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GENDER AND MILD COGNITIVE IMPAIRMENT DIFFERENCES IN THE LINK BETWEEN ADVERSITY AND INFLAMMATION

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A thesis submitted in partial fulfillment of the requirements for a baccalaureate degree in Biobehavioral Health with honors in Biobehavioral Health Reviewed and approved* by the following:

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Abstract

The lifelong effects of early life adversity (ELA) are well documented and implicate important health outcomes for a growing elderly population. Prior studies indicate that ELA amplifies crosstalk between peripheral inflammation and neural circuitries, which subsequently results in chronic inflammation, and inflammatory states are differentially associated with MCI (Nusslock & Miller, 2016; Cherbuin et al., 2022). The present study predicts that mild cognitive impairment (MCI) has a moderating effect on ELA and inflammation. In addition, gender may be an important differentiating factor (Knight et al., 2022). For these reasons, it is critical to investigate the associations between gender and MCI in the link between ELA and inflammation. This study focused on participants in Bronx County, New York as part of the Einstein Aging Study, ages 70+, and examined this link in terms of multiple inflammatory markers: basal and stimulated cytokines IL-1β, IL-4, IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP).

The results of this study found significant correlations with regard to gender and MCI differences in the link between ELA and inflammation in later adulthood. Specifically, there was a significant positive correlation (correlation was significant at the 0.05 level (2-tailed)) between ELA and increased inflammatory markers for men, namely IL-6 (r = .24, p = .04), IL-8 (r = .228, p = .046), and stimulated IL-1β (r = .25, p = .04), but not women. Participants who were determined to be No-MCI ("normal cognition") showed a significant correlation between a greater number of adverse experiences and higher IL-6 (r = .16, p = .04), and those with more severe adverse experiences showed higher CRP (r = .16, p = .04). No significant correlations were found for participants with No-MCI when gender was separately examined. Participants with MCI showed a significant correlation between a greater number of adverse experiences and

lower TNF-α (r = -.28, p = .03). When gender was analyzed separately, for men with MCI, there was a significant positive correlation between adverse experiences and increased levels of inflammatory markers, namely IL-4 (r = .62, p = .008) and CRP (r = .54, p = .02), and men with MCI who had more severe adverse experiences also showed higher CRP (r = .59, p = .01). Interestingly, for women with MCI, adverse experiences were correlated with decreased levels of IL-1β (r = -.41, p = .02), and TNF-α (r = -.33, p = .04), and more severe adverse experiences were correlated with lower levels of stimulated IL-1β (r = -.40, p = .02).

This study adds to the existing literature on the associations between ELA and inflammation, including important differences in inflammatory response patterns based on gender. A prior study by Knight and colleagues (2022) may provide an explanation for the gender differences identified in the present study. That prior cross-sectional and longitudinal study determined that negative psychological states were negatively associated with ex vivo LPS-stimulated cytokine responses for women, but positively associated for men (Knight et al., 2022). The present study further supports the importance of considering gender as a factor in health research.

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Chapter 1

Introduction

Background

Early life adversity (ELA) is defined as a myriad of negative, stress-inducing experiences, including neglect, physical and emotional trauma, witnessing and experiencing violence at home or in the community, profound loss (such as the loss of a parent or caregiver), poverty, low socioeconomic status, and other chronically stressful circumstances (Hanson et al., 2021). ELA is associated with adverse effects on child mental health and development, and those effects can persist into adolescence, adulthood, and late life (Hanson et al., 2021; Cowan et al., 2015; Nusslock & Miller, 2016). Nusslock and Miller (2016) argue that ELA amplifies crosstalk between peripheral inflammation and neural circuitries, which subsequently results in chronic inflammation. Cherbuin and colleagues (2022) built on prior studies showing a possible link between inflammation and MCI, and concluded based on a large number of markers that inflammatory states were differentially associated with MCI. Moreover, systemic inflammation has been associated with many chronic diseases and negative health outcomes and is a risk factor for cognitive decline and neurodegeneration (but associations between inflammation and mild cognitive impairment (MCI) are mixed) (Nusslock & Miller, 2016; Cherbuin et al., 2022). Given that the size of the elderly population has been steadily increasing and is expected to continue to rise globally (Jongsiriyanyong & Limpawattana, 2018), it is imperative to understand more about the link between ELA and MCI. The present study posits that MCI may have a moderating effect on systemic inflammation and ELA, discussed further below.

In addition, studies suggest that gender may play a role in the health outcomes of adults who were exposed to ELA, including gender differences in inflammatory responses to negative

psychological states (Nusslock & Miller, 2016; Knight et al., 2022). This is in keeping with prior research indicating that gender is an important factor in the prevalence, detection and progression of neurodegenerative diseases; for example, one study of aging adults focusing on cognitive function and inflammation showed that women had greater systemic inflammation than men (Noss et al., 2022). Gender (a social construct) and sex (biological distinction between male and female) are often used to reference sex in research, but these terms are not interchangeable (Blakeman, 2020). Gender is an important factor in studies involving inflammation because men and women may have different inflammatory response patterns (Majd et al., 2018; Knight et al., 2022). Because ELA is associated with systemic inflammation in adulthood, inflammation may be associated with MCI, and gender may play a role, it is critical to study gender and MCI in the link between ELA and inflammation.

Cognitive Impairment

MCI is defined as the functional stage between normal cognitive decline in aging and early dementia (Petersen, 2016). MCI has been diagnosed by reference to changes in cognition, abnormal cognitive function in at least one domain, the ability to function normally in daily activities, and the absence of dementia (Jongsiriyanyong & Limpawattana, 2018). MCI may be diagnosed based on neuropsychological test scores on working memory, episodic memory, and processing speed, as well as fluid and crystalized intelligence (Jongsiriyanyong & Limpawattana, 2018). One concern for patients diagnosed with MCI is the potential for progression to dementia (Jongsiriyanyong and Limpawattana, 2018). A better understanding of the long-term risks associated with ELA has important implications for policymakers striving to reduce the risks for adverse health outcomes in the aging population, including MCI.

One of the most significant long-term risks associated with ELA is Alzheimer's disease (AD). By 2050, nearly 13 million Americans age 65 or older are expected to be affected by AD (Alzheimer's Association, 2022). There are more women with AD and dementia than men: the lifetime risk for women is 20%, compared with 10% for men, and 66% of Americans with the disease are women (Alzheimer's Association, 2022). Moreover, older Black Americans are nearly twice as likely to develop dementia than their White counterparts, and Hispanic Americans are 1.5 times more likely to develop dementia than their White counterparts (Alzheimer's Association, 2022). Similarly, AD and other forms of dementia are expected to cost the United States almost a trillion dollars by the year 2050 (Alzheimer's Association, 2022). When looking more broadly at cognitive impairment, about 11.1% of all adults in the United States currently experience some form of cognitive impairment (Centers, 2019). As it currently stands, more than 11 million Americans are providing unpaid care for those with AD and other forms of dementia and cognitive impairment (Alzheimer's Association, 2022). In 2021, these unpaid caregivers provided over 16 billion hours of care, which is valued at approximately $272 billion (Alzheimer's Association, 2022).

Corney and others conducted a systematic review of studies focusing on the association between ELA and AD and found that ELA is associated with an increased risk of AD (2022). AD is a degenerative disease that causes neuronal death (Breijyeh & Karaman, 2020). It is the most common cause of dementia, representing about 70% of all cases (Corney et al., 2022). Currently, there are few treatment options, and there is no cure (Alzheimer's Association, 2022). There are two main hypotheses regarding the cause of AD (Breijyeh & Karaman, 2020). One hypothesis is that a decrease in cholinergic innervation within the cerebral cortex region of the brain is responsible for cognitive impairment associated with AD (Hampel et al., 2018). The

second main hypothesis centers around the idea that abnormal tau protein metabolism, free radical damage, and the inflammatory responses also influence the development of AD (Breijyeh & Karaman, 2020). Specifically, hyperphosphorylated tau protein can form into intracellular neurofibrillary tangles in the brains of AD patients, which can lead to neuronal loss (Breijyeh & Karaman, 2020). Further, tau protein can accumulate at synaptic sites and may eventually lead to a loss of dendritic spines and interfere with neurotransmitters at presynaptic terminals (Breijyeh & Karaman, 2020). Other factors like age, vascular diseases, genetic differences, and head injuries are also associated with increased risk for incidences of AD (Breijyeh & Karaman, 2020).

Numerous studies have found an association between ELA and AD, although the exact etiology of AD is not yet known (Corney et al., 2022). Two of these studies were longitudinal analyses derived from the Cache County Study on Memory Health and Aging and focused on rural populations in Utah (Corney et al., 2022). A third cross-sectional study was focused on the rural and urban Aboriginal population from New South Wales, Australia (Corney et al., 2022). All three studies utilized an internationally recognized clinical diagnostic tool in identifying AD, but they did not all take account of the same covariates (Corney et al., 2022). For example, only the two Utah studies adjusted for gender and education, and only one Utah study adjusted for socioeconomic status (Corney et al., 2022). However, all three studies found an association between ELA and AD (Corney et al., 2022). Corney and others noted that ELA may increase the risk of AD through pathways in the development of AD, such as inflammation, depression, and smoking (2022). In addition, ELA may interfere with normal psychological development, alter stress responses, and contribute to negative health outcomes (Corney et al., 2022).

Lifetime Adversity

As described above, ELA is a broad term for a variety of negative, stress-inducing experiences, including trauma, deep loss, poverty, and other chronically stressful circumstances (Hanson et al., 2021). The evidence supporting the associations between ELA and its short-term consequences is well-documented (Smith & Pollak, 2020). Experiences in early life can impact a child's mental and physical health (Smith & Pollak, 2020). Not only can ELA influence a child's psychological and behavioral development, it also impacts neurological development by influencing the prefrontal and dopaminergic circuits, according to some studies in humans and other species (Smith & Pollak, 2020). Children raised in poverty show increased atypical ventrolateral prefrontal cortex-amygdala connectivity, and children exposed to other forms of early life stress show atypical changes in the prefrontal cortex (Smith & Pollak, 2020). Likewise, rodents exposed to maternal abuse or separation as pups showed decreased dendritic arborization in the prefrontal circuits (Smith & Pollak, 2020). Certain factors at play in ELA, including parental mental illness, violence, and neglect, are strongly associated with childhood mental health disorders and reportedly account for approximately half of all such disorders in children (Cowan et al., 2015).

While the association between ELA and later life mental disorders is not as strong as child-onset mental disorders, the association is present and reportedly accounts for approximately 30% of such disorders (Cowan et al., 2015, Hanson et al., 2021). Studies indicate that ELA is also associated with higher levels of stress, anxiety, and depression later in life (Hanson et al., 2021). This association extends to a heightened risk for suicide and substance abuse (Hanson et al., 2021). Further, research suggests that accumulated exposure to ELA may further exacerbate the risk of anxiety in old age (Lähdepuro et al., 2019). The association

between ELA and higher levels of stress and increased incidence of mood disorders suggests alterations of the circuits of the brain that regulate reward and motivation, including the mesocorticolimbic circuit and ventral tegmental area-hippocampal connectivity (Hanson et al., 2021). Imbalances within these brain systems are strongly correlated with mood and psychiatric disorders (Hanson et al., 2021).

Interestingly, different forms of ELA have been associated with varying degrees of increased anxiety in adulthood (Lähdepuro et al., 2019). Anxiety is a risk factor for cognitive impairment, including AD (Corney et al., 2022). One study indicates that emotional trauma, physical trauma, and low socioeconomic status in childhood are each most strongly associated with higher anxiety levels, including clinically significant anxiety, compared with other forms of early adversity (Lähdepuro et al., 2019). For example, the study conducted by Lähdepuro and others did not reveal an association between the death of a family member in childhood and increased levels of anxiety in late adulthood (2019). However, Lähdepuro and others concluded that the accumulation of multiple forms of ELA is associated with higher late-life levels of anxiety (2019). In fact, the co-occurrence of as few as any two forms of ELA, such as parental divorce coupled with low socioeconomic status, may significantly increase the risk for anxiety in late adulthood compared to one form of ELA (Lähdepuro et al., 2019).

Moreover, ELA may also increase sensitization to stressful events in adulthood (McLaughlin et al., 2009). One study examined the impact of childhood adversity on adults undergoing stressful life events and found an increased association between a stressful adult-life event and depression for participants who were exposed to childhood adversity compared with participants who were not exposed to childhood adversity (McLaughlin et al., 2009). A factor that places individuals at increased risk for depression associated with stressful adult-life events

is stress sensitization, or the reduced tolerance to stressful events (McLaughlin et al., 2009). Researchers posit that ELA may reduce the ability that adults have to cope with and withstand stressful events in adulthood (McLaughlin et al., 2009). In other words, ELA may diminish resilience for dealing with stress over the course of an exposed child's life. For example, prior studies concluded that individuals exposed to childhood trauma, including particularly maltreatment, were more likely to develop post-traumatic stress disorder in adulthood than adults who had not experienced traumatic events in childhood (McLaughlin et al., 2009). Similar to previous studies, one study found that stress sensitization was exacerbated in participants with three or more forms of ELA (McLaughlin et al., 2009). The study further noted the presence of the association between ELA and stress sensitization with respect to post-traumatic stress disorder and other forms of anxiety, as well as depression (McLaughlin et al., 2009). Likewise, other studies show increased stress sensitization in adults who experienced ELA, and sensitization was evident with respect to both high and low levels of stress in adult life and in circumstances of chronic stress in adulthood (McLaughlin et al., 2009). Thus, studies support the conclusion that ELA diminishes resilience in later adulthood under a variety of circumstances (McLaughlin et al., 2009).

While there are numerous studies establishing the association between ELA and increased levels of stress, anxiety and depression in late adulthood, researchers also note that some individuals exposed to ELA do not develop mood disorders or experience higher levels of stress in adulthood (Hanson et al., 2021). To the contrary, some research indicates that exposure to moderate levels of childhood adversity leads to the development of resilience in later life (Hanson et al., 2021). Animal studies of non-human primates and rats support the association between moderate, but not extreme, exposure to adversity in early life and less anxiety in later

life (Hanson et al., 2021). These results, however, appear to conflict with studies showing an association between ELA and decreased resilience in later life. These results indicate the need for further study into the levels of ELA and its associations with anxiety, depression, stress and mood in later life.

Inflammation

As noted above, ELA is a risk factor for systemic inflammation (Nusslock & Miller, 2016; Cherbuin et al., 2022). Inflammation is part of the body's defenses to harmful stimuli (Chen et al., 2017). Stimuli activate inflammatory cells and induce them to produce, among other things, inflammatory cytokines, which serve as biomarkers for inflammation (Chen et al., 2017). Peripheral cytokines and other proinflammatory markers can signal an immune response, but they also can signal psychological stress in healthy adults (Carpenter et al., 2010). A growing body of evidence indicates that ELA is positively associated with systemic inflammation in adulthood, and studies have assessed this association by measuring pro-inflammatory cytokines, such as IL-1β, IL-6, tumor necrosis factor-α (TNF-α), which are important factors in inflammation (Chen et al., 2017; Hirano, 2021).

In studying inflammation, basal and lipopolysaccharide (LPS) stimulated cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, and TNF-α) and C-reactive protein (CRP) are important biomarkers. IL-1β is involved in pro-inflammation, proliferation, apoptosis, and differentiation (Chen et al., 2017). IL-4 is an anti-inflammatory cytokine that regulates Th cell differentiation, cell proliferation, apoptosis, and expression of numerous genes (Luzina et al., 2012). IL-6 is a pleiotropic, pro-inflammatory cytokine involved in bone metabolism, embryonic development and other processes (Hirano, 2021). IL-8, a pro-inflammatory cytokine, activates neutrophils,

induces chemotaxis, initiates a release of lysosomal enzymes, and upregulates adhesion molecules in inflammatory environments, among other things (Bernhard et al., 2021). IL-10 is an anti-inflammatory cytokine that inhibits: (i) T helper 1 cell activation, (ii) antigen presentation by dendritic cells, and (ii) macrophage activation, with the secondary effect of reducing proinflammatory cytokine expression (Steen et al., 2020). TNF-α is involved in pro-inflammation, cytokine production, cell proliferation, apoptosis, and anti-infection (Chen et al., 2017). CRP is an inflammatory protein involved in apoptosis, phagocytosis, nitric oxide release, and cytokine production (including IL-6 and TNF-α) (Sproston & Ashworth, 2018). Because a growing body of evidence indicates that ELA is positively associated with systemic inflammation in adulthood, it is useful to assess gender and MCI differences in the link between ELA and inflammation by measuring a broad group of inflammatory markers.

Hypotheses

Based on prior research by Nusslock and Miller (2016), it was hypothesized that there would be a positive correlation between ELA and inflammation. It was also hypothesized based on work by Noss and colleagues (2022) that there would be a stronger correlation between ELA and inflammation in women, compared with men. Additionally, a stronger correlation was expected, based on work by Cherbuin and others (2022), between ELA and inflammation in individuals with MCI, compared with those determined to be No-MCI ("normal cognition"). It was also hypothesized that there would be a stronger correlation between ELA and inflammation in women with MCI, compared with men with MCI, based on prior research by Cherbuin and others (2022) and Noss and others (2022).

This study will add to the existing literature on the associations between ELA and inflammation, including important differences based on gender and MCI status. It will also provide evidence of gender differences in inflammatory response patterns and underscores the need to examine gender as a factor in health research. In addition, this study will add to existing literature focusing on associations between ELA and inflammation in individuals exhibiting MCI and those with normal cognition.

Chapter 2

Methods

Data

The present study examined gender and MCI differences in the association between ELA and inflammation in later adulthood. This current study utilized data from the Einstein Aging Study (EAS), a longitudinal study of cognitive aging and dementia, including AD (Katz et al., 2012). EAS data included surveys, cognitive assessments, and blood samples collected over decades (Katz et al., 2012). Annual assessments of participants were performed annually, including clinical evaluations, standardized assessments of daily living activities, neuropsychological battery, and self-reports of memory and cognitive complaints, psychosocial measures and medical histories (Katz et al., 2016). MCI status was determined based on objective neuropsychological tests, and the absence of functional decline, absence of impairment, measured in the IADL Lawton Brody scale, and absence of dementia (Katz et al., 2016). For the purposes of this thesis, the first year or "burst" of data were utilized for the data analysis.

Study Design

EAS collected (and continues to collect) data from over 255 Bronx residents ages 70 and up (Medicine, 2022). The participants were selected from Medicare and New York City's Registered Voter List (RVL), which were acquired from the Board of Elections (Van Bogart et al., 2022). Systematic probability sampling was utilized in order to ensure that the sample was representative of the population (Van Bogart et al., 2022). In order to be eligible, participants must have been willing to participate, aged 70 or older, dementia-free, ambulatory, fluent in English, and free of visual impairment that would interfere with operating the study smartphone

(Van Bogart et al., 2022). Exclusionary criteria included being unable to complete smartphone surveys throughout the day (Van Bogart et al., 2022). Letters of introduction that explained the project's goals and how the recipient was identified were sent to participants within each block (Van Bogart et al., 2022). Follow-up telephone calls were conducted to establish rapport, identify exclusions, and enroll participants in the study (Van Bogart et al., 2022).

Participants engaged in multiple lab visits, lab-based dispositional surveys, ecological momentary assessment (EMA) with smartphone surveys and cognitive exercises, and a wrap-up visit with blood draws and additional health assessments. Because blood samples were collected over time and not all participants followed all protocols exactly, not all eligible participants provided samples containing all inflammatory markers. Similarly, only 233 of the 255 original participants provided information to allow an assessment of MCI status. Of the 233, 174 (75%) were determined to be No-MCI, and 59 (25%) were determined to be with MCI. The participants were monetarily compensated based on how closely they followed the study's protocol.

Participants

For the present study, EAS data were utilized. Data were collected from 255 subjects between the ages of 70 and 90 with a mean age of 76.85 years and a standard deviation of 4.763. Table 1 provides descriptive statistics for participant age. Women comprised 67% (171), and men comprised 33% (84). Gender was utilized rather than sex for this study because the data for sex assigned at birth was not recorded and . gender is a broader identity category than biological sex because they are influenced by social and cultural expectations (Blakeman, 2020) which has been shown to be important in other studies XXX. Approximately 40% (104) of the participants

are non-Hispanic Black, 46% (117) are non-Hispanic white, and 11% (29) are Hispanic. Table 2 provides demographic information for participant race/ethnicity.

Materials and Measures

The variables that were collected from the EAS data and utilized in this thesis include: inflammatory biomarkers, MCI status, ELA, and demographic information (age, gender, and race). Inflammatory markers were successfully collected from blood samples in 233 of the eligible 255 participants, of which 33% (76/233) were men and 67% (157/233) were women. MCI status was determined based on a battery of objective neuropsychological tests, and the absence of functional decline, impairment, and dementia. ELA and associated risk factors were collected to examine the number of adverse events as well as the severity. Demographic information was self-disclosed by participants.

Biomarkers

The plasma cytokines analyzed in the present study were collected from blood samples and included basal and stimulated cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, and TNF-α) and plasma CRP. Blood samples were initially collected in heparin-coated tubes; after 67 samples were collected, the protocol was changed, and the remainder of samples were collected in ethylenediamine tetraacetic acid (EDTA)-coated tubes (Van Bogart et al., 2022). After excluding samples collected with heparin-coated tubes, it was determined for the present study that results did not change, so all samples were retained (Van Bogart et al., 2022). Subsamples of 1 mL were taken from each sample and incubated with lipopolysaccharide (LPS) (1 μg/mL, E. coli 055:B5, Sigma Aldrich) on a rotational shaker at 37°C with 5% carbon dioxide for two hours (Van Bogart

et al., 2022). All samples were centrifuged for 15 minutes at 1,500 g, and the resulting supernatant was aliquoted and stored at −80°C (Van Bogart et al., 2022). A multiplex (V-plex) assay was used to quantify basal and LPS-stimulated cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-α) and CRP (Van Bogart et al., 2022). The minimum detection limit for all cytokines (stimulated and basal) ranged between 0.02 and 0.07 pg/mL, and was 1.33 mg/L for CRP (Van Bogart et al., 2022). Duplicates were run for all samples, and sample pairs with coefficients of variation less than 15% were rerun (Van Bogart et al., 2022).

Statistical Analysis and Procedures

SPSS version 29.0 statistical analysis software was used to analyze the data, and multiple correlation tables were generated. The present study utilized data collected from inflammatory markers, gender, and MCI-status to determine correlations (as opposed to a regression study) and whether those correlations were statistically significant. No covariates were utilized for the present study. No additional corrections were made to correct for having multiple comparisons or outcomes. Statistical significance was identified when p-values were lower than 0.05 ($p < 0.05$).

Specifically, this study examined the association between ELA, as determined based on self-reported adversity events experienced by eligible participants, and inflammation, as determined by multiple inflammatory markers, including basal and stimulated cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, and TNF-α) and CRP. Gender was separately analyzed. ELA and inflammation were examined in participants with MCI and without MCI, and gender was separately analyzed in assessing MCI in the link between ELA and inflammation.

Chapter 3

Results

Inflammation and Adversity

There were no significant correlations for all participants (n = 235) in the link between ELA and inflammation. However, there were significant correlations between early adversity count and early adversity severity, as shown in Table 3, which displays the results of all of the participants and the correlations between ELA and inflammation.

When gender was separately analyzed for all eligible participants (n = 233) (not all participants provided blood samples for all inflammatory markers), there were no significant links for women (n = 157) with respect to any inflammatory markers. Table 4, below, displays the results of all women participants and the correlations between ELA and inflammation. However, for all eligible participants who were men, there were some correlations evident between a greater number of adverse experiences and several inflammatory markers. Men (n = 76) with adverse experiences showed higher IL-6 ($r = .24$, $p = .04$), IL-8 ($r = .228$, $p = .046$), and stimulated IL-1β ($r = .25$, $p = .04$). The other inflammatory markers that were analyzed were not deemed significant in the link between ELA and inflammation. Table 5, below, displays the results of all men participants and the correlations between ELA and inflammation.

Mild Cognitive Impairment (MCI) in the Link between ELA and Inflammation

For all participants determined to be No-MCI (n = 174), there was a significant positive correlation between a greater number of adverse experiences and higher IL-6 ($r = .16$, $p = .04$). Similarly, there was a significant positive correlation for participants (n = 174) who reported

more severe adversity and higher CRP (r = .16, p = .04). For participants with MCI (n = 59), a greater number of adverse experiences was correlated with lower TNF-α (r = -.28, p = .03).

Again, gender was separately analyzed for MCI status and the ELA/inflammation link. In men determined to be No-MCI (n = 58), there were no significant correlations between adverse experience and any of the inflammatory markers (see Table 8). Similarly, women determined to be No-MCI (n = 116) also had no significant correlations (see Table 9). For men with MCI (n = 18), a greater number of adverse experiences was correlated with higher CRP (r = .54, p = .02) and stimulated IL-4 (r = .62, p = .008) (see Table 10). Additionally, more severe adverse experiences in men with MCI were correlated with even higher CRP (r = .59, p = .01) (see Table 10). For women with MCI (n = 41), a greater number of adverse experiences was correlated with lower TNF-α (r = -.33, p = .04) and lower stimulated IL-1β (r = -.41, p = .02) (see Table 11). Moreover, women with MCI who reported more severe adverse experiences also showed lower stimulated IL-1β (r = -.40, p = .02) (see Table 11).

Table 1. Descriptive Statistics for participant age

	N	Minimum	Maximum	Mean	SD
Age	255	70	90	76.85	4.763
Valid N (listwise)	255				

Table 2. Demographic information for participant race/ethnicity

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	White, non-Hispanic	117	45.9	46.1	46.1
	Black	104	40.8	40.9	87.0
	Hispanic, White	24	9.4	9.4	96.5
	Hispanic, Black	5	2.0	2.0	98.4
	Asian	4	1.6	1.6	100.0
	Total	254	99.6	100.0	
Missing	System	1	0.4		
Total		255	100.0		

The race and ethnicity for the 254 participants who disclosed this information is set forth in table 2 (one individual did not provide this information).

Table 3. Adversity and Inflammation - All Participants

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	stim IL1b	stim IL4	stim IL6	stim IL8	stim IL10	stim TNFa
Early Adversity Count	Pearson Correlation	1	.879**	.069	-.044	-.026	.066	.016	-.039	-.108	-.023	-.012	.002	.037	.023	-.003
	Sig. (2-tailed)		<.001	.296	.501	.693	.316	.809	.555	.100	.737	.861	.982	.596	.743	.964
	N	255	255	235	235	235	235	235	235	235	210	211	211	211	211	211
Early Adversity Severity	Pearson Correlation	.879**	1	.101	-.042	-.017	.009	-.042	-.031	-.127	-.073	-.027	-.024	.007	.010	-.020
	Sig. (2-tailed)	<.001		.124	.526	.791	.887	.519	.631	.051	.295	.696	.734	.924	.883	.770
	N	255	255	235	235	235	235	235	235	235	210	211	211	211	211	211
CRP	Pearson Correlation	.069	.101	1	.186**	.070	.284**	.090	.142*	.162*	.113	.042	.136*	.047	.061	.090
	Sig. (2-tailed)	.296	.124		.004	.289	<.001	.171	.030	.013	.105	.545	.049	.495	.381	.197
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
IL1b	Pearson Correlation	-.044	-.042	.186**	1	.323**	.133*	.162*	.116	.261**	-.009	-.054	-.142*	-.162*	.018	-.172*
	Sig. (2-tailed)	.501	.526	.004		<.001	.042	.013	.075	<.001	.895	.440	.040	.019	.800	.013
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
IL4	Pearson Correlation	-.026	-.017	.070	.323**	1	.593**	.159*	.135*	.255**	-.075	-.139*	-.164*	-.278**	-.140*	-.343**
	Sig. (2-tailed)	.693	.791	.289	<.001		<.001	.015	.038	<.001	.279	.045	.017	<.001	.044	<.001
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
IL6	Pearson Correlation	.066	.009	.284**	.133*	.593**	1	.195**	.089	.365**	.086	-.029	.077	-.057	-.054	-.075
	Sig. (2-tailed)	.316	.887	<.001	.042	<.001		.003	.172	<.001	.219	.677	.265	.411	.440	.280
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
IL8	Pearson Correlation	.016	-.042	.090	.162*	.159*	.195**	1	.099	.193**	.069	-.016	-.095	-.094	-.074	-.133
	Sig. (2-tailed)	.809	.519	.171	.013	.015	.003		.128	.003	.324	.818	.170	.177	.288	.055
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
IL10	Pearson Correlation	-.039	-.031	.142*	.116	.135*	.089	.099	1	.111	-.071	-.065	-.184**	-.196**	.033	-.225**
	Sig. (2-tailed)	.555	.631	.030	.075	.038	.172	.128		.089	.309	.350	.008	.004	.633	.001
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
TNFa	Pearson Correlation	-.108	-.127	.162*	.261**	.255**	.365**	.193**	.111	1	.103	.040	-.007	-.114	.015	-.094
	Sig. (2-tailed)	.100	.051	.013	<.001	<.001	<.001	.003	.089		.138	.567	.923	.100	.832	.176
	N	235	235	235	235	235	235	235	235	235	208	209	209	209	209	209
stim IL1b	Pearson Correlation	-.023	-.073	.113	-.009	-.075	.086	.069	-.071	.103	1	.594**	.719**	.475**	.510**	.625**
	Sig. (2-tailed)	.737	.295	.105	.895	.279	.219	.324	.309	.138		<.001	<.001	<.001	<.001	<.001
	N	210	210	208	208	208	208	208	208	208	210	210	210	210	210	210

stim IL4	Pearson Correlation	-.012	-.027	.042	-.054	-.139*	-.029	-.016	-.065	.040	.594**	1	.726**	.651**	.661**	.646**
	Sig. (2-tailed)	.861	.696	.545	.440	.045	.677	.818	.350	.567	<.001		<.001	<.001	<.001	<.001
	N	211	211	209	209	209	209	209	209	209	210	211	211	211	211	211
stim IL6	Pearson Correlation	.002	-.024	.136*	-.142*	-.164*	.077	-.095	-.184**	-.007	.719**	.726**	1	.709**	.569**	.818**
	Sig. (2-tailed)	.982	.734	.049	.040	.017	.265	.170	.008	.923	<.001	<.001		<.001	<.001	<.001
	N	211	211	209	209	209	209	209	209	209	210	211	211	211	211	211
stim IL8	Pearson Correlation	.037	.007	.047	-.162*	-.278**	-.057	-.094	-.196**	-.114	.475**	.651**	.709**	1	.654**	.828**
	Sig. (2-tailed)	.596	.924	.495	.019	<.001	.411	.177	.004	.100	<.001	<.001	<.001		<.001	<.001
	N	211	211	209	209	209	209	209	209	209	210	211	211	211	211	211
stim IL10	Pearson Correlation	.023	.010	.061	.018	-.140*	-.054	-.074	.033	.015	.510**	.661**	.569**	.654**	1	.627**
	Sig. (2-tailed)	.743	.883	.381	.800	.044	.440	.288	.633	.832	<.001	<.001	<.001	<.001		<.001
	N	211	211	209	209	209	209	209	209	209	210	211	211	211	211	211
stim TNFa	Pearson Correlation	-.003	-.020	.090	-.172*	-.343**	-.075	-.133	-.225**	-.094	.625**	.646**	.818**	.828**	.627**	1
	Sig. (2-tailed)	.964	.770	.197	.013	<.001	.280	.055	.001	.176	<.001	<.001	<.001	<.001	<.001	
	N	211	211	209	209	209	209	209	209	209	210	211	211	211	211	211

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Significant results are **bolded**

Table 4. Adversity and Inflammation - Women

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity Count	Pearson Correlation	1	.882**	.048	.005	-.095	.033	-.057	-.012	-.090	-.112	-.106	-.048	.052	.001	-.032
	Sig. (2-tailed)		<.001	.551	.949	.238	.684	.475	.877	.261	.190	.215	.579	.541	.987	.707
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
Early Adversity Severity	Pearson Correlation	.882**	1	.039	.014	-.092	-.044	-.090	-.015	-.104	-.111	-.094	-.027	.050	.001	-.011
	Sig. (2-tailed)	<.001		.628	.864	.252	.588	.263	.849	.195	.192	.271	.752	.556	.988	.902
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
CRP	Pearson Correlation	.048	.039	1	.166*	.040	.327**	.109	.141	.130	.137	.103	.209*	.076	.053	.103
	Sig. (2-tailed)	.551	.628		.038	.617	<.001	.174	.078	.105	.107	.227	.014	.377	.533	.229
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
IL1b	Pearson Correlation	.005	.014	.166*	1	.449**	.366**	.311**	.242**	.297**	.047	-.003	-.029	-.232**	-.096	-.169*
	Sig. (2-tailed)	.949	.864	.038		<.001	<.001	<.001	.002	<.001	.580	.969	.731	.006	.260	.047
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
IL4	Pearson Correlation	-.095	-.092	.040	.449**	1	.409**	.359**	.289**	.280**	-.037	-.183*	-.244**	-.456**	-.308**	-.469**
	Sig. (2-tailed)	.238	.252	.617	<.001		<.001	<.001	<.001	<.001	.666	.031	.004	<.001	<.001	<.001
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139

IL6	Pearson Correlation	.033	-.044	.327**	.366**	.409**	1	.328**	.249**	.366**	.094	-.043	.123	-.054	-.070	-.068
	Sig. (2-tailed)	.684	.588	<.001	<.001	<.001		<.001	.002	<.001	.272	.614	.149	.525	.410	.425
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
IL8	Pearson Correlation	-.057	-.090	.109	.311**	.359**	.328**	1	.240**	.296**	.130	-.019	-.051	-.103	-.123	-.121
	Sig. (2-tailed)	.475	.263	.174	<.001	<.001	<.001		.002	<.001	.127	.826	.551	.228	.148	.155
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
IL10	Pearson Correlation	-.012	-.015	.141	.242**	.289**	.249**	.240**	1	.274**	-.017	.017	-.099	-.171*	-.046	-.206*
	Sig. (2-tailed)	.877	.849	.078	.002	<.001	.002	.002		<.001	.845	.843	.244	.044	.593	.015
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
TNFa	Pearson Correlation	-.090	-.104	.130	.297**	.280**	.366**	.296**	.274**	1	.154	.093	.035	-.127	-.092	-.079
	Sig. (2-tailed)	.261	.195	.105	<.001	<.001	<.001	<.001	<.001		.071	.277	.684	.137	.284	.354
	N	157	157	157	157	157	157	157	157	157	139	139	139	139	139	139
Stim IL1b	Pearson Correlation	-.112	-.111	.137	.047	-.037	.094	.130	-.017	.154	1	.685**	.734**	.468**	.513**	.653**
	Sig. (2-tailed)	.190	.192	.107	.580	.666	.272	.127	.845	.071		<.001	<.001	<.001	<.001	<.001
	N	139	139	139	139	139	139	139	139	139	139	139	139	139	139	139
Stim IL4	Pearson Correlation	-.106	-.094	.103	-.003	-.183*	-.043	-.019	.017	.093	.685**	1	.768**	.659**	.656**	.719**
	Sig. (2-tailed)	.215	.271	.227	.969	.031	.614	.826	.843	.277	<.001		<.001	<.001	<.001	<.001
	N	139	139	139	139	139	139	139	139	139	139	139	139	139	139	139
Stim IL6	Pearson Correlation	-.048	-.027	.209*	-.029	-.244**	.123	-.051	-.099	.035	.734**	.768**	1	.714**	.580**	.829**
	Sig. (2-tailed)	.579	.752	.014	.731	.004	.149	.551	.244	.684	<.001	<.001		<.001	<.001	<.001
	N	139	139	139	139	139	139	139	139	139	139	139	139	139	139	139
Stim IL8	Pearson Correlation	.052	.050	.076	-.232**	-.456**	-.054	-.103	-.171*	-.127	.468**	.659**	.714**	1	.688**	.846**
	Sig. (2-tailed)	.541	.556	.377	.006	<.001	.525	.228	.044	.137	<.001	<.001	<.001		<.001	<.001
	N	139	139	139	139	139	139	139	139	139	139	139	139	139	139	139
Stim IL10	Pearson Correlation	.001	.001	.053	-.096	-.308**	-.070	-.123	-.046	-.092	.513**	.656**	.580**	.688**	1	.719**
	Sig. (2-tailed)	.987	.988	.533	.260	<.001	.410	.148	.593	.284	<.001	<.001	<.001	<.001		<.001
	N	139	139	139	139	139	139	139	139	139	139	139	139	139	139	139
Stim TNFa	Pearson Correlation	-.032	-.011	.103	-.169*	-.469**	-.068	-.121	-.206*	-.079	.653**	.719**	.829**	.846**	.719**	1
	Sig. (2-tailed)	.707	.902	.229	.047	<.001	.425	.155	.015	.354	<.001	<.001	<.001	<.001	<.001	
	N	139	139	139	139	139	139	139	139	139	139	139	139	139	139	139

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. Gender = Women

Significant results are **bolded**

Table 5. Adversity and Inflammation - Men

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity	Pearson Correlation	1	.849**	.078	.056	.079	**.235***	.174	-.056	-.096	**.247***	.235	.137	.005	.093	.076

Count	Sig. (2-tailed)		<.001	.501	.630	.500	**.041**	.133	.634	.412	**.042**	.052	.261	.966	.448	.535
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
Early Adversity Severity	Pearson Correlation	.849**	1	.216	.155	.036	.159	.082	-.026	-.117	.133	.126	.047	-.097	.038	-.007
	Sig. (2-tailed)	<.001		.061	.182	.760	.169	.483	.820	.312	.279	.303	.699	.427	.759	.957
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
CRP	Pearson Correlation	.078	.216	1	.317**	.191	.425**	.075	.057	.146	.070	-.016	-.012	-.038	.060	.065
	Sig. (2-tailed)	.501	.061		.005	.099	<.001	.519	.628	.208	.571	.895	.919	.759	.622	.593
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
IL1b	Pearson Correlation	.056	.155	.317**	1	.464**	.246*	.188	.232*	.312**	-.090	-.244*	-.314**	-.277*	-.042	-.295*
	Sig. (2-tailed)	.630	.182	.005		<.001	.032	.103	.044	.006	.467	.043	.009	.021	.733	.014
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
IL4	Pearson Correlation	.079	.036	.191	.464**	1	.363**	.168	.470**	.229*	-.123	-.312**	-.348**	-.375**	-.052	-.377**
	Sig. (2-tailed)	.500	.760	.099	<.001		.001	.147	<.001	.047	.320	.009	.003	.002	.669	.001
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
IL6	Pearson Correlation	**.235***	.159	.425**	.246*	.363**	1	.089	.010	.243*	.185	.046	-.016	-.025	.008	-.003
	Sig. (2-tailed)	**.041**	.169	<.001	.032	.001		.444	.931	.034	.131	.707	.898	.838	.946	.979
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
IL8	Pearson Correlation	.174	.082	.075	.188	.168	.089	1	.138	-.017	-.092	-.118	-.220	-.082	-.021	-.193
	Sig. (2-tailed)	.133	.483	.519	.103	.147	.444		.236	.886	.458	.334	.070	.506	.866	.113
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
IL10	Pearson Correlation	-.056	-.026	.057	.232*	.470**	.010	.138	1	.240*	-.206	-.237*	-.343**	-.255*	.188	-.287*
	Sig. (2-tailed)	.634	.820	.628	.044	<.001	.931	.236		.036	.093	.050	.004	.035	.121	.017
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
TNFa	Pearson Correlation	-.096	-.117	.146	.312**	.229*	.243*	-.017	.240*	1	.029	-.017	-.092	-.216	.154	-.195
	Sig. (2-tailed)	.412	.312	.208	.006	.047	.034	.886	.036		.813	.892	.453	.074	.205	.108
	N	76	76	76	76	76	76	76	76	76	68	69	69	69	69	69
Stim IL1b	Pearson Correlation	**.247***	.133	.070	-.090	-.123	.185	-.092	-.206	.029	1	.596**	.670**	.497**	.497**	.552**
	Sig. (2-tailed)	**.042**	.279	.571	.467	.320	.131	.458	.093	.813		<.001	<.001	<.001	<.001	<.001
	N	68	68	68	68	68	68	68	68	68	68	68	68	68	68	68
Stim IL4	Pearson Correlation	.235	.126	-.016	-.244*	-.312**	.046	-.118	-.237*	-.017	.596**	1	.751**	.712**	.705**	.633**
	Sig. (2-tailed)	.052	.303	.895	.043	.009	.707	.334	.050	.892	<.001		<.001	<.001	<.001	<.001
	N	69	69	69	69	69	69	69	69	69	68	69	69	69	69	69
Stim IL6	Pearson Correlation	.137	.047	-.012	-.314**	-.348**	-.016	-.220	-.343**	-.092	.670**	.751**	1	.690**	.530**	.793**
	Sig. (2-tailed)	.261	.699	.919	.009	.003	.898	.070	.004	.453	<.001	<.001		<.001	<.001	<.001
	N	69	69	69	69	69	69	69	69	69	68	69	69	69	69	69
Stim IL8	Pearson Correlation	.005	-.097	-.038	-.277*	-.375**	-.025	-.082	-.255*	-.216	.497**	.712**	.690**	1	.650**	.789**
	Sig. (2-tailed)	.966	.427	.759	.021	.002	.838	.506	.035	.074	<.001	<.001	<.001		<.001	<.001
	N	69	69	69	69	69	69	69	69	69	68	69	69	69	69	69
Stim IL10	Pearson Correlation	.093	.038	.060	-.042	-.052	.008	-.021	.188	.154	.497**	.705**	.530**	.650**	1	.484**

	Sig. (2-tailed)	.448	.759	.622	.733	.669	.946	.866	.121	.205	<.001	<.001	<.001	<.001		<.001
	N	69	69	69	69	69	69	69	69	69	68	69	69	69	69	69
Stim TNFa	Pearson Correlation	.076	-.007	.065	-.295*	-.377**	-.003	-.193	-.287*	-.195	.552**	.633**	.793**	.789**	.484**	1
	Sig. (2-tailed)	.535	.957	.593	.014	.001	.979	.113	.017	.108	<.001	<.001	<.001	<.001	<.001	
	N	69	69	69	69	69	69	69	69	69	68	69	69	69	69	69

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. Gender = Men

Significant results are **bolded**

Table 6. Adversity and Inflammation - No MCI ("Normal"), All Participants

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity Count	Pearson Correlation	1	.884**	.093	.053	-.002	**.159***	.028	-.029	-.020	-.001	-.016	.020	.023	.044	-.022
	Sig. (2-tailed)		<.001	.223	.486	.984	**.037**	.710	.706	.793	.989	.843	.805	.771	.582	.788
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
Early Adversity Severity	Pearson Correlation	.884**	1	.156*	.105	-.034	.049	-.029	-.029	-.066	-.008	-.008	.031	.028	.062	-.006
	Sig. (2-tailed)	<.001		.040	.169	.656	.517	.705	.706	.387	.923	.922	.702	.729	.443	.941
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
CRP	Pearson Correlation	.093	.156*	1	.181*	.025	.314**	.103	.145	.109	.064	.019	.071	.011	.023	.044
	Sig. (2-tailed)	.223	.040		.017	.742	<.001	.178	.056	.152	.425	.817	.375	.895	.771	.587
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
IL1b	Pearson Correlation	.053	.105	.181*	1	.492**	.282**	.293**	.248**	.251**	.049	-.111	-.146	-.236**	-.083	-.199*
	Sig. (2-tailed)	.486	.169	.017		<.001	<.001	<.001	<.001	<.001	.543	.167	.068	.003	.303	.013
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
IL4	Pearson Correlation	-.002	-.034	.025	.492**	1	.287**	.312**	.387**	.233**	-.081	-.217**	-.378**	-.443**	-.204*	-.478**
	Sig. (2-tailed)	.984	.656	.742	<.001		<.001	<.001	<.001	.002	.315	.006	<.001	<.001	.010	<.001
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
IL6	Pearson Correlation	**.159***	.049	.314**	.282**	.287**	1	.283**	.173*	.343**	.076	-.041	.021	-.065	-.047	-.034
	Sig. (2-tailed)	**.037**	.517	<.001	<.001	<.001		<.001	.023	<.001	.344	.610	.790	.415	.557	.672
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
IL8	Pearson Correlation	.028	-.029	.103	.293**	.312**	.283**	1	.222**	.237**	.045	-.095	-.160*	-.103	-.099	-.161*
	Sig. (2-tailed)	.710	.705	.178	<.001	<.001	<.001		.003	.002	.573	.237	.046	.200	.216	.044
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
IL10	Pearson Correlation	-.029	-.029	.145	.248**	.387**	.173*	.222**	1	.281**	-.063	-.080	-.203*	-.155	.060	-.219**
	Sig. (2-tailed)	.706	.706	.056	<.001	<.001	.023	.003		<.001	.432	.320	.011	.053	.452	.006
	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
TNFa	Pearson Correlation	-.020	-.066	.109	.251**	.233**	.343**	.237**	.281**	1	.173*	.038	.031	-.111	-.039	-.075
	Sig. (2-tailed)	.793	.387	.152	<.001	.002	<.001	.002	<.001		.031	.633	.700	.165	.627	.353

	N	174	174	174	174	174	174	174	174	174	156	157	157	157	157	157
Stim IL1b	Pearson Correlation	-.001	-.008	.064	.049	-.081	.076	.045	-.063	.173*	1	.647**	.684**	.440**	.488**	.594**
	Sig. (2-tailed)	.989	.923	.425	.543	.315	.344	.573	.432	.031		<.001	<.001	<.001	<.001	<.001
	N	156	156	156	156	156	156	156	156	156	156	156	156	156	156	156
Stim IL4	Pearson Correlation	-.016	-.008	.019	-.111	-.217**	-.041	-.095	-.080	.038	.647**	1	.778**	.679**	.639**	.674**
	Sig. (2-tailed)	.843	.922	.817	.167	.006	.610	.237	.320	.633	<.001		<.001	<.001	<.001	<.001
	N	157	157	157	157	157	157	157	157	157	156	157	157	157	157	157
Stim IL6	Pearson Correlation	.020	.031	.071	-.146	-.378**	.021	-.160*	-.203*	.031	.684**	.778**	1	.714**	.549**	.814**
	Sig. (2-tailed)	.805	.702	.375	.068	<.001	.790	.046	.011	.700	<.001	<.001		<.001	<.001	<.001
	N	157	157	157	157	157	157	157	157	157	156	157	157	157	157	157
Stim IL8	Pearson Correlation	.023	.028	.011	-.236**	-.443**	-.065	-.103	-.155	-.111	.440**	.679**	.714**	1	.664**	.833**
	Sig. (2-tailed)	.771	.729	.895	.003	<.001	.415	.200	.053	.165	<.001	<.001	<.001		<.001	<.001
	N	157	157	157	157	157	157	157	157	157	156	157	157	157	157	157
Stim IL10	Pearson Correlation	.044	.062	.023	-.083	-.204*	-.047	-.099	.060	-.039	.488**	.639**	.549**	.664**	1	.606**
	Sig. (2-tailed)	.582	.443	.771	.303	.010	.557	.216	.452	.627	<.001	<.001	<.001	<.001		<.001
	N	157	157	157	157	157	157	157	157	157	156	157	157	157	157	157
Stim TNFa	Pearson Correlation	-.022	-.006	.044	-.199*	-.478**	-.034	-.161*	-.219**	-.075	.594**	.674**	.814**	.833**	.606**	1
	Sig. (2-tailed)	.788	.941	.587	.013	<.001	.672	.044	.006	.353	<.001	<.001	<.001	<.001	<.001	
	N	157	157	157	157	157	157	157	157	157	156	157	157	157	157	157

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. MCI = NO MCI ("Normal")

Significant figures are **bolded**

Table 7. MCI - Adversity and Inflammation, All Participants

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity Count	Pearson Correlation	1	.855**	.000	-.031	-.132	-.084	-.052	-.034	**-.284***	-.101	.018	-.022	.074	-.074	.054
	Sig. (2-tailed)		<.001	.998	.819	.320	.529	.693	.801	**.029**	.482	.899	.876	.606	.607	.706
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
Early Adversity Severity	Pearson Correlation	.855**	1	-.054	-.048	-.079	-.105	-.107	-.031	-.250	-.194	-.117	-.110	-.045	-.167	-.043
	Sig. (2-tailed)	<.001		.687	.719	.551	.429	.420	.815	.056	.172	.412	.442	.755	.241	.762
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
CRP	Pearson Correlation	.000	-.054	1	.332*	.280*	.442**	.035	-.036	.132	.271	.218	.308*	.173	.193	.236
	Sig. (2-tailed)	.998	.687		.010	.032	<.001	.793	.787	.321	.054	.124	.028	.225	.175	.095
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
IL1b	Pearson Correlation	-.031	-.048	.332*	1	.349**	.425**	.137	.114	.358**	-.060	.042	-.066	-.230	-.028	-.220
	Sig. (2-tailed)	.819	.719	.010		.007	<.001	.300	.392	.005	.676	.771	.646	.104	.845	.120
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
IL4	Pearson Correlation	-.132	-.079	.280*	.349**	1	.625**	.200	.146	.274*	.024	-.213	-.038	-.362**	-.307*	-.330*
	Sig. (2-tailed)	.320	.551	.032	.007		<.001	.129	.271	.036	.866	.134	.790	.009	.028	.018
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
IL6	Pearson Correlation	-.084	-.105	.442**	.425**	.625**	1	.158	.152	.297*	.237	.021	.212	.041	-.030	-.068
	Sig. (2-tailed)	.529	.429	<.001	<.001	<.001		.232	.251	.022	.093	.882	.135	.773	.835	.635
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
IL8	Pearson Correlation	-.052	-.107	.035	.137	.200	.158	1	.119	.103	.139	.044	-.012	-.025	-.016	-.067
	Sig. (2-tailed)	.693	.420	.793	.300	.129	.232		.369	.436	.331	.758	.936	.859	.909	.640
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
IL10	Pearson Correlation	-.034	-.031	-.036	.114	.146	.152	.119	1	.232	-.041	-.051	-.171	-.293*	.000	-.231
	Sig. (2-tailed)	.801	.815	.787	.392	.271	.251	.369		.078	.774	.721	.229	.037	1.000	.102
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
TNFa	Pearson Correlation	**-.284***	-.250	.132	.358**	.274*	.297*	.103	.232	1	.045	.115	-.081	-.243	.030	-.170
	Sig. (2-tailed)	**.029**	.056	.321	.005	.036	.022	.436	.078		.754	.423	.573	.085	.834	.233
	N	59	59	59	59	59	59	59	59	59	51	51	51	51	51	51
Stim IL1b	Pearson Correlation	-.101	-.194	.271	-.060	.024	.237	.139	-.041	.045	1	.707**	.797**	.570**	.566**	.698**
	Sig. (2-tailed)	.482	.172	.054	.676	.866	.093	.331	.774	.754		<.001	<.001	<.001	<.001	<.001
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51
Stim IL4	Pearson Correlation	.018	-.117	.218	.042	-.213	.021	.044	-.051	.115	.707**	1	.718**	.683**	.793**	.751**
	Sig. (2-tailed)	.899	.412	.124	.771	.134	.882	.758	.721	.423	<.001		<.001	<.001	<.001	<.001
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51
Stim IL6	Pearson Correlation	-.022	-.110	.308*	-.066	-.038	.212	-.012	-.171	-.081	.797**	.718**	1	.717**	.639**	.843**

	Sig. (2-tailed)	.876	.442	.028	.646	.790	.135	.936	.229	.573	<.001	<.001		<.001	<.001	<.001
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51
Stim IL8	Pearson Correlation	.074	-.045	.173	-.230	-.362**	.041	-.025	-.293*	-.243	.570**	.683**	.717**	1	.714**	.806**
	Sig. (2-tailed)	.606	.755	.225	.104	.009	.773	.859	.037	.085	<.001	<.001	<.001		<.001	<.001
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51
Stim IL10	Pearson Correlation	-.074	-.167	.193	-.028	-.307*	-.030	-.016	.000	.030	.566**	.793**	.639**	.714**	1	.788**
	Sig. (2-tailed)	.607	.241	.175	.845	.028	.835	.909	1.000	.834	<.001	<.001	<.001	<.001		<.001
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51
Stim TNFa	Pearson Correlation	.054	-.043	.236	-.220	-.330*	-.068	-.067	-.231	-.170	.698**	.751**	.843**	.806**	.788**	1
	Sig. (2-tailed)	.706	.762	.095	.120	.018	.635	.640	.102	.233	<.001	<.001	<.001	<.001	<.001	
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. MCI = MCI

Significant figures are **bolded**

Table 8. Adversity and Inflammation - No MCI ("Normal"), Men

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity Count	Pearson Correlation	1	.833**	-.028	.090	.108	.247	.095	-.045	-.122	.169	.095	.077	-.079	.063	.013
	Sig. (2-tailed)		<.001	.835	.503	.422	.061	.477	.739	.362	.236	.505	.588	.578	.657	.926
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
Early Adversity Severity	Pearson Correlation	.833**	1	.131	.186	.041	.121	.025	-.010	-.158	.023	.020	-.008	-.194	.019	-.072
	Sig. (2-tailed)	<.001		.326	.162	.762	.367	.855	.940	.237	.873	.888	.954	.169	.895	.612
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
CRP	Pearson Correlation	-.028	.131	1	.366**	.246	.450**	.157	.132	.148	-.037	-.128	-.138	-.176	-.013	-.051
	Sig. (2-tailed)	.835	.326		.005	.063	<.001	.241	.322	.267	.799	.365	.330	.212	.929	.719
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
IL1b	Pearson Correlation	.090	.186	.366**	1	.509**	.231	.311*	.239	.266*	-.018	-.260	-.307*	-.285*	-.005	-.290*
	Sig. (2-tailed)	.503	.162	.005		<.001	.081	.017	.071	.043	.898	.062	.027	.041	.972	.037
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
IL4	Pearson Correlation	.108	.041	.246	.509**	1	.348**	.277*	.506**	.285*	-.140	-.329*	-.416**	-.352*	.047	-.421**
	Sig. (2-tailed)	.422	.762	.063	<.001		.007	.035	<.001	.030	.329	.017	.002	.011	.740	.002
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
IL6	Pearson Correlation	.247	.121	.450**	.231	.348**	1	.189	.002	.257	.183	.037	-.013	-.042	.020	-.012
	Sig. (2-tailed)	.061	.367	<.001	.081	.007		.155	.986	.052	.198	.794	.930	.767	.887	.936

	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
IL8	Pearson Correlation	.095	.025	.157	.311*	.277*	.189	1	.091	.003	-.125	-.204	-.226	-.052	-.011	-.166
	Sig. (2-tailed)	.477	.855	.241	.017	.035	.155		.497	.983	.382	.147	.107	.713	.938	.239
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
IL10	Pearson Correlation	-.045	-.010	.132	.239	.506**	.002	.091	1	.264*	-.111	-.200	-.320*	-.198	.299*	-.256
	Sig. (2-tailed)	.739	.940	.322	.071	<.001	.986	.497		.045	.438	.155	.021	.160	.031	.067
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
TNFa	Pearson Correlation	-.122	-.158	.148	.266*	.285*	.257	.003	.264*	1	.158	.032	-.053	-.228	.203	-.207
	Sig. (2-tailed)	.362	.237	.267	.043	.030	.052	.983	.045		.267	.822	.709	.104	.148	.142
	N	58	58	58	58	58	58	58	58	58	51	52	52	52	52	52
Stim IL1b	Pearson Correlation	.169	.023	-.037	-.018	-.140	.183	-.125	-.111	.158	1	.573**	.620**	.444**	.502**	.493**
	Sig. (2-tailed)	.236	.873	.799	.898	.329	.198	.382	.438	.267		<.001	<.001	.001	<.001	<.001
	N	51	51	51	51	51	51	51	51	51	51	51	51	51	51	51
Stim IL4	Pearson Correlation	.095	.020	-.128	-.260	-.329*	.037	-.204	-.200	.032	.573**	1	.812**	.695**	.745**	.620**
	Sig. (2-tailed)	.505	.888	.365	.062	.017	.794	.147	.155	.822	<.001		<.001	<.001	<.001	<.001
	N	52	52	52	52	52	52	52	52	52	51	52	52	52	52	52
Stim IL6	Pearson Correlation	.077	-.008	-.138	-.307*	-.416**	-.013	-.226	-.320*	-.053	.620**	.812**	1	.680**	.498**	.752**
	Sig. (2-tailed)	.588	.954	.330	.027	.002	.930	.107	.021	.709	<.001	<.001		<.001	<.001	<.001
	N	52	52	52	52	52	52	52	52	52	51	52	52	52	52	52
Stim IL8	Pearson Correlation	-.079	-.194	-.176	-.285*	-.352*	-.042	-.052	-.198	-.228	.444**	.695**	.680**	1	.583**	.778**
	Sig. (2-tailed)	.578	.169	.212	.041	.011	.767	.713	.160	.104	.001	<.001	<.001		<.001	<.001
	N	52	52	52	52	52	52	52	52	52	51	52	52	52	52	52
Stim IL10	Pearson Correlation	.063	.019	-.013	-.005	.047	.020	-.011	.299*	.203	.502**	.745**	.498**	.583**	1	.394**
	Sig. (2-tailed)	.657	.895	.929	.972	.740	.887	.938	.031	.148	<.001	<.001	<.001	<.001		.004
	N	52	52	52	52	52	52	52	52	52	51	52	52	52	52	52
Stim TNFa	Pearson Correlation	.013	-.072	-.051	-.290*	-.421**	-.012	-.166	-.256	-.207	.493**	.620**	.752**	.778**	.394**	1
	Sig. (2-tailed)	.926	.612	.719	.037	.002	.936	.239	.067	.142	<.001	<.001	<.001	<.001	.004	
	N	52	52	52	52	52	52	52	52	52	51	52	52	52	52	52

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. MCI = NO MCI ("Normal"), Gender = Men

Significant figures are **bolded**

Table 9. No MCI (“Normal”), Women

	Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa

Early Adversity Count	Pearson Correlation	1	.901**	.137	.028	-.056	.136	.007	-.008	.040	-.047	-.057	-.002	.059	.034	-.032
	Sig. (2-tailed)		<.001	.143	.762	.548	.144	.941	.933	.666	.633	.562	.981	.551	.731	.747
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
Early Adversity Severity	Pearson Correlation	.901**	1	.158	.062	-.076	.038	-.043	-.022	-.011	-.004	-.020	.050	.101	.073	.024
	Sig. (2-tailed)	<.001		.090	.507	.420	.684	.648	.817	.905	.965	.839	.613	.305	.458	.811
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
CRP	Pearson Correlation	.137	.158	1	.075	-.089	.261**	.082	.167	.104	.111	.075	.177	.091	.037	.091
	Sig. (2-tailed)	.143	.090		.427	.344	.005	.383	.074	.266	.261	.446	.071	.353	.707	.356
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
IL1b	Pearson Correlation	.028	.062	.075	1	.481**	.325**	.291**	.271**	.261**	.087	-.048	-.055	-.218*	-.124	-.149
	Sig. (2-tailed)	.762	.507	.427		<.001	<.001	.002	.003	.005	.377	.624	.577	.026	.206	.129
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
IL4	Pearson Correlation	-.056	-.076	-.089	.481**	1	.276**	.337**	.345**	.230*	-.054	-.177	-.360**	-.490**	-.317**	-.503**
	Sig. (2-tailed)	.548	.420	.344	<.001		.003	<.001	<.001	.013	.587	.071	<.001	<.001	.001	<.001
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
IL6	Pearson Correlation	.136	.038	.261**	.325**	.276**	1	.324**	.259**	.374**	.027	-.070	.036	-.071	-.073	-.049
	Sig. (2-tailed)	.144	.684	.005	<.001	.003		<.001	.005	<.001	.786	.480	.715	.470	.457	.619
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
IL8	Pearson Correlation	.007	-.043	.082	.291**	.337**	.324**	1	.292**	.349**	.110	-.048	-.126	-.125	-.140	-.162
	Sig. (2-tailed)	.941	.648	.383	.002	<.001	<.001		.001	<.001	.263	.626	.201	.204	.155	.100
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
IL10	Pearson Correlation	-.008	-.022	.167	.271**	.345**	.259**	.292**	1	.276**	-.057	-.013	-.131	-.127	-.080	-.212*
	Sig. (2-tailed)	.933	.817	.074	.003	<.001	.005	.001		.003	.566	.895	.182	.198	.418	.030
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
TNFa	Pearson Correlation	.040	-.011	.104	.261**	.230*	.374**	.349**	.276**	1	.165	.047	.067	-.056	-.133	-.026
	Sig. (2-tailed)	.666	.905	.266	.005	.013	<.001	<.001	.003		.092	.637	.498	.571	.175	.790
	N	116	116	116	116	116	116	116	116	116	105	105	105	105	105	105
Stim IL1b	Pearson Correlation	-.047	-.004	.111	.087	-.054	.027	.110	-.057	.165	1	.674**	.713**	.446**	.491**	.634**
	Sig. (2-tailed)	.633	.965	.261	.377	.587	.786	.263	.566	.092		<.001	<.001	<.001	<.001	<.001
	N	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
Stim IL4	Pearson Correlation	-.057	-.020	.075	-.048	-.177	-.070	-.048	-.013	.047	.674**	1	.770**	.675**	.600**	.699**
	Sig. (2-tailed)	.562	.839	.446	.624	.071	.480	.626	.895	.637	<.001		<.001	<.001	<.001	<.001
	N	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
Stim IL6	Pearson Correlation	-.002	.050	.177	-.055	-.360**	.036	-.126	-.131	.067	.713**	.770**	1	.732**	.575**	.845**
	Sig. (2-tailed)	.981	.613	.071	.577	<.001	.715	.201	.182	.498	<.001	<.001		<.001	<.001	<.001
	N	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
Stim IL8	Pearson Correlation	.059	.101	.091	-.218*	-.490**	-.071	-.125	-.127	-.056	.446**	.675**	.732**	1	.697**	.861**
	Sig. (2-tailed)	.551	.305	.353	.026	<.001	.470	.204	.198	.571	<.001	<.001	<.001		<.001	<.001
	N	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
Stim IL10	Pearson Correlation	.034	.073	.037	-.124	-.317**	-.073	-.140	-.080	-.133	.491**	.600**	.575**	.697**	1	.700**

	Sig. (2-tailed)	.731	.458	.707	.206	.001	.457	.155	.418	.175	<.001	<.001	<.001	<.001		<.001
	N	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
Stim TNFa	Pearson Correlation	-.032	.024	.091	-.149	-.503**	-.049	-.162	-.212*	-.026	.634**	.699**	.845**	.861**	.700**	1
	Sig. (2-tailed)	.747	.811	.356	.129	<.001	.619	.100	.030	.790	<.001	<.001	<.001	<.001	<.001	
	N	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
a. MCI = NO MCI ("Normal"), Gender = Women
Significant figures are **bolded**

Table 10. MCI, Men

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity Count	Pearson Correlation	1	.923**	**.541***	-.138	-.045	.190	.392	-.102	.037	.478	**.621****	.317	.272	.207	.284
	Sig. (2-tailed)		<.001	**.020**	.586	.859	.449	.108	.686	.884	.052	**.008**	.215	.292	.426	.270
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
Early Adversity Severity	Pearson Correlation	.923**	1	**.589***	-.034	.020	.313	.285	-.092	.119	.424	.441	.228	.229	.110	.216
	Sig. (2-tailed)	<.001		**.010**	.894	.938	.206	.251	.718	.637	.089	.077	.378	.376	.674	.404
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
CRP	Pearson Correlation	**.541***	**.589***	1	-.008	-.091	.166	-.109	-.344	.165	.361	.352	.444	.490*	.387	.516*
	Sig. (2-tailed)	**.020**	**.010**		.975	.719	.511	.667	.163	.514	.154	.166	.074	.046	.125	.034
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
IL1b	Pearson Correlation	-.138	-.034	-.008	1	.152	.451	-.267	.184	.705**	-.380	-.257	-.476	-.309	-.322	-.402
	Sig. (2-tailed)	.586	.894	.975		.548	.060	.283	.465	.001	.133	.319	.054	.228	.207	.110
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
IL4	Pearson Correlation	-.045	.020	-.091	.152	1	.556*	-.153	.266	-.125	-.051	-.281	-.119	-.481	-.516*	-.209
	Sig. (2-tailed)	.859	.938	.719	.548		.017	.543	.287	.621	.847	.274	.650	.051	.034	.421
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
IL6	Pearson Correlation	.190	.313	.166	.451	.556*	1	-.146	.125	.226	.083	.090	-.020	.040	-.091	-.009
	Sig. (2-tailed)	.449	.206	.511	.060	.017		.562	.622	.367	.752	.731	.939	.878	.729	.972
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
IL8	Pearson Correlation	.392	.285	-.109	-.267	-.153	-.146	1	.292	-.106	.048	.047	-.222	-.147	-.033	-.246
	Sig. (2-tailed)	.108	.251	.667	.283	.543	.562		.239	.676	.855	.858	.391	.574	.899	.342
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
IL10	Pearson Correlation	-.102	-.092	-.344	.184	.266	.125	.292	1	.080	-.454	-.390	-.456	-.497*	-.341	-.427
	Sig. (2-tailed)	.686	.718	.163	.465	.287	.622	.239		.753	.067	.122	.066	.042	.181	.087
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
TNFa	Pearson Correlation	.037	.119	.165	.705**	-.125	.226	-.106	.080	1	-.427	-.220	-.278	-.188	-.119	-.168

	Sig. (2-tailed)	.884	.637	.514	.001	.621	.367	.676	.753		.087	.397	.281	.470	.648	.520
	N	18	18	18	18	18	18	18	18	18	17	17	17	17	17	17
Stim IL1b	Pearson Correlation	.478	.424	.361	-.380	-.051	.083	.048	-.454	-.427	1	.670**	.813**	.654**	.532*	.704**
	Sig. (2-tailed)	.052	.089	.154	.133	.847	.752	.855	.067	.087		.003	<.001	.004	.028	.002
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Stim IL4	Pearson Correlation	**.621****	.441	.352	-.257	-.281	.090	.047	-.390	-.220	.670**	1	.613**	.760**	.619**	.675**
	Sig. (2-tailed)	**.008**	.077	.166	.319	.274	.731	.858	.122	.397	.003		.009	<.001	.008	.003
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Stim IL6	Pearson Correlation	.317	.228	.444	-.476	-.119	-.020	-.222	-.456	-.278	.813**	.613**	1	.716**	.646**	.913**
	Sig. (2-tailed)	.215	.378	.074	.054	.650	.939	.391	.066	.281	<.001	.009		.001	.005	<.001
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Stim IL8	Pearson Correlation	.272	.229	.490*	-.309	-.481	.040	-.147	-.497*	-.188	.654**	.760**	.716**	1	.887**	.822**
	Sig. (2-tailed)	.292	.376	.046	.228	.051	.878	.574	.042	.470	.004	<.001	.001		<.001	<.001
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Stim IL10	Pearson Correlation	.207	.110	.387	-.322	-.516*	-.091	-.033	-.341	-.119	.532*	.619**	.646**	.887**	1	.801**
	Sig. (2-tailed)	.426	.674	.125	.207	.034	.729	.899	.181	.648	.028	.008	.005	<.001		<.001
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Stim TNFa	Pearson Correlation	.284	.216	.516*	-.402	-.209	-.009	-.246	-.427	-.168	.704**	.675**	.913**	.822**	.801**	1
	Sig. (2-tailed)	.270	.404	.034	.110	.421	.972	.342	.087	.520	.002	.003	<.001	<.001	<.001	
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. MCI = MCI, Gender = Men

Significant figures are **bolded**

Table 11. MCI, Women

		Early Adversity Count	Early Adversity Severity	CRP	IL1b	IL4	IL6	IL8	IL10	TNFa	Stim IL1b	Stim IL4	Stim IL6	Stim IL8	Stim IL10	Stim TNFa
Early Adversity Count	Pearson Correlation	1	.848**	-.166	-.048	-.180	-.161	-.234	-.030	**-.326***	**-.414***	-.312	-.217	-.058	-.224	-.078
	Sig. (2-tailed)		<.001	.300	.764	.260	.316	.141	.854	**.038**	**.015**	.072	.218	.745	.202	.663
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
Early Adversity Severity	Pearson Correlation	.848**	1	-.276	-.122	-.157	-.233	-.242	-.042	-.281	**-.395***	-.297	-.219	-.119	-.238	-.110
	Sig. (2-tailed)	<.001		.081	.447	.326	.142	.128	.793	.075	**.021**	.088	.213	.501	.175	.536
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
CRP	Pearson Correlation	-.166	-.276	1	.318*	.291	.429**	.154	.000	.183	.234	.170	.283	.113	.171	.186
	Sig. (2-tailed)	.300	.081		.042	.065	.005	.336	.998	.251	.182	.338	.105	.524	.334	.291
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
IL1b	Pearson Correlation	-.048	-.122	.318*	1	.330*	.369*	.333*	.081	.368*	-.022	.090	.009	-.212	.041	-.187

	Sig. (2-tailed)	.764	.447	.042		.035	.017	.033	.616	.018	.902	.615	.960	.228	.817	.290
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
IL4	Pearson Correlation	-.180	-.157	.291	.330*	1	.609**	.397*	.105	.372*	.023	-.225	-.019	-.318	-.249	-.368*
	Sig. (2-tailed)	.260	.326	.065	.035		<.001	.010	.515	.016	.896	.200	.914	.067	.156	.032
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
IL6	Pearson Correlation	-.161	-.233	.429**	.369*	.609**	1	.318*	.137	.356*	.268	-.009	.284	.092	.003	-.064
	Sig. (2-tailed)	.316	.142	.005	.017	<.001		.043	.391	.022	.126	.959	.104	.603	.988	.721
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
IL8	Pearson Correlation	-.234	-.242	.154	.333*	.397*	.318*	1	.060	.177	.211	.051	.129	.052	-.015	.041
	Sig. (2-tailed)	.141	.128	.336	.033	.010	.043		.709	.268	.231	.773	.466	.769	.931	.816
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
IL10	Pearson Correlation	-.030	-.042	.000	.081	.105	.137	.060	1	.272	.094	.062	-.069	-.204	.123	-.155
	Sig. (2-tailed)	.854	.793	.998	.616	.515	.391	.709		.086	.596	.726	.696	.248	.489	.380
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
TNFa	Pearson Correlation	**-.326***	-.281	.183	.368*	.372*	.356*	.177	.272	1	.146	.192	-.042	-.287	.059	-.183
	Sig. (2-tailed)	**.038**	.075	.251	.018	.016	.022	.268	.086		.409	.277	.812	.100	.741	.299
	N	41	41	41	41	41	41	41	41	41	34	34	34	34	34	34
Stim IL1b	Pearson Correlation	**-.414***	**-.395***	.234	-.022	.023	.268	.211	.094	.146	1	.721**	.792**	.550**	.590**	.707**
	Sig. (2-tailed)	**.015**	**.021**	.182	.902	.896	.126	.231	.596	.409		<.001	<.001	<.001	<.001	<.001
	N	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
Stim IL4	Pearson Correlation	-.312	-.297	.170	.090	-.225	-.009	.051	.062	.192	.721**	1	.766**	.664**	.875**	.795**
	Sig. (2-tailed)	.072	.088	.338	.615	.200	.959	.773	.726	.277	<.001		<.001	<.001	<.001	<.001
	N	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
Stim IL6	Pearson Correlation	-.217	-.219	.283	.009	-.019	.284	.129	-.069	-.042	.792**	.766**	1	.729**	.639**	.814**
	Sig. (2-tailed)	.218	.213	.105	.960	.914	.104	.466	.696	.812	<.001	<.001		<.001	<.001	<.001
	N	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
Stim IL8	Pearson Correlation	-.058	-.119	.113	-.212	-.318	.092	.052	-.204	-.287	.550**	.664**	.729**	1	.631**	.799**
	Sig. (2-tailed)	.745	.501	.524	.228	.067	.603	.769	.248	.100	<.001	<.001	<.001		<.001	<.001
	N	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
Stim IL10	Pearson Correlation	-.224	-.238	.171	.041	-.249	.003	-.015	.123	.059	.590**	.875**	.639**	.631**	1	.782**
	Sig. (2-tailed)	.202	.175	.334	.817	.156	.988	.931	.489	.741	<.001	<.001	<.001	<.001		<.001
	N	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34
Stim TNFa	Pearson Correlation	-.078	-.110	.186	-.187	-.368*	-.064	.041	-.155	-.183	.707**	.795**	.814**	.799**	.782**	1
	Sig. (2-tailed)	.663	.536	.291	.290	.032	.721	.816	.380	.299	<.001	<.001	<.001	<.001	<.001	
	N	34	34	34	34	34	34	34	34	34	34	34	34	34	34	34

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. MCI = MCI, Gender = Women

Significant figures are **bolded**

Chapter 4

Discussion

Prior studies showed that ELA is associated with systemic inflammation (Nusslock & Miller, 2016). Inflammatory states have also been associated with MCI (Cherbuin et al., 2020). In addition, studies suggest that gender influences the health outcomes of adults who were exposed to ELA, including gender differences in inflammatory responses (Nusslock & Miller, 2016; Knight et al., 2022). Women generally have higher levels of inflammatory markers (Van Bogart et al., 2022). However, based on prior research, few studies have examined gender and MCI-status in the link between ELA and inflammation. This study examined the gender and MCI differences in the link between ELA and inflammation in later adulthood with specific focus on selected inflammatory markers (basal and stimulated cytokines and CRP). In contrast to other studies, the present study did not find significant links between ELA and inflammation in the sample group as a whole (n = 233). This result in the present study is inconsistent with prior research, which provides evidence that ELA sensitizes the immune cells that initiate and sustain inflammation by prime monocytes and macrophages to respond more aggressively, and this sensitization persists into adulthood (Nusslock & Miller, 2016; Carpenter et al., 2010). Evidence from past studies shows that the mechanism by which ELA sensitizes immune cells may be the result of negative, stress-inducing experiences themselves as well as disproportionate exposure to pollutants, second-hand smoke, dietary sugars and fats, and psychological stressors, all of which prime monocytes and macrophages to respond more aggressively (Nusslock & Miller, 2016). The absence of significant links between ELA and inflammation in the sample group as a whole in the present study may be due to the sample size, the fact that the data were

taken from a single burst (the first year of data), or gender differences in inflammatory response patterns (Knight et al., 2022). See the Limitations section, below.

When gender was examined for all participants in the study for whom inflammatory markers were provided, there were no significant links for women (n = 157), but there were significant correlations between a greater number of adverse experiences and higher IL-6, IL-8, and stimulated IL-1β for men (n = 76). Interestingly, in a study of the associations between depression and inflammatory markers, higher depressive symptoms in women were associated with significantly lower stimulated TNF-α and IL-10, and marginally lower stimulated IL-6, while higher depressive symptoms in men were associated with significantly higher stimulated TNF-α and marginally higher stimulated IL-6 (Majd et al., 2018). Majd and colleagues suggest that there may be gender differences in inflammatory response patterns in stimulated cytokines and collected very similar data from Bronx residents ages 25-65 years old. Similarly, a recent cross-sectional and longitudinal analyses from three annual waves determined that negative psychological states (depressive symptoms, negative affect, rumination, and perceived stress) were negatively associated with ex vivo LPS-stimulated cytokine responses for women, but positively associated for men (Knight et al., 2022). These studies may provide an explanation for the gender differences identified in the present study. The results in the present study may be due to differing inflammatory responses between men and women, the sample size, or the fact that the data were taken from a single burst, rather than a longitudinal study. (See Limitations, below). Thus, the data did not support the hypotheses with respect to the correlation between ELA and inflammation (*i.e.,* that there would be a significant correlation between ELA and inflammation) or with respect to gender in the link between ELA and inflammation (*i.e.,* that there would be a stronger correlation between ELA and inflammation in women, compared with

men). These differences based on gender may also be attributable to resilience factors, including whether men and women respond differently to adverse experiences, but further research is required.

This study also examined MCI as a moderator between ELA and inflammation. For participants with MCI (n = 59), a greater number of adverse experiences was correlated with lower TNF-α. When gender was separately analyzed, women with MCI who had a greater number of adverse experiences showed lower TNF-α and IL-1β. Moreover, women with MCI who reported more severe adverse experiences also displayed lower stimulated IL-1β. However, men with MCI who had a greater number of adverse experiences showed higher stimulated IL-4 and higher CRP, and more severe adverse experiences also were correlated with higher CRP. As noted above, past studies provide evidence for gender differences in inflammatory response patterns in stimulated cytokines, which may explain the results of the present study and underscores the need to examine gender as a factor in future studies (Majd et al., 2018; Knight, et al., 2022). Thus, the present study did not support the hypothesis that there would be a stronger correlation between ELA and inflammation in women with MCI, compared with men with MCI. On the contrary, men with MCI showed elevated immune responses while women with MCI showed blunted immune responses. Again, this suggests the need for further research regarding gender differences in inflammatory response patterns.

With respect to those participants with No-MCI as a group (n = 174), a greater number of adverse experiences was associated with higher IL-6, and more severe adversity was associated with higher CRP. Interestingly, when the results were examined based on gender for MCI status and inflammation, there were no significant relationships between adverse experiences and any of the variables examined for men or women who were determined to be No-MCI. This may be

due to the sample size of women (n = 116) and men (n = 58) determined to be No-MCI. While this is not a particularly small sample size, a larger sample could aid in creating stronger inferences.

Limitations

Support for the hypothesis confirming the associations between gender and MCI in the link between ELA and systemic inflammation in late adulthood was not conclusively identified. One possible reason for the lack of evidence could be the self-reported measures. It is impossible to objectively measure or ensure accurate reporting of ELA. These events occurred in the past and participants may not have wanted to disclose such personal information, may not have remembered the events accurately, or could have been exaggerating or minimizing their past experiences. Similarly, participants could have been biased in their recall of ELA and other self-reported measures. This limitation is shared by other studies, which also relied on self-reports of ELA (Carpenter et al., 2010; Corney et al., 2022)

In addition, not all participants provided all the requested blood samples, so data on all inflammatory markers was not collected for all participants. This may have reduced the strength of the results. If more participants had followed the protocol more closely, then the results may have varied. Notwithstanding these limitations, the results do show promising evidence of gender and MCI-status differences in the association between ELA and inflammation, and adds to the body of evidence indicating that men and women may exhibit different inflammatory response patterns (Majd et al., 2018; Knight et al., 2022)..

Another potential limitation of this study is the sample size. Despite the participants being selected using systematic probability sampling, there were still only 255 participants that

were able to be used for the data collection relevant to this thesis. Although every effort was made to collect complete data during the Covid-19 pandemic, it was a challenging time for researchers and participants and unfortunately interrupted the collection of data. Had a larger number of participants had been included, the data may have been more inclusive and a better representation of the local population being studied. Moreover, this study had more participants who identified as women than men. There were 157 women who consented to participate in the study but only 76 men. In addition, only 59 participants were determined to have MCI while 174 participants were determined to be No-MCI. If these numbers were larger, then the data may show stronger relationships between the variables. No additional analyses were conducted to determine the minimum sample size that would be needed to detect effects.

Despite these limitations, the present study contributes to the growing body of literature on gender and MCI differences in the link between ELA and inflammation. Further research is needed to better understand the influence that gender may have on ELA and inflammation. Similarly, more research is required to fully grasp the effect that ELA has on MCI.

Chapter 5

Conclusions and Future Directions

It was hypothesized that there would be significant correlations between gender and MCI in the link between ELA and systemic inflammation in late adulthood. The study provides evidence of a significant positive correlation between ELA and increased inflammatory markers for men. Participants who were determined to be No-MCI ("normal cognition") also showed a significant correlation between ELA and inflammation, although significant correlations were not found for participants with No-MCI when gender was examined separately. Participants with MCI showed a significant correlation between a greater number of adverse experiences and lower TNF-α. When gender was analyzed separately, for men with MCI, there was a significant positive correlation between adverse experiences and increased levels of inflammatory markers (IL-4 and CRP), and men with MCI who had more severe adverse experiences also showed higher CRP. For women with MCI, adverse experiences were correlated with decreased levels of stimulated IL-1β and TNF-α, and more severe adverse experiences were correlated with lower levels of stimulated IL-1β. Like prior studies (Majd et al., 2018; Knight et al., 2022), the results of this study provide evidence of gender differences in inflammatory response patterns and underscores the need to examine gender as a factor in health research. Here, these results demonstrate the importance of understanding how gender impacts the links among MCI, ELA, and inflammation, and may have important implications for health in clinical and research settings. Further investigation into the gender differences in inflammatory response patterns would improve clinicians' understanding of how and why women may exhibit blunted immune responsiveness while men exhibit elevated immune responsiveness (Majd et al., 2018; Knight et al., 2022).

As a result, there are several possible adjustments that could be advantageous for future studies. Collecting data from a larger sample could aid in finding more significant associations, as could better adherence by a greater number of participants to the collection of inflammatory markers. Moreover, analyzing multiple "bursts" or years of data longitudinally would likely strengthen causal inference. In addition, resilience may have also impacted the differing results between men and women. There is currently little research surrounding resilience as a trait and how it may be impacted by gender and inflammation. Furthermore, conducting regression analyses and including potential confounding variables, such as resilience, could alter the results as well. Further research into the interplay among resilience, adversity, gender, and MCI may augment and build upon the developing understanding of gender and MCI differences in the link between ELA and inflammation and resulting health outcomes for the aging population.

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ACADEMIC VITA

Anna C. Capria

Education

The Pennsylvania State University, Schreyer Honors College — University Park, PA
Bachelor of Science in Biobehavioral Health — 2023 (expected)
Minor: Bioethics and Medical Humanities — **GPA**
Thesis: "Gender and MCI Differences in the Link between Adversity and Inflammation"
Honors and Awards

- Schreyer Honors College Scholarship, Pennsylvania State University Dean's List, Phi Eta Sigma Honors Society, National Society of Leadership and Success-Pennsylvania State University Chapter

Internship Experience

Circle of Women - Non-profit — Remote
Title: Director of Project Development — 2022-Present

- Oversee development of all projects from idea development to approved proposal
- Created proposal and won funding for girls' dormitory in rural Niger
- Drafting contract documents for funding

Necessary Behavior - Non-profit — Remote
Title: Social Media Intern — 2022

- Creating and managing social media content on multiple platforms, editorial writing, public speaking, effective communication

Clifford Chance Law firm — Remote
Title: Climate Change Intern — 2021

- Research, writing, and analyzing data

Leo Cussen Centre for Law — Remote
Title: Human Rights Law Virtual Internship — Summer 2020

- Summarized client information, memorandum regarding grounds to challenge deportation order, research regarding human rights international conventions or treaties

Research and Teaching Experience

Pennsylvania State University — State College, PA
Stress and Immunity Lab, **Research Assistant** — 2021-Present

- Research, writing, and analyzing data regarding the associations between stress, cognitive aging, hormonal regulation, and inflammatory biomarkers, and how those factors predict health outcomes

Decision Neuroscience Lab, Research Assistant — 2021

- Research and analyze neuroimaging data regarding adolescent decision-making; assist in writing Institutional Review Board protocol; communicate with participants and research team

Context and Development Lab, Research Assistant — 2020

- Translated interviews of Hispanic adolescents in low socioeconomic areas regarding their perceptions of how poverty, racism, and cultural differences impact their life experiences;
- Created and organized a database of participant records; qualitative coding

Brain Development Lab, **Research Assistant** — 2020

- Coding infant brain responses to interactions with mothers; group and independent research

Pennsylvania State University — State College, PA
Undergraduate Teaching Intern (Women's Health Issues) — 2022

- Class preparation, facilitating and monitoring student participation in class, grading, creating reviews, holding office hours

Teaching Assistant (Interdisciplinary Integration in Biobehavioral Health) — 2020-2021

- Class preparation, facilitating and monitoring student participation in class, grading, creating reviews, holding office hours

Part-Time Employment

Pennsylvania State University — State College
Information Desk Attendant — 2021-Present
- Respond to inquiries, Microsoft Excel, event management, mail organization

Private Childcare
Nanny/Childcare Provider
- Cared for infant and 5-year old for family in Huntingdon, PA — 2020-Present
- Cared for two children in Wexford, PA — 2017-2019

DoorDash — Wexford, PA
Delivery Driver — 2022
- Pick up and deliver meal orders

Owl Cleaners — Wexford
Front Desk Attendant — 2018-2020
- Opening and closing store, customer service, answering the telephone, cashier, sorting clothing and labeling

Leadership and Activities

Council of Commonwealth Student Government
Director of Student Affairs — 2021-2022
- Writing legislation, public speaking, effective communication

Elections Committee Member — 2021-2022
- Created policy for student council elections, amended the student government's constitution

Office of Sexual Misconduct Prevention & Response — 2021-2022
Board Member
- Advocated for revisions of policy and increased student resources for genderual misconduct on campus

Student Orientation and Transition Programs Planning Committee — 2021-2022
Committee Member
- Organized transition day programs for transfer students

Human Health and Development Student Council — 2022
Member
- Advocate for increased resources for students, organized professional develop events

Phi Alpha Delta - Undergraduate Chapter (Law Fraternity)
Secretary & Diversity Committee Chair — 2020-Present
- Organized philanthropic events, networking events, and volunteer work
- Created and revised diversity statements and policies

Remote Area Medical
Volunteer — 2019-Present
- Volunteered at medical clinics and learning about health care, Spanish translation

Schreyer Honors College Student Council (Social Committee) — 2019
- Planned events for the honors college, participated in THON activities, fundraised for THON and the Honors College