# Childhood Maltreatment, Lifetime Traumatic Experiences, and Change in Inflammation Over Time

by

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**Background:** Trauma throughout the lifespan is associated with adverse health outcomes, potentially via inflammatory processes. Traumatic experiences in both childhood and adulthood are related to increased levels of inflammation. However, more work is needed to investigate how trauma relates to inflammation over time and to test how traumatic experiences in childhood and adulthood independently or collectively relate to adult inflammation.

**Methods:** This study tested relations between child maltreatment, lifetime trauma, and inflammation in a cohort of 298 peri and postmenopausal women aged 40-60. Participants were invited back 5 years later to participate in the ongoing follow-up study (n=170). Measures of child maltreatment, lifetime trauma, demographics, and a fasting blood draw were collected. Multiple regression analyses were conducted testing associations between child and adult trauma in relation to inflammation controlling for demographics, body mass index, and immune medication both cross sectionally and longitudinally. Moderation effects were modeled by interaction terms and tests for mediation utilized bootstrapping.

**Results:** 44% of women (N=132) reported some form of maltreatment and 60% of women (N=178) reported some form of lifetime trauma. At baseline, a history of child emotional abuse or physical neglect was associated with higher levels of IL-6 [emotional abuse: b(SE)=0.12(0.05), p=.046; physical neglect: b(SE)=0.12(0.06), p=.02]. At follow-up, a history of being in a natural disaster was associated with higher levels of CRP, while a history of being physically attacked was

associated with lower levels of TNF- α [natural disaster: b(SE)=0.29(0.12), p=.04; physical attack: b(SE)=-0.37(0.10), p=.0002]. In longitudinal analyses, a history of being in a natural disaster was associated with a greater increase in IL-6 over time and experiencing the death of a child was associated with a greater increase in CRP over time [natural disaster: b(SE)=0.19(0.07), p=.007; death of a child: b(SE)=0.34(0.13), p=.009]. Analyses did not support independent, interactive, or explanatory relationships between child maltreatment, lifetime trauma, and inflammation either cross sectionally or longitudinally.

**Conclusion:** Trauma throughout the lifespan was prevalent in this sample of midlife women. Associations between childhood maltreatment, lifetime trauma, and inflammation were observed for specific subtypes of maltreatment or trauma, but were not consistent across time or immune marker.

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# 1.0 Introduction

## 1.1 Childhood Maltreatment and Later Risk for Disease

Multiple studies have found an association between childhood maltreatment and a range of adverse health outcomes in adulthood. For example, the Adverse Childhood Experiences (ACE) Study conducted amongst a large cohort in the Kaiser Permanente healthcare system found a graded relationship between the number of retrospectively-reported childhood adverse experiences (including abuse/neglect) and risk for ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease.[1] Women in the Nurses' Health Study II who retrospectively reported childhood abuse utilizing a validated questionnaire, had increased risk for diabetes and hypertension.[2,3] Further, a meta-analytic review of over 48,000 individuals found that childhood physical, sexual, emotional abuse and/or neglect was associated with increased risk for or severity of cardiovascular disease, respiratory or gastrointestinal problems, diabetes and obesity, gynecological problems, neurological problems, and/or musculoskeletal problems with a small to medium effect size.[4] Another meta-analysis exploring the relationship between childhood sexual abuse and adult physical health outcomes found that those with a history of childhood sexual abuse were more likely to endorse poor health outcomes such as cardiopulmonary, gastrointestinal, gynecologic symptoms, and obesity, with a small to medium effect size.[5] Taken together, these studies indicate a relationship between childhood maltreatment and worse adult physical health.

The pathways between childhood maltreatment and later adverse health outcomes are likely many. Previous studies have proposed behavioral mechanisms such as substance abuse, obesity, high risk sexual behavior, smoking, and/or sleep difficulties.[6–8] Given the relationship

between childhood maltreatment and disorders such as depression and post-traumatic stress disorder (PTSD), emotional factors have also been proposed as a pathway between maltreatment and later adult health.[6–8] Indeed, a population study found that health behaviors such as smoking, poor nutrition, high alcohol consumption, and higher-risk sexual practices as well as a history of anxiety, depression, bipolar disorder, or bulimia partially mediated the relationship between childhood abuse and indicators of adult physical health.[9] In addition, a combination of cognitive and social factors have been proposed as potential pathways between childhood maltreatment and adult health. For example, research proposes that those exposed to childhood maltreatment may be especially vigilant of threat, mistrusting of others, and possess a chronically negative worldview, which may lead to dysfunctional interpersonal styles, more conflict, less social support, and in turn worse physical health outcomes.[6,10]

Lastly, studies have proposed that childhood maltreatment induces a range of biological changes during childhood that can be observed into adulthood, such as a smaller prefrontal cortex and hippocampus volume, lower basal cortisol levels, an elevated adrenocorticotropic hormone response to psychological stressors, and changes in endothelial function and insulin resistance, that may explain the relationship between childhood maltreatment and later disease.[7,11–13] Research also indicates that inflammatory processes may play a significant role in the relationship between childhood maltreatment and later disease risk. It is proposed that childhood maltreatment is related to small and sustained increases of circulating markers of inflammation.[14] These small increases in circulating levels of inflammation in healthy populations are predictive of later disease risk.[15] Given its well-established links to a diverse set of disease processes,[16–18] it may be of particular importance to consider inflammation in the relationship between childhood maltreatment and later health.

## 1.2 The Immune System and Inflammation as a Predictor of Later Disease Risk

The primary function of the immune system is to maintain homeostasis by preventing or limiting infection. Besides physical barriers such as skin and mucosal membranes, the immune system is comprised of two main branches; the innate and the adaptive immune systems. Both systems utilize structural features on cells to differentiate between foreign particles and cells endogenous to the self. The innate system responds quickly to commonly recognized bacteria/viruses and utilizes white blood cells such as macrophages, neutrophils, and natural killer cells. The adaptive immune system utilizes its "immune memory" to respond quickly and effectively to previously encountered pathogens by upregulating the activity of B or T cells.[19] These two systems act in concert; The innate system collects and integrates information that directs the adaptive immune system on details of the immune response such as the location of the immune challenge and what cell types to utilize. One of the ways that these two systems communicate is through immune modulators called cytokines, which act as signaling molecules.[19]

### 1.2.1 Immune Modulators

In addition to facilitating communication between the innate and adaptive immune system, cytokines are involved in a host of immunomodulatory activities. As a part of the innate immune system, activated phagocytic cells such as macrophages release proinflammatory cytokines that amplify the immune response by recruiting other cells to the site of the immune challenge. In addition to activating or modulating the immune response, a subtype of cytokines known as anti-inflammatory cytokines can inhibit the immune system. These anti-inflammatory mediators slow the inflammatory cascade by binding to receptors on immune cells to reduce cell proliferation rate

or by blocking the stimulatory signals of other cytokines. Thus, cytokines play an active and varied role in inflammatory processes.[19]

Research on psychosocial factors and immune function often consider immune modulators important to the inflammatory cascade of the innate immune system, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). TNF-α, produced by activated macrophages, is one of the principle mediators that facilitates the host response to immune challenges as part of the innate immune system. Locally, TNF-α increases the adhesion of leukocytes to the site of immune challenge by increasing the expression of adhesion molecules on the endothelium. TNF-α also enters the blood to enhance the production of immune cells such as neutrophils in the bone marrow. Further, TNF-α can stimulate phagocytes to produce other cytokines such as interleukin-1 (IL-1) and to secrete IL-6 into circulation.[20] In clinical studies, small increases in circulating levels of TNF-α, thought to reflect systemic levels of inflammation, have been linked to inflammatory diseases such as arthritis, inflammatory bowel disease,[21] as well as cardiovascular disease,[22] and cancer.[23]

IL-6 is a cytokine that has both local and systemic effects as part of the innate inflammatory cascade. IL-6 is synthesized by mononuclear phagocytes, by vascular endothelial cells, and in response from TNF-α. IL-6 induces the synthesis of a subtype of plasma proteins called acute phase reactants and enhances the production of neutrophils in the bone marrow.[20] In clinical studies, elevated levels of IL-6 have been associated with diseases such as arthritis,[24] cardiovascular disease events,[25] and type II diabetes.[26] In some situations, IL-6 is produced by T cells and serves an anti-inflammatory function; however, circulating levels are more often considered a measure of systemic inflammation.

In addition to proinflammatory cytokines, circulating levels of another immune modulator, acute phase proteins, are also measured as a marker of systemic levels of inflammation. The acute phase response is the rapid rise of plasma protein levels in response to injury or infection. C-reactive protein (CRP) is a widely-measured acute phase protein that is released in response to the stimulation of hepatocytes by IL-6, IL-1 and TNF-α.[27] CRP initiates the classical component pathway which detects and binds to microbes and activates a cascade that promotes the phagocytosis of the microbes.[20] CRP levels are known to be elevated in diseases of chronic inflammation such as rheumatoid arthritis and in cardiovascular disease.[15,28]

### 1.2.2 Levels of Inflammation Predictive of Later Disease

While large increases in circulating levels of cytokines reflect acute infection or clinical disease, small and sustained increases of circulating markers of inflammation that are in the physiologically normal range are predictive of later disease risk.[29] For instance, small and/or sustained increases in proinflammatory biomarkers (conceptualized as heightened levels of systemic inflammation) have been related to diseases such as autoimmune disorders, as well as type II diabetes, and cardiovascular disease.[15,30,31] The mechanisms by which these small increases in circulating levels of immune markers predict future disease risk are likely many. Increases could reflect lifestyle factors, genetics, or the cumulative wear and tear of subclinical inflammatory processes, such as atherosclerosis.[32–34] Thus, small sustained increases in systemic inflammation, such as that which may be observed with psychosocial stressors, may have implications for health.

### 1.3 Childhood Maltreatment and Inflammation

Previous findings indicate a link between childhood maltreatment recalled in adulthood and circulating markers of inflammation in adulthood. A study of healthy older adults, half of whom were dementia family caregivers and half of whom were non-caregivers, found that those with a history of childhood abuse exhibited heightened IL-6 and TNF-α compared to older adults without this history. These results were not explained by factors such as age, caregiving status, gender, body mass index (BMI), exercise, and sleep.[35] Furthermore, a history of sexual and emotional abuse, emotional and physical neglect, and the total number of types of abuse were associated with higher CRP levels in the Study of Women's Health Across the Nation (SWAN), a cohort of mid-life women.[36] This relationship persisted after adjusting for ethnicity, education, smoking status, hormone therapy, depression symptoms, and blood pressure medication, but was attenuated after adjusting for BMI. In a sample from the Midlife in the United States (MIDUS) study, early life adversity was associated with increased IL-6, but not CRP among African Americans, while there was no relationship between adversity and any inflammatory marker among Whites. This relationship was attenuated when controlling for covariates BMI, smoking status, and exercise levels.[37]

In contrast to childhood abuse recalled in adulthood, several studies have examined the relationship between prospectively reported childhood maltreatment and adult inflammation. A study utilizing longitudinal data from the Avon Study of Parents and Children found that adverse events from birth to age 8 were associated with higher levels of IL-6 at age 10 and higher levels of CRP at ages 10 and 15 when adjusting for gender, age, ethnicity, family income, mother's education, and medication use.[38] The associations between cumulative adverse events and levels

of IL-6 and CRP were mediated by BMI. In a longitudinal study of the Dunedin cohort, childhood maltreatment was associated with higher CRP levels in a dose-response relationship 20 years later even after adjusting for childhood risk factors, adult SES, depression, high perceived stress, cardiovascular disease risk cluster (which included being overweight), and health behaviors.[39] Thus, several studies have found an association between reports of childhood maltreatment and later inflammation, while also highlighting the importance of considering adiposity and behavioral factors in this relationship.

Several reviews and meta-analyses have examined the relationship between childhood maltreatment and inflammation. A 2016 meta-analysis found that individuals with a history of childhood maltreatment demonstrated elevated levels of inflammation with small effect sizes for CRP, IL-6, and TNF-α.[40] However, this meta-analysis noted that associations between trauma and inflammation were heterogeneous among studies, potentially because of marked differences in immune marker and childhood trauma measurement, and inconsistent exclusion criteria based on acute illness. In addition, there were larger effect sizes in the relationship between trauma and inflammation for studies that utilized validated measures of childhood trauma.[40] A systematic review of the relationship between childhood maltreatment and adult levels of circulating markers of inflammation among clinical samples found that childhood maltreatment was most consistently associated with higher levels of CRP, with more mixed results for IL-6 or TNF-α. Further, this review noted that many studies had a low number of subjects with history of childhood maltreatment and that studies were again heterogeneous in childhood maltreatment assessment and definition.[14]

Research typically utilizes retrospective self-report questions about the presence or absence of various types of abuse/neglect. While retrospective reports have advantages such as

convenience, low cost, and utility in adult populations, individuals tend to underreport childhood maltreatment, and infrequently these reports may include false positives.[41] Prospective reports of childhood maltreatment by family members or by the children themselves have advantages such as avoiding memory biases. However, parental reports of maltreatment increase the possibility that if the parent is the perpetrator, some forms of abuse/neglect may be underreported.[41] The rigor of official reports to government agencies (including an initial report, an investigation, and a substantiation decision) reduces the possibility of false positives.[42] However, whether abuse is reported depends on a range of factors such as severity of abuse, socioeconomic status (SES), and race,[43] and these reports often greatly underrepresent the amount of actual maltreatment in the population.[44] Regardless of whether a study utilizes retrospective, prospective, or official reports of childhood maltreatment, it is important to clearly define the form of maltreatment being queried and to ask multiple specific questions about each form of maltreatement.[41]

Thus, while research indicates that there is a relationship between childhood maltreatment and heightened markers of inflammation, several questions remain. For example, while some studies utilized validated scales of childhood maltreatment,[35,36] others used non-standardized/validated measurements,[37,39] which may result in underestimates of certain subtypes of abuse.[38] While the relationship between childhood maltreatment and heightened levels of circulating inflammation was independent of BMI or weight in some samples,[35,39] this relationship was mediated by BMI in other studies.[36–38] Further, previous studies have not consistently excluded based on acute illness, which may lead to heterogeneity among studies.[40] Thus, there is a need for future studies to utilize validated measures of abuse and neglect and to consider the effects of potential physical, psychological, and demographic confounders in a sample free of acute illness.

There are several potential mechanisms that may link trauma to inflammation. Childhood maltreatment is associated with sympathetic nervous system dysregulation,[45] which may lead to changes in levels of inflammatory markers via the reciprocal innervation of primary and secondary lymphoid tissue which partake in immune processes.[46] In addition, chronic stress is associated with marked changes in the HPA axis,[47] and lower levels of anti-inflammatory glucocorticoids may lead to higher levels of systemic inflammation.[48] Trauma throughout the lifespan has also been associated with increased alcohol consumption, greater levels of adipose tissue, and depressive disorders later in life,[49–51] which could also explain the relationship between trauma and changes in levels of inflammation.[32,52–54]

### 1.4 Lifetime Trauma and Inflammation

In addition to an association between trauma that happened during childhood and later inflammation, research indicates that a traumatic event that occurred anywhere in the lifespan, including adulthood, is associated with increases in circulating markers of inflammation. In a small community sample, women who experienced rape in the past 72 hours demonstrated significantly elevated levels of CRP, interleukin-10 (IL-10), and IL-6 as compared to women in the control group.[55] In a sample of older female primary care patients, lifetime history of sudden loss of a loved one was associated with higher levels of IL-6 even after adjusting for race, age, education, income, depression and obesity. There was a linear relationship between ordered categories of lifetime loss (0, 1, 2-5, 5+) and increases in IL-6.[56] A study of participants in the Heart and Soul cohort with stable cardiovascular disease found that higher lifetime levels of a range of trauma exposures (i.e. sexual/physical assault, serious accidents, or the death of a loved one) were related

to increased levels of a composite score of proinflammatory markers of inflammation (including IL6, TNF-α, CRP, and resistin) at baseline and 5 years later even when adjusting for age, gender, education, psychiatric and medical comorbidities. However, the relationship between higher lifetime trauma exposure and the composite proinflammatory score 5 years later was attenuated when adjusting for tobacco, drug use, and sleep quality.[57] A 2014 meta-analysis considered the association between trauma exposure throughout the lifespan (including childhood adversity) and proinflammatory markers in adulthood and found that trauma exposure was significantly associated with higher levels of CRP) interleukin-1beta (IL-1β), IL-6, and TNF-α all of moderate to large correlations.[58] The meta-analysis noted that the relationship between trauma and inflammation was especially pronounced in clinical vs non-clinical samples and that the inclusion of relevant covariates was related to heterogeneity in effect sizes.

Indeed, previous research has not consistently considered relevant confounders such as BMI or depressive symptoms,[55,58] has focused on specific traumas,[55,56,59] and/or has been conducted among small samples.[55,56,59] Thus, while research indicates that trauma throughout the lifespan is associated with increased levels of inflammation, there is a need for larger studies of non-clinical samples with well-characterized demographic, psychological, and health factors that consider a wide range of traumatic experiences. Further, while research indicates that there are independent relationships between childhood maltreatment, lifetime traumatic experiences and inflammation, less is known about the potential independent, interactive, or synergistic effects of childhood maltreatment and lifetime traumas on later inflammation.

## 1.5 Childhood Maltreatment, Lifetime Trauma, and Inflammation

We will consider three models detailing how childhood maltreatment and lifetime trauma may collectively relate to adult inflammation: the stress sensitization model, the stress generation model, and the stress accumulation model (see Figure 1).

### 1.5.1 Stress Sensitization Model

The stress sensitization model hypothesizes that early life is a sensitive developmental period and that childhood trauma may shape reactions to stressors later in life such that those with a history of childhood maltreatment will demonstrate amplified biological responses to adverse life events. Research indicates that childhood trauma, but not adult trauma, is associated with increased transcription of proinflammatory genes later in life.[60] Further, it was found that adults with a history of maltreatment exhibit low basal cortisol levels and an elevated adrenocorticotropic hormone response to psychological stressors.[11] Thus, it is posited that childhood maltreatment will have long lasting effects on stress response systems and that it will synergistically amplify reactions to later life stress.

Most studies examining the relationship between childhood maltreatment, lifetime trauma, and inflammation have found support for the stress-sensitization model. One study examining the relationship between childhood adversity, adult stressors, and inflammation in a diverse sample of young adults found that childhood adversity and adult stressors were independently associated with a composite inflammation score of pro- and anti-inflammatory immune markers. Further, there was a significant interaction between childhood adversity and adult stressors such that those with both child trauma and adult stressors exhibited heightened levels of inflammation.[61] A study

conducted in a sample of older adult caregivers found that a history of childhood abuse and multiple daily life stressors were independently associated with greater levels of IL-6. There was a significant interaction between childhood abuse history and daily stressors such that those with a history of childhood abuse had larger IL-6 responses to multiple daily stressors.[62] However, a study conducted in a large population-based sample found that a history of childhood adversity and adult trauma were independently associated with higher levels of CRP, but that there was not a significant interaction between childhood adversity and adult trauma on levels of CRP.[63] Thus, while there is evidence supporting the stress-sensitization model, findings are not entirely consistent.

### 1.5.2 Stress Generation Model

The stress generation model of the relationship between childhood abuse and lifetime traumatic experiences hypothesizes that childhood stress predisposes people to experience more stressful experiences later in life. It is posited that later psychosocial stressors, rather than the childhood maltreatment itself, is what is related later health in adulthood.[64] Indeed, a previous study examining potential mediators of the relationship between childhood maltreatment and poor adult physical health found that adverse life events in adulthood accounted for 25% of the association between childhood maltreatment and chronic medical conditions.[65] Further, individuals who have experienced child maltreatment are at increased risk for revictimization in adulthood. A prospective cohort study of almost 900 individuals found that those who experienced childhood maltreatment reported a higher number of traumas and victimization experiences than controls when interviewed approximately 30 years later.[66] Although the pathways between victimization in childhood and revictimization in adulthood are likely many, childhood adversity

is associated with emotional dysregulation and engagement in risky behaviors.[67] Further, childhood adversity tends to correlate with lower SES in the general population,[68] potentially subjecting the individual to a harsh environment. Thus, the environmental correlates and emotional sequela of childhood adversity may predispose individuals to experience more frequent traumatic adult life experiences, which may account for the relationship between childhood maltreatment and later inflammation.

A handful of studies have tested the stress generation model of the relationship between childhood maltreatment, lifetime traumatic experiences, and inflammation. In a sample from the MIDUS study, the relationship between early life adversity and increased levels of circulating IL-6 was attenuated when controlling for adult stressors. However, adult stressors were not significantly related to levels of IL-6.[37] In addition, a prospective study of the Dunedin cohort found that the relationship between early life adversity and increased levels of circulating CRP was not explained by stress experienced in adulthood.[39] Thus far, there has been no evidence supporting the stress generation model of the relationship between childhood maltreatment, lifetime trauma, and inflammation.

### 1.5.3 Stress Accumulation Model

The stress accumulation model posits that childhood adversity and lifetime trauma have independent influences on inflammation.[69] Previous research has established independent associations between childhood adversity and inflammation as well as lifetime traumatic experiences and inflammation.[14,58] Further, research suggests a graded relationship between childhood adversity and mental or physical health outcomes such that the greater number of categories of adversity were associated with a heightened risk for adverse outcomes.[1,70] Thus, the

stress accumulation model posits that a greater number of stressors throughout the lifespan will have independent and cumulative physiologic implications.

Many of the studies investigating the relationship between childhood maltreatment, lifetime trauma, and inflammation specifically examine the stress sensitization hypothesis and do not formally test for or discuss other models of the relationship between childhood adversity and lifetime trauma. However, one previous study specifically examines the relationship between childhood adversity, lifetime trauma, and inflammation by testing the stress sensitization, stress generation, and stress accumulation model. This study was conducted in a sample of 1180 middle-aged and older adults from the MIDUS study and found that childhood adversity and adult stressors were independently associated with a pro-inflammatory composite score (IL-6, CRP, fibrinogen, E-selectin, and intercellular adhesion molecule-1) and that the interaction between childhood adversity and adult stressors was not significant, supporting the stress accumulation model.[71]

### 1.6 Present Study

In the present study, we propose to test three models of the relationship between child maltreatment, lifetime trauma, and inflammation in women whose markers of inflammation (IL-6 and CRP) were characterized at two time points over midlife. This study will utilize a validated measure of childhood abuse or neglect, the Child Trauma Questionnaire, which has additional favorable characteristics such as assessing multiple types of trauma and reporting stronger psychometric properties compared to other self-report measures.[72] In addition, we will consider multiple demographic, behavioral, psychological, and health confounders. Further, this study will examine this relationship in women, who experience higher rates of specific subtypes of abuse,[73,74]

and for whom midlife represents a period of hormonal change and physiologic vulnerability.[75–77] In exploratory analyses, we will examine specific subtypes of abuse as well as relations between abuse, trauma, and additional inflammatory markers collected at a single time point (TNF-α and IL-10). This study will be the first to rigorously test three competing models of the relationship between child maltreatment, lifetime trauma, and inflammation in women whose markers of inflammation were characterized over midlife. We will test the following aims:

Aim 1: Is childhood maltreatment associated with higher levels of inflammatory markers over midlife in women? *We hypothesize that women with a history of childhood maltreatment will show higher levels of CRP and IL-6 and greater increases in CRP and IL-6 over midlife as compared to those without this history*.

Aim 2: Are lifetime traumatic life events associated with higher levels of inflammatory markers over midlife in women? *We hypothesize that women with a history of lifetime traumatic experiences will have higher levels of CRP and IL-6 and greater increases in CRP and IL-6 over midlife as compared to those without this history*.

Aim 3: What role does lifetime traumatic experiences play (i.e. independent, interactive) in the relationship between child maltreatment and inflammation? *We hypothesize that there will be an interaction between childhood maltreatment and lifetime traumatic life events in relation to levels of inflammation over time, such that the association between traumatic life events and higher levels of as well as greatest increases in inflammation over time will be most pronounced among individuals with a history of childhood maltreatment.*

Exploratory aim: We will examine whether specific subtypes of abuse (sexual, physical, emotional abuse, physical, and/or emotional neglect) or lifetime traumatic events (serious accident, natural disaster, serious illness, being attacked, unwanted sexual contact, death of a child, sexual

harassment) are related to markers of inflammation in exploratory analyses. Further, we will explore the relationship between childhood maltreatment, lifetime trauma, and IL-10 and TNF-α, which were collected at a single time point.

## 2.0 Research Design and Methods

### 2.1 Participants

This study was conducted among participants of the MsHeart Study, a study originally designed to investigate the relation between menopausal vasomotor symptoms and cardiovascular health.[77] MsHeart enrollment was conducted between January 2012 and May 2015 and included 307 nonsmoking, late peri- and post-menopausal women aged 40 to 60. Approximately half of the sample reported daily vasomotor symptoms (n=153) while the other half reported no vasomotor symptoms in the prior three months (n=154). Participants have been invited back 5 years later to participate in the MsBrain study, a study designed to investigate the relation between vasomotor symptoms and brain health. MsBrain recruitment is ongoing and expected that 230 women, aged 45-67 will complete the protocol by March 2021. For MsBrain, it is anticipated that 170 women from the MsHeart cohort will return, and recruitment from the community will be conducted to recruit the additional 60 women to reach a full MsBrain sample of 230 women. Thus, among 170 women, MsHeart and MsBrain collectively comprise two waves of a longitudinal study.

MsHeart exclusion criteria included hysterectomy and/or bilateral oophorectomy; a reported history of heart disease, stroke, arrhythmia, gynecological cancer, pheochromocytoma, pancreatic tumor, kidney failure, seizures, Parkinson disease, or Raynaud phenomenon; current pregnancy; or having used the following medications (due to their impact on key study measures) within the past 3 months: estrogen or progesterone, selective estrogen receptor modulators, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, gabapentin, insulin, beta-blockers, calcium channel blockers, alpha-2 adrenergic agonists, other antiarrhythmic

agents. Women who had undergone endometrial ablation, endarterectomy, or lymph node removal or who were undergoing chemotherapy, hemodialysis, or peritoneal dialysis were excluded.[77] MsBrain exclusion criteria were a reported history of stroke or cerebral vascular accident, brain injury, dementia, Parkinson's disease, carotid stent, active substance use, or current pregnancy; or having used the following medications (due to their impact on key study measures) within the past 3 months: exogenous estrogen or progesterone, selective estrogen receptor modulators, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, or aromatase inhibitors.

At baseline (MsHeart), up to eight women were excluded due to missing abuse/neglect data depending on the subscale (physical neglect: n=1 to sexual abuse: n=8), one woman was excluded due to missing lifetime trauma information (death of a child: n=1), and three people were excluded due to missing inflammation data (CRP: n=3). Nine women were excluded due to a history of inflammatory medical disorders or use of immunosuppressive medications and nineteen women were excluded due to CRP values greater than 10 mg/L. Thus, at baseline final sample sizes ranged from N=268 to N=298. At follow-up (MsBrain), up to five women were excluded due to missing abuse/neglect data depending on the subscale (physical neglect: n=1 to sexual abuse: n=5), up to three woman was excluded due to missing lifetime trauma information (death of a child: n=1 to witnessing a traumatic event: n=3), and up to three people were excluded due to missing inflammation data (CRP: n=2 to IL-6: n=3). Twenty-two women were excluded due to a history of inflammatory medical disorders or use of immunosuppressive medications and 16 women were excluded due to CRP values greater than 10 mg/L. At follow-up, final sample sizes ranged from N=121 to N=148. Women were not excluded from analyses due to missing covariate data at either time point. At baseline, women excluded from analyses were more likely to be non-white [$\chi^2$ (1,

N=298) =14.28 p<.001] and on average had higher BMIs [t(46)=-3.15, p<0.01]. At follow-up, women excluded from analyses on average had higher BMIs [t(31)=-2.76, p<0.01].

## 2.2 Designs and Procedures

At both study waves, participants underwent a telephone and in person screening, and completed physical measurements (e.g., height, weight, blood pressure), a fasting blood draw, and psychosocial questionnaires. Procedures were approved by the University of Pittsburgh Institutional Review Board. Participants provided written informed consent.

## 2.3 Measures

### 2.3.1 Child Trauma Questionnaire

The Child Trauma Questionnaire was completed at baseline. The Child Trauma Questionnaire is a validated 28 item self-report measure that assesses child abuse and neglect.[78] Examples of questions include "People in my family said hurtful or insulting things to me" and "I got hit so hard by someone in my family that I had to see a doctor or go to the hospital". Item scores range from 0 (never true) to 5 (very often true). The Child Trauma Questionnaire includes five subscales (sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect). Child Trauma Questionnaire short form has validated clinical cut off points.[79] Scoring at or above 8 on the sexual abuse subscale, 8 on the physical abuse subscale, 10 on the emotional

abuse subscale, 8 on the physical neglect subscale, or 15 on the emotional neglect subscale indicates an instance of abuse/neglect. If a participant scored at or above any clinical threshold for one or more subscale, the participant was classified as having been exposed to any childhood maltreatment. The participant was considered as not exposed to childhood maltreatment if a participant scored below clinical thresholds on all abuse/neglect subscales.

### 2.3.2 The Brief Trauma Questionnaire

The Brief Trauma Questionnaire was completed at both time points. This questionnaire was adapted from the Brief Trauma Interview[80,81] for the Nurse's Health Study II.[82] This 9 item self-report measure assesses a history of traumatic events. Participants can respond yes or no to having experienced any of the following events in their lifetime: serious accident, natural or human disaster, serious or life-threatening illness, physical attacks, unwanted sexual contact, death of a child, sexual harassment, any other situation in which you were seriously injured or feared serious injury, or witnessing a severe injury or death. If a participant endorsed experiencing any of the subtypes of traumatic events, they were classified as having been exposed to any lifetime trauma.

### 2.3.3 Immune Markers

Phlebotomy was performed at both time points after a 12-hr overnight fast. All women were free of acute illness (e.g. colds) when blood was drawn. At baseline, phlebotomy was performed at the Health Studies Research Center, Department of Epidemiology, University of Pittsburgh and assays were performed by the Chemistry and Nutrition Laboratory, Graduate School of Public Health, University of Pittsburgh. High sensitivity CRP was measured using a

high sensitivity (hs-CRP) reagent set (Beckman Coulter, Brea, CA). IL-6 was measured with an R&D Systems (Minneapolis, MN; Cat # HS600) high sensitivity kit. At follow-up, phlebotomy was performed at the University of Pittsburgh Women's Biobehavioral Health Laboratory and assays were performed by the Clinical Ligand Assay Service Satellite lab, School of Public Health, Department of Epidemiology, University of Michigan. IL-6 was measured using a high sensitivity R&D Systems Quantikine Human IL-6 ELISA immunoassay (Minneapolis, MN; HS600C). CRP was measured with an R&D systems human high sensitivity reagent set (Minneapolis, MN, DCRP00). Interleukin-10 (IL-10) was measured using a Quantikine Human IL-10 ELISA immunoassay (R&D Systems; D1000B). TNF-α was measured using a Quantikine Human TNF-α ELISA immunoassay R&D Systems (Minneapolis, MN; DTA00D). Detection ranges, as well as intra- and inter-assay coefficients of variation for each assay are presented in Table 1. Standard procedures for phlebotomy and specimen processing/storage were conducted at both time points.

### 2.3.4 Covariates

Demographics (age, education, race/ethnicity) were self-reported at baseline. Education was evaluated as highest degree attained and was categorized into high school and/or some college or vocational school or college degree or higher. Due to small cell sizes of non-white ethnicities (African American, Hispanic, Asian American), race was coded as white or non-white. Height and weight were measured via a fixed stadiometer and a balance beam scale. BMI was calculated ($kg/m^2$). Non-steroidal anti-inflammatory medication usage was documented during the medical history interview. Depressive symptoms, alcohol use, physical activity, and menopause status were self-reported via questionnaires. Depressive symptoms were determined via the Center for Epidemiological Studies Depression Scale (CES-D).[83] Possible scores on the CES-D ranged from

0-60 with higher scores representing greater symptomatology. Alcohol use was determined via self-report and was categorized as less than one drink per month or greater than one drink per month. Physical activity levels were determined using the International Physical Activity Questionnaire (IPAQ) and were scored as minutes of physical activity.[84] Menopause status was determined from self-reported bleeding patterns over the year preceding the visit and was categorized as peri-menopausal or post-menopause using Stages of Reproductive Aging Workshop +10 criteria.[85]

## 2.4 Statistical Analysis Plan

Descriptive statistics, distributions, missing values, and outliers were examined for covariates, predictor variables, and outcome variables. Individuals with CRP values > 10 mg/L, extreme immune value outliers, or with inflammatory medical conditions or taking immunosuppressive medications were excluded. Immune values were log transformed to conform to model assumptions of normality. Chi-square analyses and t tests were conducted to determine if women missing childhood maltreatment, lifetime trauma, or inflammation data, or women excluded based on inflammatory medical conditions or taking immunosuppressive medications differed systematically from women with complete records. Multiple regression analyses testing independent as well as interactive effects of child and lifetime trauma in relation to inflammation controlling for age, race/ethnicity, education, BMI, and non-steroidal anti-inflammatory medication were conducted. Each inflammatory marker was considered separately. Childhood maltreatment was assessed at baseline and lifetime traumatic experiences were assessed at both time points. For analyses of change in inflammation, we considered cumulative lifetime trauma

exposure between the two visits. Covariates age, race/ethnicity, education, BMI, and non-steroidal anti-inflammatory drug use were selected based on known associations with both inflammation and childhood maltreatment.[32,49,51,52,86] Covariates alcohol use, physical activity, depressive symptoms, and menopause status have proposed associations with inflammation and were considered as additional covariates in secondary analyses.[32,52] Analyses were performed with R studio version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Models were two-sided with $\alpha$=.05.

We tested aim 1 using multiple linear regression to evaluate cross-sectional associations between any instance of childhood maltreatment and levels of circulating markers of inflammation at both baseline and follow-up. Associations between any instance of childhood maltreatment and change in markers of inflammation over time were also assessed. We tested aim 2 using multiple linear regression to evaluate cross-sectional associations between any lifetime traumatic experience and levels of circulating markers of inflammation at baseline and follow-up. Associations between any lifetime traumatic experience and change in markers of inflammation over time were also assessed. We tested aim 3 using multiple linear regression to evaluate the relationship between childhood maltreatment, lifetime trauma, and inflammation. To test the stress accumulation model, both childhood maltreatment and lifetime traumatic experiences were included in the same model. Independent associations between child maltreatment and inflammation as well as lifetime trauma and inflammation were considered as support for the stress accumulation model. To examine the early life stress sensitization model, multiple linear regression was conducted to evaluate the interaction term between childhood maltreatment and lifetime traumatic experiences in relation to inflammation cross sectionally as well as to change in inflammation over time. A significant interaction in which the association between traumatic life

events and higher levels of as well as greater increases in inflammation over time was most pronounced among individuals with a history of childhood maltreatment was considered support for the early life stress sensitization model. To test the stress generation model, tests for mediation were conducted by calculating indirect effect of lifetime trauma in the relationship between child maltreatment and inflammation, which describes the proportion of the association between child maltreatment and inflammation that is explained by lifetime trauma. Although there are multiple methods for assessing the indirect effect (i.e. causal steps strategy, product of coefficients, distribution of the product),[87,88] bootstrapping was utilized as it demonstrates higher power while maintaining reasonable control over the Type I error rate.[89,90]

For all models in Aims 1-3, change in markers of inflammation over time were evaluated by examining levels of inflammation at follow-up while adjusting for baseline levels of inflammation. Although there is no universal approach for examining change over two time points, analyzing follow-up scores while including baseline scores as a predictor empirically fits a regression coefficient to the relationship between baseline and follow-up scores.[91] Immune markers were considered separately in all models. To evaluate the exploratory aim, separate multiple linear regression models were performed to examine whether specific subtypes of maltreatment (sexual, physical, emotional abuse, physical and/or emotional neglect) or lifetime traumatic events (serious accident, natural disaster, serious illness, being attacked, unwanted sexual contact, death of a child, sexual harassment) were related to markers of inflammation. Each subtype of trauma was considered separately. Multiple linear regression was conducted to examine whether childhood maltreatment, lifetime traumatic experiences, or the relationship between childhood maltreatment and lifetime traumatic experiences were related to markers IL-10 and TNF-α, with IL-10 and TNF-α considered in separate models.

## 3.0 Results

At baseline, participants were on average 54 years old, white, overweight, and had attained a college education or higher. See Table 2. Approximately a quarter of women (n=63) identified as African American. One hundred thirty-two women (44% of the sample) reported some form of abuse or neglect; emotional abuse (24%) was the most common form of abuse/neglect. One hundred seventy-eight women (60% of the sample) reported some form of lifetime trauma; unwanted sexual contact (21%) was the most common form of lifetime trauma. See Table 3. Women who returned for the follow-up visit 5 years later (N=170) did not differ from the original sample on key study variables such as age, race/ethnicity, education, BMI, immune medication usage, history of abuse/neglect, or history of lifetime trauma (p's>.05).

Women with less than a college education and non-white women were more likely to report childhood abuse/neglect.[92] Women with a history of childhood abuse/neglect were more likely to report a experiencing a lifetime traumatic event and on average had higher depressive symptomatology. See Table 4. Levels of inflammatory markers and average BMI were comparable to those reported in a similar sample of midlife women.[93] See Table 5. There was a significant positive association between CRP measured at baseline and follow-up [$\rho = .77$, $p < .01$], as well as IL6 measured at baseline and follow-up [$\rho = .67$, $p < .01$].

At baseline, a history of any instance of childhood abuse or neglect was not significantly associated with CRP or IL-6. See Table 6. In considering subscales, a history of childhood emotional abuse or physical neglect was associated with higher levels of IL-6, with associations persisting controlling for covariates. At baseline, neither a history of any instance of lifetime

trauma nor specific traumatic experiences were significantly associated with CRP or IL-6. See Table 7.

At follow-up, neither a history of any instance of childhood abuse/neglect nor specific types of child abuse or neglect were significantly associated with CRP, IL-6, TNF-α, or IL-10. At follow-up, a history of any instance of lifetime trauma was not significantly associated with inflammatory markers. However, a history of being in a natural disaster was associated with higher levels of CRP, while a history of being physically attacked was associated with lower levels of TNF- α. See Table 7. Associations persisted controlling for covariates.

In longitudinal analyses, neither a history of any instance of childhood abuse/neglect nor specific types of abuse or neglect were associated with change in levels of inflammatory markers over 5 years. See Table 6. A history of any instance of a lifetime traumatic experience was not associated with change in levels of inflammatory markers over 5 years. See Table 7. In considering specific traumatic experiences, a history of being in a natural disaster was associated with a greater increase in IL-6 over time and experiencing the death of a child was associated with a greater increase in CRP over time. Associations persisted controlling for covariates.

Potential associations between childhood abuse/neglect, lifetime trauma, and levels of inflammatory markers were examined. When considering any childhood abuse/neglect and any lifetime trauma in the same model, neither childhood abuse/neglect nor lifetime trauma were independently associated with levels of inflammatory markers at baseline, follow-up, or with change in levels of inflammatory markers over time. See Table 8. A history of any childhood abuse/neglect did not significantly modify the association between any lifetime traumatic event and levels of inflammation at baseline, follow-up, or change in levels of inflammatory markers over time. See Table 9. Although main effects of childhood abuse and inflammation and lifetime

trauma and inflammation were not observed, tests of mediation were conducted to investigate the stress generation model of the relationship between trauma over the lifespan and later inflammation. A history of any lifetime traumatic event did not mediate the relationship between a history of any childhood abuse/neglect and levels of inflammatory markers at baseline, follow-up, or change in levels of inflammatory markers over time.

We conducted several secondary analyses. Associations between childhood abuse/neglect or lifetime trauma and change in levels of inflammation over time was examined using a raw difference score (rather than predicting follow-up scores while controlling for baseline values), and conclusions were unchanged (data not shown). Second, we considered menopause status, levels of leisure time physical activity, alcohol consumption, and symptoms of depression as additional covariates in relations between childhood abuse/neglect or lifetime trauma and later levels of inflammation. Including symptoms of depression as an additional covariate changed the relationship between childhood physical neglect and baseline levels of IL-6 from significant to marginal [B(SE)=0.11 (0.06), p=.06], but all other conclusions were unchanged (data not shown). Lastly, we excluded individuals with TNF-α levels below the assay's lower limit of detection (N=30) when examining the associations between trauma and later levels of inflammation. The relationship between being physically attacked and lower levels of TNF-α at follow-up changed from significant to marginal [B(SE)=-.16 (0.09), p=0.097]. All other conclusions were unchanged (data not shown).

## 4.0 Discussion

Among a well-characterized sample of midlife women who completed measurements of systemic levels of inflammation, 44% of the cohort reported a history of childhood abuse/neglect and 60% reported a history of a lifetime traumatic event. Neither overall exposure to childhood abuse/neglect nor lifetime traumatic experiences were related to circulating levels of inflammation, while individual subtypes of abuse/neglect and lifetime trauma were associated with inflammation. Specifically, at baseline, a history of childhood emotional abuse or physical neglect was associated with higher levels of IL-6. At follow-up, a history of experiencing a natural disaster was associated with higher levels of CRP, while a history of experiencing a physical attack was associated with lower levels of TNF-α. In longitudinal analyses, a history of experiencing the death of a child was associated with greater increases in CRP over time and a history of experiencing a natural disaster was associated with a greater increase in IL-6 over time. Given the lack of consistency in associations, these results must be interpreted with caution. Collectively they suggest that in this sample of midlife women, trauma throughout the lifespan was inconsistently associated with inflammation.

These findings contribute to the literature on trauma over the lifespan and later adverse health outcomes. Similar to other studies of midlife and older adults, a history of abuse/neglect and lifetime trauma were common in this sample.[2,36,63] While previous research indicates that childhood maltreatment is associated with heightened levels of inflammation measured later in life both cross sectionally and longitudinally,[38–40] findings have also been mixed.[37,62,94] Previous research has not consistently utilized standardized/validated measurements of childhood measurements,[37,39] which may result in underestimates in certain subtypes of abuse.[38] In addition,

studies examining childhood trauma and adult inflammation have not consistently excluded on acute infection, which may contribute to heterogeneity in findings.[40] Research also indicates that experiencing a traumatic event in adulthood is associated with higher levels of levels of inflammation measured both cross sectionally and longitudinally, [56–58] although other studies have failed to find significant associations.[95,96] Previous research has not consistently considered relevant confounders such as BMI or depressive symptoms[55,58] and has focused on specific traumas such as sexual violence or death of a loved one.[55,56,59] This study attempted to address these limitations in the literature by examining relationships between childhood abuse/neglect, lifetime traumatic experiences, and inflammation while utilizing validated measures of multiple types of adversity in a well-characterized, acute illness-free, longitudinal sample. Although associations between childhood abuse/neglect, lifetime trauma, and inflammation were observed both cross sectionally and longitudinally, associations were not consistent across time or subtype of trauma and suggest that in this sample there was not a clear association between trauma and inflammation.

While previous research has found associations between childhood abuse/neglect or lifetime trauma and inflammation, less is known about how childhood maltreatment and lifetime trauma collectively relate to adult inflammation. The stress sensitization model of the relationship between childhood maltreatment, lifetime trauma, and inflammation proposes that childhood trauma may shape reactions to stressors later in life such that those with a history of childhood maltreatment will demonstrate amplified biological responses to later adverse life events. The stress generation model hypothesizes that childhood stress predisposes individuals to experience more stressful experiences later in life and that these later stressors account for health effects seen in adulthood. Finally, the stress accumulation model posits that childhood adversity and lifetime trauma have independent influences on inflammation. While previous research has found the most

support for the stress sensitization model,[61,62] there has also been support for the stress generation[65] and stress accumulation models.[71] Only one study has compared these three potential models of the relationship between childhood maltreatment, lifetime traumatic experiences, and inflammation in the same study,[71] and to date no studies have examined these relationships longitudinally. Thus, the present study is notable for being one of the few studies that compares three proposed models of the relationship between childhood abuse/neglect, lifetime traumatic experiences, and inflammation in a well-characterized longitudinal sample. However, given the relatively few observed relationships between childhood abuse, lifetime trauma, and inflammation in this study, analyses did not find support for either the stress sensitization, stress generation, or stress accumulation models.

In this study of midlife women, associations between childhood abuse/neglect, lifetime trauma, and inflammation were observed for specific subtypes of abuse/neglect or trauma and were not consistent across time. The relationship between maltreatment and IL-6 or CRP observed in the literature is small (IL6: Cohen's d=.16, CRP: d=.20).[40] In order to detect an effect of this magnitude, a sample size of over one thousand participants would be required. Thus, this study may have been underpowered to detect associations. While we observed relationships between emotional abuse and physical neglect and higher levels of IL6 at baseline, these associations did not persist at follow-up. Notably, the sample size at follow-up (N=170) was considerably smaller than that at baseline (N=307). As the effect sizes for associations between physical neglect (but not emotional abuse) with IL-6 were similar at both baseline (d=.211) and at follow-up (d=.18), the smaller sample size at follow-up may have limited the power to detect these associations at follow-up. Associations between physical neglect and IL-6 were also comparable to those reported in the broader literature. This study found that specific lifetime traumatic experiences, such as

being in a natural disaster or experiencing the death of a child, were associated with higher levels of inflammation at follow-up and with greater increases in inflammation over time. Previous research has found associations between experiencing a natural disaster or the loss of a child and later physical health,[97–101] and experiencing the death of a child is considered an especially potent traumatic event compared to losing other loved ones.[100,102,103] However, the lack of consistency in associations warrants interpreting observed relationships with caution. A history of being physically attacked was associated with lower levels of TNF-α at follow-up. To our knowledge, no previous study has reported an inverse relationship between trauma and TNF-α, and after excluding individuals who demonstrated TNF-α levels below the lower limit of detection, this relationship changed from significant to marginal. Thus, the reliability of the observed association between being physically attacked and lower levels of TNF-α is questionable and should be interpreted with caution.

Several characteristics of the current study sample warrant consideration in interpreting the study results. It is noteworthy that the present midlife cohort excluded individuals who took SSRIs, SNRIs, insulin, or beta-blockers, individuals with a history of medical conditions such as heart disease or stroke, and smokers. As trauma is associated with increased risk for depression,[51] behavior changes such as smoking and a more sedentary lifestyle,[1,86] and worse health,[104,105] the current sample may represent a less acutely distressed and healthier population which could partially explain inconsistent associations between trauma and inflammation. Thus, this sample is distinct from other studies of midlife women that have found consistent associations between trauma and inflammation.[36]

This study should be considered in light of several limitations. Childhood maltreatment was measured by retrospective self-report, which is prone to inaccuracies.[41] The stress

sensitization model assumes childhood maltreatment occurred during a sensitive period in childhood, however, measures of childhood maltreatment in this study did not assess age of exposure. Further, lifetime trauma was assessed at two time points and demonstrated low consistency, independent of new events reported. Lifetime traumatic events were assessed by a checklist of events, while research suggests multiple questions about specific events yields greater reliability.[41] Although a quarter of the sample was non-white, Asian and Hispanic women were under-represented, and men were not included. The sample size was approximately halved from baseline to follow-up, which limits the power to detect associations. Examining subscales of traumatic events increased the number of statistical tests, which heightened the probability of type 1 error. Two visits prohibit more intensive longitudinal analyses such as examining trajectories in change over time.

The present study had several strengths. It was conducted in a well-characterized sample of midlife women who underwent extensive measurements of abuse, lifetime trauma, inflammation, and relevant demographic, behavioral, psychological, and health covariates. This study utilized a well validated measure of childhood abuse/neglect. This is the first study to examine three proposed models of how traumas over the lifespan relate and/or interact to influence later inflammation longitudinally, which further advances the literature on the long-term sequelae of childhood abuse. In conclusion, this study found that childhood abuse/neglect and lifetime trauma were prevalent in this sample of midlife women. Although associations between adverse experiences throughout the lifespan and inflammation were not consistent in this sample, trauma should routinely be considered when examining women's health at midlife.

## Appendix A Figures

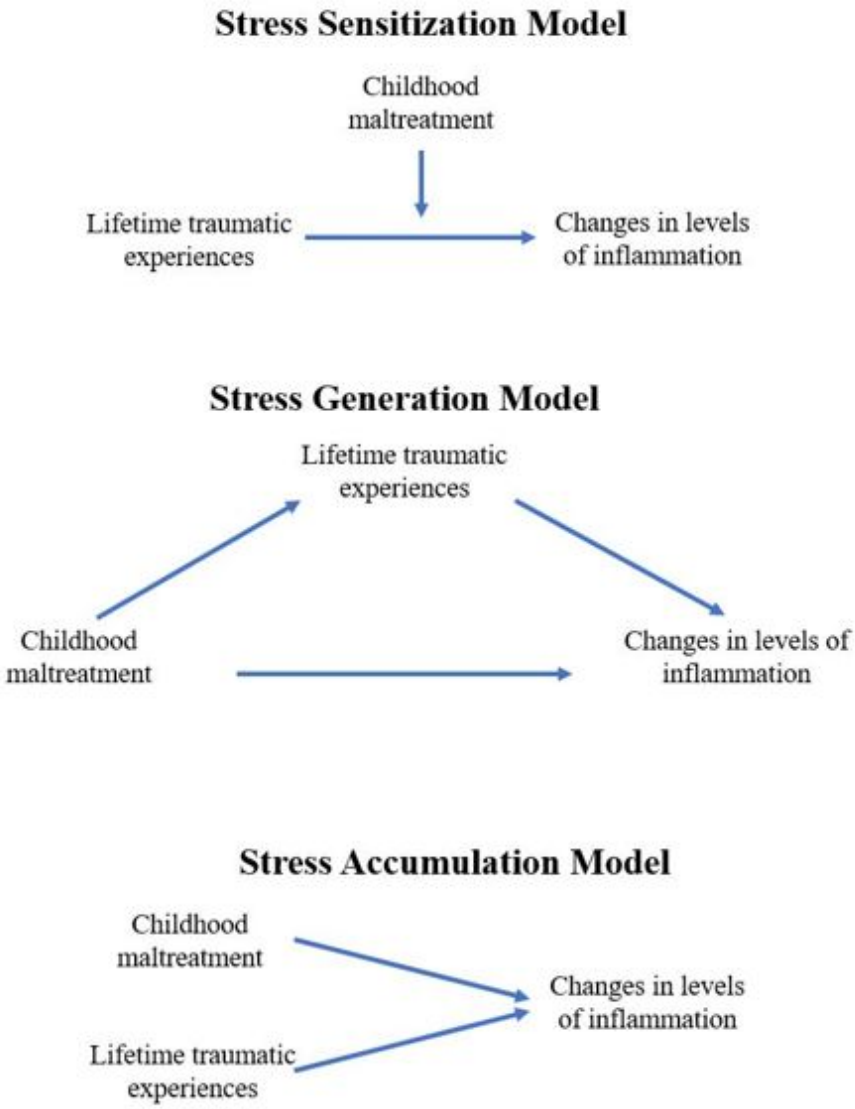


**Figure 1 Visual Representations of the Stress Sensitization, Stress Generation, and Stress Accumulation Models.**

## Appendix B Tables

**Table 1 Assay Detection Range and Intra- and Inter-Assay Coefficients of Variation**

| Assay | Detection Range | Intra-assay coefficient of variation | Inter-assay coefficient of variation |
|---|---|---|---|
| MsHeart | | | |
| Hs-CRP | 0.5-20 mg/L | 5.5% | 3.0% |
| IL-6 | 0.15-10 pg/mL | 9.1% | 10.2% |
| MsBrain | | | |
| Hs-CRP | 0.78-125 mg/L | 5.5% | 6.5% |
| IL-6 | 0.156-10 pg/mL | 2.3% | 9.9% |
| IL-10 | 2.0-500 pg/mL | 3.7% | 6.9% |
| TNF-α | 2.6-1,000 pg/mL | 2.6% | 7.7% |

**Table 2 Sample Characteristics**

| | Baseline (N=298) (2012-2015) | Follow-up (N=148) (2017-2020) |
|---|---|---|
| Age, M (SD) | 54.1 (4.0) | 59.0 (4.1) |
| Race, n (%) | | |
| White | 218 (73) | 105 (71) |
| African American, Hispanic, other | 80 (27) | 43 (29) |
| BMI, M (SD) | 28.9 (6.8) | 29.6 (7.12) |
| Education, n (%) | | |
| High school, vocational school | 127 (43) | 59 (40) |
| College education or higher | 171 (57) | 89 (60) |
| Child abuse/neglect (yes), n (%) | 132 (44) | 62 (42) |
| Lifetime trauma (yes), n (%) | 178 (60) | 95 (64) |
| Non-steroidal anti-inflammatory medications, n (%) | 48 (16) | 42 (28) |
| Physical activity (IPAQ), median (IQR) | 450 (0, 1386) | 486 (0, 1401) |
| Depressive symptoms (CESD), median (IQR) | 5 (2, 11) | 6 (2, 11) |
| Current alcohol use, n (%) | | |
| > 1 drink/month | 172 (58) | 86 (58) |
| < 1 drink/month | 126 (42) | 62 (42) |

BMI = body mass index, SD= standard deviation

**Table 3 Number of Women Reporting Trauma Across Timepoints**

| N (%) | Baseline (N=298) | Follow-up (N=148) | Either time point (N=145) |
|---|---|---|---|
| Any childhood maltreatment | 132 (44) | 62 (42) | 62 (43) |
| Physical abuse | 60 (20) | 30 (20) | 30 (21) |
| Sexual abuse | 38 (13) | 19 (13) | 19 (13) |
| Emotional abuse | 72 (24) | 34 (23) | 34 (23) |
| Emotional neglect | 52 (17) | 26 (18) | 26 (145) |
| Physical neglect | 61 (20) | 29 (20) | 29 (20) |
| Any lifetime trauma | 178 (60) | 95 (64) | 101 (70) |
| Serious accident | 53 (18) | 28 (19) | 34 (23) |
| Natural or human disaster | 32 (11) | 16 (11) | 23 (16) |
| Serious or life-threatening illness | 17 (6) | 7 (5) | 7 (5) |
| Physical attacks | 56 (19) | 17 (11) | 29 (20) |
| Unwanted sexual contact | 64 (21) | 34 (23) | 41 (28) |
| Death of a child | 19 (6) | 9 (6) | 12 (8) |
| Sexual harassment | 59 (20) | 33 (22) | 43 (30) |
| Any other situation | 41 (14) | 18 (12) | 30 (21) |
| Witnessing a severe injury or death | 65 (22) | 32 (22) | 43 (30) |

**Table 4 Characteristics of Women with a History of Abuse or Neglect Compared to Those Without That History at Baseline**

| | No abuse/neglect (n=162) | Abuse/neglect (n=132) |
|---|---|---|
| Age, M (SD) | 54.3 (3.8) | 53.8 (4.2) |
| Race, n (%) | | |
| White | 129 (80) | 86 (65)** |
| African American, Hispanic, other | 33 (20) | 46 (35) |
| BMI, M (SD) | 28.7 (6.0) | 29.3 (7.6) |
| Education, n (%) | | |
| High school, vocational school | 59 (36) | 66 (50)* |
| College education or higher | 103 (64) | 66 (50) |
| Lifetime trauma (yes), n (%) | 82 (51) | 94 (71)*** |
| Non-steroidal anti-inflammatory medications, n (%) | 25 (15) | 23 (17) |
| Physical activity, leisure time, IPAQ, median (IQR) | 565.5 (99, 1484) | 297 (0, 1049) |
| Depressive symptoms (CESD), median (IQR) | 4 (1.3, 8.8) | 8 (3, 14)*** |
| Current alcohol use, n (%) | | |
| > 1 drink/month | 94 (58) | 75 (57) |
| < 1 drink/month | 68 (42) | 57 (43) |

***p<.001, **p<.01, *p<.05, †p<0.10

BMI = body mass index, SD= standard deviation

**Table 5 Level of Immune Markers**

| | Baseline (N=298) (2012-2015) | Follow-up (N=148) (2017-2020) | Change over time (N= 145) (5 years) |
|---|---|---|---|
| Hs CRP (mg/L), median (IQR) | 1.4 (0.7, 3.7) | 1.6 (0.8, 4.9) | 0.2 (-0.3, 1.1) |
| IL-6 (pg/mL), median (IQR) | 2.1 (0.9, 2.2) | 1.5 (1.00, 2.7) | 0.1 (-0.3, 0.6) |
| TNF-α (pg/mL), median (IQR) | ---- | 4.1 (2.9, 5.4) | ---- |
| IL-10 (pg/mL), median (IQR) | ---- | 4.1 (3.2, 5.6) | ---- |

IQR = interquartile range

*Note:* Baseline values for women who returned for follow-up (n=148): HsCRP (mg/L), median (IQR) = 1.4 (0.7, 4.1); IL-6 (pg/mL), median (IQR) = 1.4 (0.9, 2.2)

**Table 6 Associations Between Child Abuse/Neglect and Inflammation**

| | Baseline (N=268-298) (2012-2015) | | Follow-up (N=121-148) (2017-2020) | | | | Change over time (N=115-145) (5 years) | |
|---|---|---|---|---|---|---|---|---|
| | Hs CRP B (SE) | IL-6 B (SE) | Hs CRP B (SE) | IL-6 B (SE) | TNF-α B (SE) | IL-10 B (SE) | Hs CRP B (SE) | IL-6 B (SE) |
| Sexual Abuse | -0.06 (0.08) | 0.03 (0.07) | -0.10 (0.12) | -0.01 (0.09) | 0.02 (0.10) | -0.10 (0.10) | -0.12 (0.11) | -0.04 (0.09) |
| Physical Abuse | -0.04 (0.07) | 0.07 (0.06) | 0.09 (0.10) | 0.04 (0.07) | -0.06 (0.08) | 0.08 (0.09) | 0.07 (0.09) | 0.02 (0.07) |
| Emotional Abuse | -0.03 (0.06) | **0.12 (0.05)*** | -0.01 (0.09) | 0.05 (0.07) | 0.00 (0.08) | 0.10 (0.09) | 0.09 (0.09) | 0.02 (0.07) |
| Physical Neglect | -0.06 (0.07) | **0.12 (0.06)*** | 0.04 (0.10) | 0.13 (0.08) † | -0.12 (0.08) | -0.02 (0.09) | 0.10 (0.09) | 0.11 (0.07) |
| Emotional Neglect | -0.06 (0.07) | 0.07 (0.06) | -0.01 (0.10) | 0.03 (0.08) | 0.00 (0.09) | 0.15 (0.09) | 0.01 (0.09) | 0.02 (0.07) |
| Any childhood abuse/neglect | 0.00 (0.06) | 0.05 (0.05) | 0.12 (0.08) | 0.06 (0.06) | -0.10 (0.07) | 0.05 (0.07) | 0.14 (0.08) † | 0.03 (0.06) |

**p<.01, *p<.05, †p<0.10

*Note:* Each type of abuse considered as presence versus absence according to Child Trauma Questionnaire clinical cut points

*Note:* Immune values were log transformed

Covariates for cross sectional models: age, race/ethnicity, education, body mass index (BMI), and immune medication; covariates for longitudinal models: baseline age, race/ethnicity, education, inflammatory marker level, average BMI, immune medication usage at either time point, and time between visits

**Table 7 Associations Between Lifetime Trauma and Inflammation**

| | Baseline (N=268-298) (2012-2015) | | Follow-up (N=121-148) (2017-2020) | | | | Change over time (N=115-145) (5 years) | |
|---|---|---|---|---|---|---|---|---|
| | Hs CRP B (SE) | IL-6 B (SE) | Hs CRP B (SE) | IL-6 B (SE) | TNF-α B (SE) | IL-10 B (SE) | Hs CRP B (SE) | IL-6 B (SE) |
| Serious accident | 0.00 (0.07) | -0.06 (0.06) | 0.05 (0.10) | -0.10 (0.07) | -0.05 (0.08) | -0.07 (0.09) | -0.02 (0.08) | -0.11 (0.06)† |
| Natural disaster | 0.09 (0.09) | 0.03 (0.07) | **0.29 (0.12)*** | 0.11 (0.09) | -0.07 (0.10) | 0.04 (0.11) | 0.16 (0.09)† | **0.19 (0.07)**** |
| Serious illness | 0.02 (0.11) | -0.05 (0.10) | 0.00 (0.19) | -0.08 (0.13) | -0.09 (0.15) | 0.02 (0.16) | 0.05 (0.17) | 0.00 (0.13) |
| Physical attack | 0.03 (0.07) | 0.09 (0.06) | 0.03 (0.13) | 0.05 (0.09) | **-0.37 (0.10)**** | -0.04 (0.11) | 0.00 (0.09) | 0.04 (0.07) |
| Unwanted sexual contact | 0.00 (0.06) | 0.01 (0.05) | -0.05 (0.10) | 0.03 (0.07) | -0.13 (0.08) | -0.04 (0.09) | 0.00 (0.08) | 0.03 (0.06) |
| Death of a child | 0.03 (0.11) | 0.03 (0.09) | 0.22 (0.16) | -0.02 (0.12) | 0.01 (0.13) | 0.00 (0.14) | **0.34 (0.13)**** | -0.03 (0.10) |

**Table 7 (continued)**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sexual harassment | 0.13 (0.07)† | 0.04 (0.06) | 0.05 (0.09) | 0.10 (0.07) | -0.10 (0.08) | -0.01 (0.08) | 0.10 (0.07) | 0.04 (0.06) |
| Any other threatening situation | 0.01 (0.08) | 0.06 (0.06) | 0.04 (0.12) | 0.03 (0.09) | -0.17 (0.10) † | -0.08 (0.11) | -0.07 (0.09) | -0.02 (0.07) |
| Witness any dangerous situation | -0.01 (0.06) | -0.06 (0.05) | 0.08 (0.09) | 0.02 (0.07) | -0.10 (0.08) | 0.01 (0.08) | 0.03 (0.08) | -0.06 (0.06) |
| Any trauma | 0.07 (0.05) | 0.00 (0.05) | 0.16 (0.08)† | 0.07 (0.06) | 0.00 (0.07) | -0.01 (0.07) | 0.08 (0.08) | 0.06 (0.07) |

**p<.01, *p<.05, †p<0.10

*Note:* Each type of trauma considered as presence versus absence according to Nurses' Health Study life events questionnaire. Trauma was considered as presence versus absence at either time point in longitudinal analyses

*Note:* Immune values were log transformed

Covariates for cross sectional models: age, race/ethnicity, education, body mass index (BMI), immune medication; covariates for longitudinal models: baseline age, race/ethnicity, education, inflammatory marker level, average BMI, immune medication usage at either time point, and time between visits

**Table 8 Independent Effects of Child Abuse/Neglect and Lifetime Trauma**

| | Baseline (N=276-298) | | Follow-up (N=129-148) | | | | Change over time (N=122-145) | |
|---|---|---|---|---|---|---|---|---|
| | Hs CRP B (SE) | IL-6 B (SE) | Hs CRP B (SE) | IL-6 B (SE) | TNF-α B (SE) | IL-10 B (SE) | Hs CRP B (SE) | IL-6 B (SE) |
| Any child abuse/neglect | -0.08 (0.06) | 0.06 (0.05) | 0.08 (0.09) | 0.04 (0.06) | -0.11 (0.07) | 0.05 (0.08) | 0.13 (0.08)† | 0.01 (0.06) |
| Any trauma | 0.07 (0.06) | -0.01 (0.05) | 0.14 (0.09) | 0.07 (0.06) | 0.02 (0.07) | -0.02 (0.08) | 0.06 (0.08) | 0.05 (0.06) |

**p<.01, *p<.05, †p<0.10

*Note:* Each type of abuse considered as presence versus absence according to Child Trauma Questionnaire clinical cut points. Each type of trauma considered as presence versus absence according to Nurses' Health Study life events questionnaire. Trauma was considered as presence versus absence at either time point in longitudinal analyses

*Note:* Immune values were log transformed

Covariates for cross sectional models: age, race/ethnicity, education, body mass index (BMI), immune medication; covariates for longitudinal models: baseline age, race/ethnicity, education, inflammatory marker level, average BMI, immune medication usage at either time point, and time between visits

**Table 9 Interactions Between Child Abuse/Neglect and Lifetime Trauma**

| | Baseline (N=276-298) (2012-2015) | | Follow-up (N=129-148) (2017-2020) | | | | Change over time (N=122-145) (5 years) | |
|---|---|---|---|---|---|---|---|---|
| | Hs CRP B (SE) | IL-6 B (SE) | Hs CRP B (SE) | IL-6 B (SE) | TNF-α B (SE) | IL-10 B (SE) | Hs CRP B (SE) | IL-6 B (SE) |
| Any child abuse/neglect | -0.05 (0.11) | 0.00 (0.08) | 0.12 (0.16) | -0.11 (0.12) | -0.06 (0.13) | 0.24 (0.14)† | **0.34 (0.16)*** | -0.07 (0.13) |
| Any trauma | 0.09 (0.08) | -0.04 (0.06) | 0.15 (0.11) | 0.01 (0.08) | 0.04 (0.09) | 0.06 (0.09) | 0.14 (0.10) | 0.01 (0.08) |
| Any abuse * any trauma | -0.03 (0.13) | 0.09 (0.10) | -0.05 (0.19) | 0.19 (0.14) | -0.06 (0.15) | -0.26 (0.16) | -0.26 (0.18) | 0.11 (0.14) |

**p<.01, *p<.05, †p<0.10

*Note:* Each type of abuse considered as presence versus absence according to Child Trauma Questionnaire clinical cut points. Each type of trauma considered as presence versus absence according to Nurses' Health Study life events questionnaire. Trauma was considered as presence versus absence at either time point in longitudinal analyses

*Note:* Immune values were log transformed

Covariates for cross sectional models: age, race/ethnicity, education, body mass index (BMI), immune medication; covariates for longitudinal models: baseline age, race/ethnicity, education, inflammatory marker level, average BMI, immune medication usage at either time point, and time between visits

## Appendix C Supplementary Materials

**Table 10 Spearman's Correlations for Baseline Study Variables (N=298)**

| Variable | CRP | IL-6 | Child abuse | Lifetime trauma | Age | Education | Race/ethnicity | Immune medication |
|---|---|---|---|---|---|---|---|---|
| 1. CRP | | | | | | | | |
| 2. IL-6 | 0.59* | | | | | | | |
| 3. Any childhood abuse/neglect | -0.01 | 0.10† | | | | | | |
| 4. Any lifetime trauma | 0.00 | -0.01 | 0.21** | | | | | |
| 5. Age | 0.05 | 0.11† | -0.04 | -0.01 | | | | |
| 6. Education | -0.15* | -0.19* | -0.14* | 0.09 | 0.06 | | | |
| 7. Race/ethnicity | -0.13* | -0.14* | -0.16* | -0.02 | 0.11† | 0.26* | | |
| 8. Immune medication | -0.01 | -0.09 | 0.01 | -0.03 | -0.01 | 0.00 | 0.03 | |
| 9. BMI | 0.68* | 0.61* | 0.00 | -0.08 | 0.05 | -0.28* | -0.11† | 0.02 |

**p<.01, *p<.05, †p<0.10

BMI = body mass index

**Table 11 Spearman's Correlations for Follow-up Study Variables (N=148)**

| Variable | CRP | IL-6 | TNF-α | IL-10 | Child abuse | Lifetime trauma | Age | Education | Race/ethnicity | Immune medication |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. CRP | | | | | | | | | | |
| 2. IL-6 | 0.60* | | | | | | | | | |
| 3. TNF-alpha | 0.36* | 0.44* | | | | | | | | |
| 4. IL-10 | 0.20* | 0.13 | 0.39* | | | | | | | |
| 5. Any childhood abuse/neglect | 0.02 | 0.11 | -0.10 | 0.05 | | | | | | |
| 6. Any lifetime trauma | 0.07 | 0.05 | -0.01 | -0.1 | 0.27** | | | | | |
| 7. Age | 0.17* | 0.15† | 0.22* | -0.01 | -0.17* | -0.07 | | | | |
| 8. Education | -0.08 | -0.14† | -0.09 | -0.07 | -0.19* | 0.00 | 0.11 | | | |
| 9. Race/ethnicity | -0.17* | -0.16† | 0.10 | 0.02 | -0.18* | 0.11 | 0.23* | 0.36* | | |
| 10. Immune medication | 0.10 | 0.04 | 0.04 | 0.01 | 0.09 | -0.06 | 0.11 | -0.04 | 0.07 | |
| 11. BMI | 0.69* | 0.66* | 0.34* | 0.13 | 0.01 | 0.03 | 0.10 | -0.26* | -0.17 | 0.15 |

**p<.01, *p<.05, †p<0.10

BMI = body mass index

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