
| **2** | 55 | 42 | 13 | | | |
| **3** | 37 | 30 | 7 | | | |
| **4** | 25 | 19 | 6 | | | |
| **5** | 18 | 14 | 4 | | | |
| **6** | 12 | 10 | 2 | | | |
| **7** | 18 | 14 | 4 | | | |
| **8** | 5 | 4 | 1 | | | |
| **Mean ACEs** | 2.38 (2.13) | 2.72 (2.20) | 2.04 (2.06) | −2.27 | 246 | **0.02*** |
| | **Total (n = 306)** | **Cortisol (232)** | **Without cortisol (74)** | **t** | **df** | **p-value** |
| **CRP** | 3639.61 (551.10) | 4001.90 (5911.10) | 2503.7 (3821.50) | −2.54 | 196.66 | **0.01*** |
| **IL-6** | 0.49 (0.56) | 0.48 (0.57) | 0.52 (0.53) | 0.60 | 304 | 0.55 |
| **sIL-6Rα** | 6484.19 (2635.60) | 6539.90 (2734.00) | 6309.40 (2308.30) | −0.65 | 304 | 0.51 |
| **gp130** | 50168.02 (15775.22) | 50609.20 (16422.00) | 48784.80 (13557.90) | −0.87 | 304 | 0.38 |
| **TNFα** | 6.25 (4.91) | 9.82 (28.47) | 7.21 (4.88) | −1.11 | 177.72 | 0.27 |
| **sTNFr1** | 1245.70 (622.84) | 1384.80 (551.60) | 1606.10 (926.50) | 1.81 | 84.90 | 0.07 |
| **sTNFr2** | 461.25 (209.12) | 530.70 (174.10) | 579.20 (231.20) | 1.72 | 97.16 | 0.13 |
| **IFNγ** | 24.52 (16.41) | 30.50 (15.67) | 26.90 (13.34) | −1.60 | 222 | 0.11 |

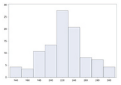
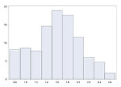
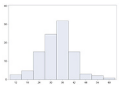
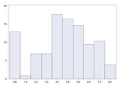
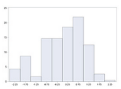
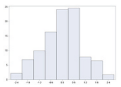
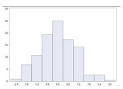
*$p < 0.05$, two tailed.
[a]Nonsteroidal anti-inflammatory drug – includes aspirin or ibuprofen.
[b]Prescription medication usage (Presc. Med.) – includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[c]Smoking variable has 2 missing data.
[d]Perceived stress scale.
[e]Adverse childhood experiences (ACEs).

**Table a2**
Normality assessment for regression analysis and principal component

| | [1]Skewness | [2]Kurtosis | [3]Z-score (Skewness) | [3]Z-score (Kurtosis) | Anderson-Darling p-value | Histogram |
|---|---|---|---|---|---|---|
| Cortisol | 0.01 | −0.13 | 0.04 | −0.42 | 0.25 |  |
| CRP | −0.01 | −0.82 | −0.03 | −2.57 | **0.04*** |  |
| IL-6 | 0.06 | −0.20 | 0.19 | −0.63 | **0.01*** |  |
| sIL6Rα | −0.16 | −0.37 | −0.50 | −1.17 | 0.08 | |

(*continued on next page*)

**Table a2** (*continued*)

| | [1]Skewness | [2]Kurtosis | [3]Z-score (Skewness) | [3]Z-score (Kurtosis) | Anderson-Darling p-value | Histogram |
|---|---|---|---|---|---|---|
| gp130 | −0.05 | 0.14 | −0.17 | 0.45 | **0.01*** |  |
| TNFα | −0.02 | −0.58 | −0.07 | −1.82 | **0.04*** |  |
| sTNFr1 | 0.10 | 0.70 | 0.33 | 2.21 | 0.21 |  |
| sTNFr2 | 0.09 | 0.62 | 0.28 | 1.95 | **0.01*** |  |
| IFNγ | −0.35 | −0.69 | −1.08 | −2.16 | **0.01*** |  |
| Factor1 | −0.52 | −0.38 | −3.24 | −1.20 | **0.01*** |  |
| Factor2 | −0.24 | −0.10 | −1.51 | −0.31 | **0.01*** |  |
| Factor3 | 0.09 | −0.03 | 0.56 | −0.10 | 0.25 |  |

[1]Standard Error of Skewness = 0.16.
[2]Standard Error of Kurtosis = 0.32.
[3]Z-values above 3.29 indicates violation of normality.

**Table a3**
OLS regression of Cortisol on ACEs while controlling for covariates (n = 231)

| | Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | b | p-value | 95% CI | | b | p-value | 95% CI | |
| **ACEs[1]** | 0.01 | 0.89 | −0.09 | 0.10 | 0.01 | 0.82 | −0.10 | 0.12 |
| **Sex (male)[2]** | **0.54** | **0.01** | **0.13** | **0.94** | **0.58** | **0.04** | **0.02** | **1.15** |
| **NSAIDs usage[3]** | **−0.39** | **0.04** | **−0.76** | **−0.01** | **−0.39** | **0.04** | **−0.77** | **−0.01** |
| **Presc. Med.[4]** | 0.64 | 0.11 | −0.15 | 1.43 | 0.63 | 0.12 | −0.16 | 1.43 |
| **Daily smoker[5]** | 0.29 | 0.49 | −0.54 | 1.11 | 0.30 | 0.47 | −0.53 | 1.14 |
| **Occasional smoker[6]** | 0.39 | 0.35 | −0.44 | 1.23 | 0.41 | 0.34 | −0.44 | 1.26 |
| **PSS[7]** | 0.01 | 0.71 | −0.02 | 0.04 | 0.01 | 0.72 | −0.02 | 0.04 |
| **Body mass index** | 0.01 | 0.62 | −0.02 | 0.04 | 0.01 | 0.62 | −0.02 | 0.04 |

(*continued on next page*)

**Table a3** (*continued*)

| | Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | b | p-value | 95% CI | | b | p-value | 95% CI | |
| **Education** | 0.01 | 1.00 | −0.16 | 0.16 | 0.01 | 0.99 | −0.16 | 0.15 |
| **ACEs x Sex** | | | | | −0.02 | 0.82 | −0.22 | 0.18 |
| **Intercept** | 2.26 | 0.01 | 0.81 | 3.72 | 2.25 | 0.01 | 0.79 | 3.71 |
| **R-square** | 0.07 | | | | 0.07 | | | |

*p < 0.05, two tailed.
[1]Adverse childhood experiences (ACEs).
[2]Reference category is female.
[3]Nonsteroidal anti-inflammatory drug – includes aspirin or ibuprofen.
[4]Prescription medication usage (Presc. Med.)– includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[5]Reported daily smoker – reference category is occasional smoker and non-smoker.
[6]Reported occasional smoker – reference category is daily smoker and non-smoker.
[7]Perceived stress scale. b (Unstandardized regression coefficients), 95% CI (95% confidence intervals).

**Table a4**
OLS regression of Soluble TNF receptors/IFNγ on ACEs score controlling for covariates, cortisol, and ACEs x Sex (n = 231).

| | Model 1 | | | | Model 2 | | | | Model 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | b | p-value | 95% CI | | b | p-value | 95% CI | | b | p-value | 95% CI | |
| **ACEs**[1] | −0.01 | 0.77 | −0.08 | 0.06 | −0.01 | 0.76 | −0.08 | 0.06 | −0.04 | 0.26 | −0.12 | 0.03 |
| **Sex (male)**[2] | **−0.39** | **0.01** | **−0.68** | **−0.09** | **−0.39** | **0.01** | **−0.68** | **−0.09** | **−0.64** | **0.01** | **−1.05** | **−0.23** |
| **NSAIDs usage**[3] | 0.15 | 0.28 | −0.12 | 0.43 | 0.15 | 0.28 | −0.12 | 0.43 | 0.17 | 0.23 | −0.10 | 0.44 |
| **Presc. Med.**[4] | −0.25 | 0.39 | −0.83 | 0.32 | −0.25 | 0.40 | −0.83 | 0.33 | −0.21 | 0.48 | −0.79 | 0.37 |
| **Daily smoker**[5] | 0.26 | 0.39 | −0.34 | 0.86 | 0.26 | 0.39 | −0.34 | 0.86 | 0.18 | 0.56 | −0.43 | 0.79 |
| **Occasional smoker**[6] | −0.03 | 0.92 | −0.64 | 0.58 | −0.03 | 0.92 | −0.64 | 0.58 | −0.13 | 0.68 | −0.75 | 0.48 |
| **PSS**[7] | 0.01 | 0.85 | −0.02 | 0.02 | 0.01 | 0.85 | −0.02 | 0.02 | 0.01 | 0.79 | −0.02 | 0.02 |
| **Body mass index** | **0.02** | **0.04** | **0.01** | **0.04** | **0.02** | **0.04** | **0.01** | **0.04** | **0.02** | **0.04** | **0.01** | **0.04** |
| **Education** | 0.01 | 0.96 | −0.11 | 0.12 | 0.01 | 0.96 | −0.11 | 0.12 | 0.01 | 0.90 | −0.11 | 0.12 |
| **Cortisol** | | | | | −0.01 | 0.92 | −0.01 | 0.01 | −0.01 | 0.84 | −0.01 | 0.01 |
| **ACEs x Sex** | | | | | | | | | 0.13 | 0.08 | −0.01 | 0.27 |
| **Intercept** | −0.69 | 0.20 | −1.74 | 0.37 | −0.68 | 0.21 | −1.75 | 0.38 | −0.63 | 0.25 | −1.69 | 0.43 |
| **R-square** | 0.07 | | | | 0.07 | | | | 0.08 | | | |

*p < 0.05, two tailed.
[1]Adverse childhood experiences (ACEs).
[2]Reference category is female.
[3]Nonsteroidal anti-inflammatory drug (NSAID) – includes aspirin or ibuprofen.
[4]Prescription medication usage (Presc. Med.) – includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[5]Reported daily smoker – reference category is occasional smoker and non-smoker.
[6]Reported occasional smoker – reference category is daily smoker and non-smoker.
[7]Perceived stress scale (PSS).

**Table a5**
OLS regression of Soluble IL-6 receptors on ACEs score controlling for covariates, cortisol, and ACEs x Sex (n = 231)

| | Model 1 | | | | Model 2 | | | | Model 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | b | p-value | 95% CI | | b | p-value | 95% CI | | b | p-value | 95% CI | |
| **ACEs**[1] | 0.02 | 0.58 | −0.05 | 0.09 | 0.02 | 0.56 | −0.05 | 0.09 | 0.05 | 0.20 | −0.03 | 0.13 |
| **Sex (male)**[2] | **0.31** | **< 0.05** | **0.01** | **0.61** | 0.30 | 0.05 | 0.01 | 0.60 | **0.54** | **0.01** | **0.12** | **0.96** |
| **NSAIDs usage**[3] | −0.27 | 0.06 | −0.55 | 0.01 | −0.27 | 0.06 | −0.56 | 0.01 | **−0.29** | **0.04** | **−0.57** | **−0.01** |
| **Presc. Med.**[4] | −0.15 | 0.62 | −0.73 | 0.44 | −0.17 | 0.57 | −0.77 | 0.42 | −0.21 | 0.48 | −0.80 | 0.38 |
| **Daily smoker**[5] | 0.30 | 0.33 | −0.31 | 0.92 | 0.30 | 0.34 | −0.32 | 0.91 | 0.37 | 0.24 | −0.25 | 0.99 |
| **Occasional smoker**[6] | 0.11 | 0.73 | −0.51 | 0.73 | 0.11 | 0.72 | −0.51 | 0.73 | 0.20 | 0.53 | −0.43 | 0.83 |
| **PSS**[7] | −0.01 | 0.49 | −0.03 | 0.01 | −0.01 | 0.50 | −0.03 | 0.01 | −0.01 | 0.45 | −0.03 | 0.01 |
| **Body mass index** | 0.01 | 0.99 | −0.02 | 0.02 | 0.01 | 0.97 | −0.02 | 0.02 | 0.01 | 0.94 | −0.02 | 0.02 |
| **Education** | −0.04 | 0.48 | −0.16 | 0.07 | −0.04 | 0.48 | −0.16 | 0.07 | −0.05 | 0.44 | −0.16 | 0.07 |
| **Cortisol** | | | | | 0.01 | 0.49 | −0.01 | 0.01 | 0.01 | 0.43 | −0.01 | 0.01 |
| **ACEs x Sex** | | | | | | | | | −0.12 | 0.11 | −0.27 | 0.03 |
| **Intercept** | 0.42 | 0.45 | −0.67 | 1.50 | 0.38 | 0.50 | −0.71 | 1.47 | 0.33 | 0.56 | −0.76 | 1.41 |
| **R-square** | 0.06 | | | | 0.06 | | | | 0.07 | | | |

*p < 0.05, two tailed.
[1]Adverse childhood experiences (ACEs).
[2]Reference category is female.
[3]Nonsteroidal anti-inflammatory drug (NSAID) – includes aspirin or ibuprofen.
[4]Prescription medication usage (Presc. Med.) – includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[5]Reported daily smoker – reference category is occasional smoker and non-smoker.

[6]Reported occasional smoker – reference category is daily smoker and non-smoker.
[7]Perceived stress scale (PSS).

**Table a6**
OLS regression of Soluble TNF receptors/IFNγ, Soluble IL-6 receptors, and low-grade inflammation on ACEs while controlling for covariates and conditionally relevant variables related to cortisol (n = 305).

| | Soluble TNF receptors[1] | | | | Soluble IL-6 receptors[2] | | | | low-grade inflammation [3] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | b | p-value | 95% CI | | b | p-value | 95% CI | | b | p-value | 95% CI | |
| **ACEs[4]** | −0.01 | 0.62 | −0.07 | 0.04 | 0.01 | 0.75 | −0.05 | 0.07 | **0.07** | **0.01** | **0.02** | **0.12** |
| **Sex (male)[5]** | **−0.33** | **0.01** | **−0.59** | **−0.06** | 0.18 | 0.20 | −0.10 | 0.45 | **−0.36** | **0.01** | **−0.59** | **−0.12** |
| **NSAIDs usage[6]** | 0.13 | 0.28 | −0.11 | 0.37 | −0.21 | 0.09 | −0.45 | 0.03 | 0.10 | 0.35 | −0.11 | 0.31 |
| **Presc. Med.[7]** | −0.22 | 0.39 | −0.72 | 0.28 | −0.14 | 0.61 | −0.65 | 0.38 | −0.14 | 0.55 | −0.58 | 0.31 |
| **Daily smoker[8]** | 0.15 | 0.53 | −0.33 | 0.63 | 0.23 | 0.37 | −0.26 | 0.72 | **0.58** | **0.01** | **0.16** | **1.00** |
| **Occasional smoker[9]** | 0.08 | 0.72 | −0.37 | 0.53 | 0.05 | 0.83 | −0.41 | 0.51 | −0.16 | 0.42 | −0.55 | 0.23 |
| **PSS[10]** | 0.01 | 0.91 | −0.02 | 0.02 | 0.01 | 0.98 | −0.02 | 0.02 | 0.01 | 0.27 | −0.01 | 0.03 |
| **Body mass index** | 0.02 | 0.08 | −0.01 | 0.03 | 0.01 | 0.49 | −0.01 | 0.02 | **0.06** | **0.01** | **0.05** | **0.08** |
| **Education** | 0.01 | 0.93 | −0.09 | 0.10 | −0.04 | 0.41 | −0.14 | 0.06 | 0.06 | 0.18 | −0.03 | 0.14 |
| **Cortisol data[11]** | **−0.65** | **0.01** | **−0.94** | **−0.36** | 0.22 | 0.14 | −0.07 | 0.52 | −0.23 | 0.08 | −0.48 | 0.02 |
| **Cortisol data x Cortisol[12]** | 0.01 | 0.85 | −0.01 | 0.01 | 0.01 | 0.41 | −0.01 | 0.01 | 0.01 | 0.69 | −0.01 | 0.01 |
| **Intercept** | 0.17 | 0.72 | −0.74 | 1.08 | −0.12 | 0.79 | −1.06 | 0.81 | −2.05 | <.0001 | −2.86 | −1.25 |
| **R-square** | 0.08 | | | | 0.03 | | | | 0.28 | | | |

b (Unstandardized regression coefficients), 95% CI (95% confidence intervals).
*p < 0.05, two tailed.
aSoluble TNF receptors – includes Soluble tumour necrosis factor receptor 1 (sTNFr1), Soluble tumour necrosis factor receptor 2 (sTNFr2).
[2]Soluble IL-6 receptors – includes Interleukin-6 receptor α (sIL-6Rα), Glycoprotein 130 (gp130), and Interferon gamma (IFNγ).
[3]Low-grade inflammation – includes C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumour Necrosis Factor α (TNFα).
[4]Adverse childhood experiences (ACEs).
[5]Reference category is female.
[6]Nonsteroidal anti-inflammatory drug (NSAID) – includes aspirin or ibuprofen.
[7]Prescription medication usage (Presc. Med.) – includes insulin, inhaled corticosteroids, or $\beta_2$ agonists.
[8]Reported daily smoker – reference category is occasional smoker and non-smoker.
[9]Reported occasional smoker – reference category is daily smoker and non-smoker.
[10]Perceived stress scale.
[11]Reference category is missing cortisol.
[12]Reference category is missing cortisol. Those with cortisol have cortisol centered around 0.

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