Childhood Maltreatment is Associated with Adult Depression: Is Inflammation to Blame?

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Thesis submitted to the faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Master of Science
in
Psychology

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December 12, 2022
Blacksburg, Virginia

Keywords: Childhood maltreatment; pro-inflammatory biomarkers; depression; MIDUS; soluble interleukin-6, tumor necrosis factor alpha, interleukin-8, c-reactive protein

Abstract

By 2030 major depression is predicted to be the leading cause of disease burden in the world; as such, it is critical to understand factors that contribute to the development of depression. The social signal transduction theory of depression hypothesizes that adversity and social threat upregulate pro-inflammatory biomarkers leading to depression. The current study examined whether pro-inflammatory biomarkers (interleukin-6, interleukin-8, c-reactive protein, and tumor necrosis factor alpha) mediate the association between various types of childhood maltreatment (physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect) and adult depression symptoms in a sample of 740 adults (372 female; *M*age= 51.6 years, *SD* = 13.6) who provided retrospective report of childhood maltreatment as part of the Midlife in the United States (MIDUS) Refresher Biomarker study. Additionally, it explored whether these relations differ for males versus females. A series of linear regression analyses were run in SPSS; separate models were run for each form of childhood maltreatment and for interleukin-6, interleukin-8, c-reactive protein, and tumor necrosis factor-alpha. The results showed that childhood maltreatment is a robust predictor of adulthood depression; however, this association did not differ between biological sexes. In addition, only interleukin-6 was shown to partially mediate the association between childhood maltreatment and adulthood depression. These findings highlight the need to explore the use of interleukin-6 to screen for depression in youth.

GENERAL AUDIENCE ABSTRACT

By 2030 major depression is predicted to be the leading cause of disease burden in the world; as such, it is critical to understand factors that contribute to the development of depression. It has been hypothesized that adversity and social threat activate pro-inflammatory biomarkers, which are proteins that can detect inflammation in the body, leading to depression. The current study examined whether several pro-inflammatory biomarkers explain the association between several types of childhood maltreatment (physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect) and adult depression symptoms in a sample of 740 adults (372 female; *M*age= 51.6 years, *SD* = 13.6) who provided report of past experiences of childhood maltreatment. Additionally, it explored whether these relations differ for males versus females. The results showed that childhood maltreatment is a robust predictor of adulthood depression for males and females. Of the inflammatory biomarkers examined, only interleukin-6 was shown to partially explain the association between childhood maltreatment and adulthood depression symptoms. These findings highlight the need to explore the use of interleukin-6 to screen for depression in youth.

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In 2019, according to the National Child Abuse and Neglect Data System, there were 656,000 victims of child abuse or neglect (Children's Bureau, 2019), indicating a significant and ongoing issue with childhood maltreatment in the United States. The Child Abuse Prevention and Treatment Act defines child neglect and abuse as "any recent act or failure to act on the part of a parent or caretaker which results in death, serious physical or emotional harm, sexual abuse or exploitation; or an act or failure to act, which presents an imminent risk of serious harm" (Children's Bureau, 2019, p. ix). Childhood maltreatment is a strong predictor of depression in adulthood (e.g., Green et al., 2010) and has been linked to pro-inflammatory biomarkers (Baumeister et al., 2016). Understanding the biological underpinnings of childhood maltreatment in the development of depression is important, especially considering depression tends to overlap with several chronic diseases such as cardiovascular disease, obesity, and chronic pain (e.g., Goodwin et al., 2004). Such research can inform intervention targets for depressed adults. As such this thesis sought to examine 1) the relationship between different forms of childhood maltreatment in a sample of adults with and without depression, 2) the mediational role of pro-inflammatory biomarkers within the relationship of childhood maltreatment and adulthood depression, and 3) the moderating effect of biological sex on the association between childhood maltreatment and adulthood depression. To help in understanding the constructs studied in this thesis, a glossary of the various terminology used throughout the document is provided in Appendix A.

Social Signal Transduction of Depression Theory

The Social Signal Transduction of Depression theory explains how activation by the nervous system due to chronic stress or social threat can lead to inflammation and later into depression (Slavich & Irwin, 2014). This theory states that adversity or social threat is processed by regions of the brain such as the dorsal anterior cingulate cortex and anterior insula (Slavich & Irwin, 2014). These brain regions project to lower-level areas in the brain (e.g., brainstem autonomic control nuclei and hypothalamus) that can activate inflammatory activity through pathways such as the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. This 'pre-injury' strategy used by the body is an evolutionary process passed down from past generations when humans were hunters and gatherers, and had to defend themselves against animals in the wilderness (Slavich & Irwin, 2014). Recent studies have shown that the same immune system genes that would have been activated in response to threat from predatory animal centuries ago are also activated from social environmental threat such as rejection, social conflict, isolation (Slavich & Irwin, 2014). This concept explains the link between the immune system and the mind's perception of social-environmental threat, which can occur either through the SNS or HPA axis.

For example, the SNS releases epinephrine and norepinephrine, and the HPA axis releases glucocorticoids (i.e., cortisol), which communicate with cytokine producing cells. Epinephrine and norepinephrine activate intracellular transcription factors that bind deoxyribonucleic acid (DNA) sequences that up-regulate inflammatory gene expression (Slavich & Irwin, 2014). Once DNA is transcribed to ribonucleic acid, it is then translated into pro-inflammatory proteins. These pro-inflammatory proteins signal the

brain to induce behavioral, emotional, and cognitive changes that include symptoms synonymous with depression (e.g., social withdrawal, fatigue, loss of appetite and anhedonia; Slavich & Irwin, 2014). Whereas, the HPA axis releases glucocorticoids, which reduces inflammation in the body and allows for the body to respond to a threat without the onset of sickness behavior. Once the threat is gone, the body will upregulate inflammation momentarily to inhibit infection caused by possible injury. However, when the HPA axis is active for an extended period of time, it can lead to increased inflammatory activity as opposed to decreased. This occurrence is referred to as glucocorticoid insensitivity and when this happens the immune system becomes less sensitive to the anti-inflammatory effects of cortisol in order to compensate for its continuous secretion (Slavich & Irwin, 2014). Therefore, when the body has developed a glucocorticoid insensitivity, the HPA axis response during social-environmental threats are altered and lead to excessive inflammation.

At the same time during a psychosocial stressor microglia in the brain are activated. Microglia make up roughly 10% of all brain cells and are significant in the initiation of neuroinflammation (Tsai, 2021). When microglia in the brain are activated, they can increase pro-inflammatory cytokines. In turn, the increase of these cytokines causes a reduction of neurotransmitters such as serotonin, which is associated with depression (Tsai, 2021).

Pro-Inflammatory Biomarkers

The innate immune system is the first line of defense when the body encounters injury or infection. It is composed of monocytes, macrophages, neutrophils, natural killer cells, and dendritic cells. These cells are circulating in the blood and are constantly

surveying the body for pathogens and viruses. The adaptive immune system is the second line of defense, if the innate system is unable to fully eradicate the problem. The adaptive immune system eliminates the pathogens based on “immunological memory” of past infections. It consists of b-cells and t-cells that help to build immunity (Slavich & Irvin, 2014). The two systems differ not only in the type of cells they are composed of, but also how each system works. The innate immune system is quick-acting, non-specific, and is involved in initiating the inflammatory cascade, whereas the adaptive immune system is slower to respond and responds to specific pathogens. The innate immune system is responsible for the inflammatory response of the body during injury and infection, which is both locally at the site of injury and systemically (Slavich & Irwin, 2014). These inflammatory responses of the body are regulated by cytokines, chemokines, and C-reactive Protein (CRP; Turner et al., 2014).

Cytokines such as Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are small proteins that are secreted by cells such as monocytes, leukocytes, and lymphocytes. They can act on nearby cells (paracrine), on cells a long distance away (endocrine), or on the cell that secreted them (autocrine). Normally, cytokines are released in cascade, meaning the release of one cytokine will stimulate another cell to release a different cytokine. For example, pro-inflammatory cytokines regulate cell activation and assist in recruiting other immune cells to areas of the body infected by pathogens (Turner et al., 2014). Specifically, TNF-α is a potent cytokine and is crucial to the inflammatory response in the innate immune system, which include activation adhesion molecules, induction of cytokine production, and growth stimulation (Turner et al., 2014). Similarly, IL-6 is involved in pathogen clearance, tissue regeneration, bone

turnover, lipid balance, tissue regeneration, bacteria clearance, and in activating B-cells to produce antibodies (McElvaney et al, 2021). Chemokines such as Interleukin-8 (IL-8) are cytokines that are produced primarily to recruit leukocyte at the site of injury or infection. Chemokines can assist T helper cell differentiation and angiogenesis (i.e., the formation of new blood vessels). IL-8 is pivotal inflammatory mediator since its main job is to recruit neutrophils. CRP is an inflammatory protein that plays a role in the production of IL-6 and TNF-α, apoptosis, and phagocytosis during times of infection (Sproston & Ashworth, 2018). In addition, CRP has been shown to have a longer half-life in plasma, which makes it a more reliable predictor of inflammation (Sesso et al., 2019).

Childhood Maltreatment, Pro-Inflammatory Biomarkers, and Depression

Inflammation is a response triggered by the immune system during times of infection or physical injury. However, as the Social Signal Transduction of Depression theory states, inflammatory activity can also be activated in the absence of physical injury or infection through chronic stress (e.g., Slavich & Irwin, 2014). Specifically, childhood abuse has been associated with pro-inflammatory biomarkers such as IL-6, CRP, and TNF-α, and these inflammatory markers have been shown to differentiate in levels of elevation depending on trauma type. Pro-inflammatory biomarker levels have been shown to vary with the type of trauma, such that individuals with a past history of physical and sexual abuse had an increase in IL-6 and TNF-α, whereas CRP was associated with parental neglect (Baumeister et al., 2016).

Additionally, Bertone-Johnson and colleagues (2012) found women who reported sexual abuse in their adolescence had elevated plasma serum levels of IL-6 compared to women who had not reported any abuse. Specifically, the concentration of IL-6 was 20-

50% higher in women reporting forced sex than those who reported no sexual abuse. In contrast, they found that physical abuse was not associated with elevated IL-6. Further, in a study assessing if harsh family climate earlier in life (i.e., birth to 14 years) was associated with pro-inflammatory activity later in life, researchers found that the young women raised in harsh environments were more susceptible to display increased inflammatory response to psychological stressors and showed an increase in resistance to the anti-inflammatory signals by cortisol (Miller & Chen., 2010). Additionally, in a study of adults with and without a history of childhood maltreatment, self-reported childhood maltreatment on the Childhood Trauma Questionnaire (CTQ) was associated with higher levels of acute IL-6 release and overall IL-6 concentration over time during the Trier Social Stress Test (Carpenter et al., 2010). Together, these findings suggest that childhood maltreatment is strongly linked to pro-inflammatory biomarkers.

Major depression is the most prevalent psychiatric disorder worldwide and 60% of individuals that recover from depressive symptoms will have a reoccurrence of symptoms within 5 years (Nanni et al., 2012). Both cross-sectional and longitudinal research has linked childhood maltreatment to depression in children, adolescents, and adults (e.g., Khan et al., 2015; Moskvina et al., 2007; Nanni et al, 2012; Negele et al., 2015; Widom et al., 2007). For example, one retrospective, cross-sectional study examining trauma in a sample of chronically depressed adults found that 75% endorsed some form of childhood maltreatment on the CTQ and 61% reported emotional trauma with 25% reporting sexual abuse (Negele et al., 2015). In a longitudinal study of adults that had experienced childhood abuse and neglect before the age of 12, they found that physical abuse and neglect were associated with higher risk for lifetime Major Depressive

Disorder (Widom et al., 2007).

When thinking about interventions for depression and other chronic health conditions associated with childhood abuse or neglect, inflammation could be a target for treatment (Danese et al., 2007). Depression tends to overlap with several chronic diseases such as cardiovascular disease, obesity, and chronic pain (e.g., Goodwin et al., 2004), which are also associated with chronic inflammation. For example, inflammation has been theorized to lead to depression because it elicits symptoms that are similar to depression (e.g., changed sleep, loss of appetite, and lethargy; Slavich & Irwin, 2014; Kapfhammer, 2006). A meta-analysis of 16 studies looking at the association of cytokines and depression found that IL-6 and TNF-α were notably higher for depressed versus non-depressed individuals (Dowlati et al., 2009). Lanquillon and colleagues (2000) found that IL-6, CRP, and TNF-α levels were higher for patients with Major Depression Disorder than controls. In addition, IL-8 serum levels were higher at baseline and at a two-year follow-up for individuals with depression (Kim et al., 2018). Together these findings suggest that inflammation may explain the link between childhood maltreatment and adult depression; however, this possible mediational relation has yet to be examined.

Sex Difference in Depression and Childhood Maltreatment

In general, mood disorders are more commonly diagnosed in women than men (Rainville & Hodes, 2019). Specifically, women are more likely to present with internalizing disorders (e.g., depression, anxiety); whereas males are more likely to present with externalizing disorder (e.g., conduct disorder, attention-deficit/hyperactivity disorder) and substance use (Meng & D’Arcy, 2016; Seedat et al., 2009). Specifically, the

female-to-male ratio in prevalence of depression disorders is 1.7:1 (Albert, 2015). Alternatively, some have suggested that the difference in depression prevalence rates between males and females are associated with hormonal changes in women (i.e., menstrual cycle, puberty, pregnancy and perimenopause). For example, pre-puberty, boys and girls have similar prevalence rates of depression with boys actually having slightly higher rates than girls; however, starting during adolescence, the rates reverse and females become twice as likely to be experience depressive symptoms than their male counterparts (Cyranowski et al., 2000).

With such a stark difference between the biological sexes in rates of adult depression, it is critical to understand whether differences in childhood maltreatment experiences may explain this difference. Specifically, Negele and colleagues (2015) found that women reported more childhood maltreatment than men; in particular, they reported more incidence of emotional and sexual abuse than men. According to the World Health Organization, 1 in 13 males and 1 in 5 females have reported being sexually abused during the ages of 0-17 years (Becker, 2022). As such, this study examined whether the associations between various forms of childhood maltreatment and adult depression symptoms differ for males and females.

Present Study

Given this backdrop, the current study investigated which pro-inflammatory biomarkers, as measured by IL-6, IL-8, CRP, and TNF-α levels, were associated with clinical levels of depression symptoms in adults. Further, it examined whether these biomarkers mediated the relation between various forms of childhood maltreatment and depression symptoms in adulthood. Additionally, it explored whether there are

differential associations between childhood maltreatment and depression symptoms for males versus females. Specifically, the aims of this thesis were to address the following research questions:

1. ***Which pro-inflammatory biomarker (i.e., IL-6, IL-8, CRP and TNF-α) is active in adults with clinical levels of depression symptoms?*** Hypothesis: Based on prior research (Birur et al., 2017; Lanquillon et al., 2000), IL-6, IL-8, CRP, and TNF-α should be elevated among participants with clinical levels of depression symptoms relative to participants without clinical depression.
2. ***Do elevations in depression symptoms in adulthood depend on type of maltreatment (i.e., physical abuse, sexual abuse, emotional abuse, physical neglect, or emotional neglect), and do pro-inflammatory biomarkers IL-6, IL-8, CRP, or TNF-α mediate these associates?*** Hypothesis: Based on prior research (Khan et al., 2015; Widom et al., 2007), it is expected that physical abuse, physical neglect, sexual abuse, and emotional abuse will be the strongest predictors of depression symptoms in adulthood. We did not expect emotional neglect to be a predictor of adult depression symptoms. Mediational analyses were exploratory in nature; as such no specific predictions were made regarding differences in mediational relations across pro-inflammatory biomarkers.
3. ***Does the relation between childhood maltreatment and depression symptoms in adulthood differ between biological sexes?*** Hypothesis: Given higher prevalence rates of adult depression in females (Albert, 2015; American Psychiatric Association, 2013) and prior research finding higher rates of childhood maltreatment in females (Becker, 2022; Negele et al., 2015), it was expected that the association between

childhood maltreatment and adult depression would be stronger for females than males.

Method

Participants

Participants for this thesis were taken from the Midlife in the United States (MIDUS) Refresher Biomarker project, which was conducted from 2012-2016. The Refresher Biomarker project is one of five projects that encompass the MIDUS Refresher: Integrative Pathways to Health and Illness study (Weinstein et al., 2019). The MIDUS Refresher is an expansion of the original MIDUS project, which was conducted in 1995-1996, and involved a survey study initially intended to investigate the linkage between biological, psychosocial, and sociodemographic factors that contribute to later profiles of mortality and morbidity. Specifically, for this study, participants completed the MIDUS Refresher study survey in 2011-2014, which consisted of 3,577 adults. Participants that completed the survey were invited to participate in this biomarker project. Out of the 3,577 adults that completed the survey, 863 adults (aged 24-74) participated in the biomarker project. Only participants that had completed both the survey and biomarker project were used in the current study; therefore, our final sample was comprised of 740 adults (372 female; *M*age= 51.6 years). Additional demographic information for the final sample is summarized in Table 1.

Procedures

Data was collected at three clinical facilities at the University of California, Los Angeles, University of Wisconsin, and Georgetown University. The participant spent 24 hours at the site for a round of data collection procedures. On day 1 (i.e., evening of the

day the participant arrives at the study site), medical history, physical examination, self-administered questionnaires, and a 12-hour urine collection began. On day 2 (i.e., the morning of the day the participant left the study site), a fasting blood draw and psychophysiological measures were collected, and the 12-hour urine collection ended.

Measures

Childhood Trauma Questionnaire - Short Form (CTQ-short; Bernstein et al., 1994, 2003)

The CTQ-short (Appendix B) is a well-known retrospective self-report measure used to assess five subtypes of childhood maltreatment (physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect). The CTQ-short consists of 28 items rated on a 5-point Likert scale ranging from 1 (*never true*) to 5 (*very often true*). The following is the scoring scale we will use for this study according to the CTQ Manual: Physical abuse (none to minimal = 5-7; low to moderate = 8-9; moderate to severe = 10-12; severe to extreme = 13 and higher), Emotional abuse (none or minimal = 5-8; low to moderate = 9-12; moderate to severe = 13-15; Severe to extreme = 16 and higher), Sexual Abuse (none or minimal = 5; low to moderate= 6-7; moderate to severe = 8-12; Severe to extreme = 13 and higher), Physical neglect (none or minimal = 5-7; low to moderate = 8-9; moderate to severe = 10-12; Severe to extreme = 13 and higher), and Emotional neglect (none or minimal = 5-9; low to moderate = 10-14; moderate to severe = 15-17; Severe to extreme = 18 and higher).

Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977)

The CES-D (Appendix C) is a self-report measure used to assess clinical levels of depression (i.e., feelings of guilt and worthlessness, depressed mood, loss of appetite,

sleep disturbance, psychomotor retardation, feeling of helplessness and hopelessness). The questionnaire is comprised of 20-items using a 4-point Likert Scale (0 = *Rarely or none of the time*; 1 = *Some or little of the time*; 2 = *Moderately or much of the time*; 3 = *Most or almost all the time*). The scores have a range from 0-60 with a clinical cutoff score of 16 or higher for depression. The CES-D has been shown to be highly reliable and consistent (Cronbach's $\alpha = 0.89$).

Cytokine Measurements

The inflammation biomarkers were obtained from fasting blood draws that were obtained from each participant on day 2 in the morning before breakfast. All blood samples were collected and processed at the research site using standardized procedures. Then samples were sent to the MIDUS BioCore Lab (University of Wisconsin, Madison, WI) for assay.

IL-8 and TNF-α were measured using a V-plex Custom Human Cytokine Kit (catalog #K151A0H-2). This technology uses a 96-well multispot plate. Each spot is precoated with a capture antibody for a particular cytokine and is connected to an electrode surface at the bottom of the plate. The samples were pipetted into the wells to allow for the cytokines to adhere to their corresponding antibody spots. After washing off the nonadherent samples, a solution containing detection antibodies tagged with ruthenium(II)tris-bipyridine-(4-methylsulfonate) N-hydroxysuccinimide ester (MSD Sulfo-tag) was pipetted into the wells and allowed to adhere to the immobilized cytokine. After washing off the unbound antibodies, a buffer is added to the wells and the plate is loaded into an imager (Meso Scale Discovery Sector Imager Model #HTS24) that measures the intensity of the emitted light to provide a quantitative measure of analytes in

each sample.

IL-6 was measured using the Quantikine High-sensitivity ELISA kit #HS600B. This ELISA uses microplates precoated with an antibody specific for IL-6. Samples and standards were pipetted into the wells. Unbound substances are washed away and an alkaline phosphatase-labeled detection antibody specific for IL-6 was added to the wells. Any unbound antibody-enzyme reagent is washed and a NADPH substrate is added, which is converted to NADH. After an incubation period, a solution containing additional enzymes (diaphorase and alcohol dehydrogenase) and their respective substrates (iodonitrotetrazolium-violet and ethanol) are added. Diaphorase converts iodonitrotetrazolium-violet to a red colored product. The reaction is stopped with sulfuric acid and the absorbance, which is proportional to the concentration of IL-6, is read at 490 nm10 using a Dynex MRXe plate reader.

Initially, CRP was measured in plasma using BNII nephelometer, which makes use of particle enhanced immunonepholometric assay. In this method, polystyrene particles are coated with monoclonal antibodies to CRP. When the antibodies come in contact with the CRP, they stick together. This causes an increase in scattered light, which is proportional to the amount of CRP present in the sample. Any sample that fell below the assay range were re-assayed by immunoelectrochemifurninescence (Meso Scale Diagnostics #K151STG). In 2016, CRP was no longer assayed in plasma due to technical difficulties, instead CRP was measured in serum.

Analytic Plan

Descriptive statistics (e.g., mean, standard deviation) and tests of normality were first analyzed for all variables of interest. Furthermore, bivariate correlations were run

between each of the main study variables (childhood maltreatment types, depression, pro-inflammatory biomarkers) and potentially relevant demographic variables. Based on recommendations from O'Connor et al. (2009), age, biological sex, socioeconomic status (SES), selective serotonin reuptake inhibitor (SSRI) use, exercise, alcohol use, waist-hip ratio, cancer history, and antihypertensive use are important demographic variables to examine when looking at pro-inflammatory markers and thus were included in bivariate correlations and as covariates in the regression analysis in the current study. Given the number of coefficients being interpreted, alpha was set at .01 to reduce the risk of committing a Type I Error.

Aim 1) Which cytokine (i.e., IL-6, IL-8, CRP, and TNF-α) is active in adults with clinical levels of depression symptoms?

Four independent sample *t*-tests were run in SPSS, Version 27 (IBM Corp, 2020) to compare adults with and without clinical levels of depression symptoms on the four cytokines (IL-6, IL-8, CRP, and TNF-α).

Aim 2) Do elevations in depression symptoms in adulthood depend on type of childhood maltreatment (i.e., physical abuse, sexual abuse, emotional abuse, physical neglect, or emotional neglect), and do pro-inflammatory biomarkers mediate these associates?

Multiple regression analyses were run in SPSS, Version 27 (IBM Corp, 2020) using the Baron and Kenny method for mediation to examine whether IL-6, IL-8, CRP, and/or TNF-α mediate the association between the various forms of childhood maltreatment and depression symptoms in adulthood. Each form of childhood maltreatment was examined as a continuous predictor variable, depression was examined

as a continuous outcome variable and IL-6, IL-8, CRP, and TNF-α were examined as continuous mediator variables. Separate models were run for each of the five types of childhood maltreatment and for the four pro-inflammatory biomarkers.

Aim 3) Does the relation between childhood maltreatment and depression symptoms in adulthood differ between biological sexes?

Multiple regression analyses were run in SPSS with an interaction variable of biological sex and maltreatment type (e.g., sex*physical abuse) to examine whether the associations between childhood maltreatment types and adult depression symptoms differ for males and females.

Results

Preliminary Analyses

After running descriptive statistics, it was discovered that there were multiple covariates that were missing significant participant data (n = 1 - 73; 0.1 – 9.9% missing). A Little's Missing Completely at Random test was run, which showed that several covariates had missing data that was not random. Therefore, instead of using listwise deletion to handle missing data, multiple imputation was performed in SPSS. Bivariate correlations were run for all variables including covariates using the pooled analyses from the multiple imputation dataset.

Descriptive statistics including bivariate correlations, means, and standard deviations for all measures of interest are summarized in Table 2. In our sample, 23.5% endorsed low to extreme physical abuse, 33% endorsed low to extreme emotional abuse, 15.3% endorsed low to extreme sexual abuse, 25% physical neglect and 61% endorsed low to extreme emotional neglect. Results demonstrate that emotional neglect was the

most endorsed form of childhood maltreatment. In addition, 16.6% of our sample scored in the clinical range on the CES-D.

Correlations showed that depression symptoms displayed significant positive, weak associations with childhood physical abuse (r = .195), emotional abuse (r = .296), sexual abuse (r = .198), physical neglect (r = .233) and emotional neglect (r = .279). Additionally, depression was significantly positively associated with IL-6 (r = .152) and marginally positively associated with CRP (r = .094). Whereas depression symptoms were not significantly correlated with IL-8 or TNF-α. Similarly, IL-6 and CRP were the only cytokines significantly associated with childhood maltreatment types. Both cytokines were weakly associated with physical abuse, sexual abuse, emotional abuse and physical neglect (rs = .088-.138) at the marginal or clinically significant level. Neither IL-6 nor CRP were significantly associated with emotional neglect. Correlations indicated that women reported more childhood history of emotional abuse and physical abuse (r = .155 and .268, respectively) and marginally higher depression symptoms (r = .086); however, these associations were all weak in magnitude.

Aim 1 Group Differences

Independent sample t-tests were performed to examine the differences in pro-inflammatory biomarkers between adults with and without clinical depression symptoms. There was a significant difference in cytokine levels between adults with and without depression for IL-6, $t(738) = -3.731$, $p < .001$. The was no significant difference in levels for IL-8, TNF-α, nor CRP between the two groups, $t(738) = -1.105$, $p = .269$, $t(738) = -0.511$, $p = .609$ and $t(738) = -1.751$., $p = .080$, respectively.

Aim 2 Mediation

Regression analyses were performed to examine the potential mediational role of pro-inflammatory biomarkers (i.e., IL-6, IL-8, TNF-α, and CRP) in the association between childhood maltreatment and adult depression. The direct effect between childhood maltreatment and adult depression symptoms was significant for emotional abuse (*b* = 0.483, *p* < .001), physical abuse (*b* = 0.404, *p* < .001), sexual abuse (*b* = 0.331, *p* < .001), emotional neglect (*b* = 0.408, *p* < .001), and physical neglect (*b* = 0.617, *p* < .001).

There was partial mediation for IL-6 in the association between emotional abuse, physical abuse, sexual abuse, physical neglect and emotional neglect with depression symptoms. Specifically, the total effect of emotional abuse (*b* = 0.458, *p* < .001), physical abuse (*b* = 0.371, *p* < .001), sexual abuse (*b* = .292, *p* < .001), emotional neglect (*b* = 0.400, *p* < .001), and physical neglect (*b* = 0.581, *p* < .001) were each still significant after including IL-6 as a mediator. The Sobel test (Sobel, 1982) was used to analyze the significance of the mediation of IL-6. The test showed that the mediation was significant for emotional abuse (z = 2.02, *p* = .043), physical abuse (*z* = 2.05, *p* = .040), sexual abuse (z = 2.45, p = .014), and physical neglect (*z* = 1.94, *p* = .050), but not for emotional neglect (*z* = 0.756, *p* = .450). Although CRP appeared to partially mediate the association between physical abuse (*b* = 0.393, *p* < .001), emotional abuse (*b* = 0.476, *p* < .001), sexual abuse (*b* = 0.325, *p* < .001), emotional neglect (*b* = 0.405, *p* < .001), and physical neglect (*b* = 0.608, *p* < .001), the Sobel test indicated that none of the mediations were significant (*zs* = 0.927 – 1.040, *p*s > .350). Lastly, no form of childhood maltreatment was significantly associated with IL-8 or TNF-α (*p*s > .187); as such,

mediation was not explored for these biomarkers.

Aim 3: Moderation

Moderation analyses are presented in Table 3. Notably, when including the interaction by sex, none of the forms of childhood maltreatment displayed significant main effects for adulthood depression symptoms. Additionally, none of the moderation models with biological sex were significant for any of the five childhood maltreatment types, suggesting that the association between childhood maltreatment and adulthood depression symptoms do not differ for males and females.

Discussion

The overall objective of this study was to examine the factors that contribute to adult depression. Specifically, the current study investigated whether pro-inflammatory biomarkers, as measured by IL-6, IL-8, CRP, and TNF-α levels, were elevated in adults with clinical levels of depression, and if these biomarkers mediated the relation between various forms of childhood maltreatment and depression in adults. The results showed that all five childhood maltreatment types (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) were associated with adult depression. There was significant difference in cytokine levels between adults with and without depression for IL-6, but there was no significant difference in cytokine levels for IL-8, TNF-α and CRP between the two groups. Similarly, IL-6 was the only biomarker to significantly mediate the association between childhood maltreatment and adulthood depression symptoms, suggesting that this is an important factor to screen for in children exposed to maltreatment. Finally, despite women displaying higher rates of emotional abuse, sexual abuse, and depression symptoms, the associations between childhood maltreatment types

and depression symptoms were not moderated by biological sex. This finding suggests that childhood maltreatment is a universal risk factor for depression, rather than explaining the elevated rates of depression seen in women. Main findings and their clinical implications are discussed next.

Elevated IL-6 Among Adults with Clinical Levels of Depression Symptoms

In our study, 16.6% of the sample scored in the clinical range for depression symptoms on the CES-D. This rate of clinical symptomatology is higher than the national prevalence rate of 8.4% of adults who have experienced at least one major depressive episode (National Institute of Mental Health, 2022). This suggests that more adults may experience clinical symptomatology for depression than the amount who seek a formal diagnosis and treatment. Alternatively, since the CES-D only assesses for symptoms, not impairment, and does not tease apart other disorders (e.g., anxiety, sleep disorders) that may contribute to depression symptoms, our sample of adults displaying clinical depression symptoms, may include individuals who do not meet diagnostic criteria for major depressive disorder.

Based on the current results and previous literature, IL-6 appears to be a consistent predictor of adult depression, despite other pro-inflammatory biomarkers such as CRP being more stable in our blood (Sesso et al., 2019). This could be due to the multifaceted interactions that IL-6 has on the body such as T-cell balance, tumorigenesis, bacterial clearance, lipid homeostasis, fever and fatigue (McElvaney et al., 2021). In contrast, current findings suggest that other pro-inflammatory biomarkers are not as consistently linked to depression symptoms. Of the biomarkers examined in this study, TNF-α has been shown to be the most consistently elevated in individuals with

depression (Dowlati et al., 2010; Himmerich et al., 2019). Prior research that has investigated TNF-α have had small sample sizes (e.g., less than 100) and used participants with a clinical diagnosis of major depression disorder. Whereas in this current study the sample size was over 700 participants and used a self-report measure that assessed depressive symptoms, which may have contributed to our lack of findings for TNF-α compared to previous studies.

CRP has had an inconsistent association with depression in previous literature. For example, Chamberlin et al. (2019) found that CPR was more elevated in treatment resistant depressed patients than treatment responsive patients. Unfortunately, a thorough medication history was not obtained for all participants in this study; therefore, this observation could not be explored. Similarly, IL-8 has been shown to both decrease and increase patients with depression (Tsai, 2021). It is important to note that these pro-inflammatory biomarkers work together throughout the immune system and are influenced by an array of environmental, biological, and psychological factors. In addition, the same cytokine can be produced by multiple cells and the same cell can release various cytokines (Himmerich et al., 2019). Therefore, depending on the research sample, significant biomarker alterations can be difficult to detect.

Mediational Role of IL-6 in the Association Between Childhood Maltreatment and Adult Depression

In our sample, a high rate of childhood maltreatment was endorsed—23.5% of adults endorsed a history of physical abuse, 33% endorsed a history of emotional abuse, 15.3% endorsed a history of sexual abuse, 25% physical endorsed a history of neglect, and 61% endorsed a history of emotional neglect. In addition, results indicated that all

five childhood maltreatment types were directly associated with adult depression symptoms. These findings reinforce previous literature which has demonstrated that childhood maltreatment is a strong predictor of adult depression (see Humphreys et al., 2020 for a review).

In contrast to hypotheses, the only pro-inflammatory biomarker to significantly mediate the association between childhood maltreatment and adult depression symptoms was IL-6. Although CRP appeared to partially mediate the association between several forms of childhood maltreatment and depression, the Sobel test indicated that none of the mediations were significant; no form of childhood maltreatment was significantly associated with IL-8 or TNF-α, precluding mediational analyses from being examined for these biomarkers. As mentioned previously, IL-6 is an acute inflammatory cytokine that is involved in numerous processes in the body such as pathogen clearance, tissue regeneration, bone turnover, lipid balance, tissue regeneration, bacteria clearance, and activating B-cells to produce antibodies (McElvaney et al., 2021). Therefore, it is no surprise that when there is a dysregulation in IL-6 activity, multiple bodily functions are also affected. In addition, IL-6 is involved in weight, smoking status, and blood pressure (O'Connor et al., 2009), which may help explain the elevated negative health outcomes experienced among individuals with depression. Although, the results overall showed partial mediation for IL-6, it only explained a small amount of the variance in the association between childhood maltreatment and depression, suggesting that inflammation is not fully to blame for this link.

The lack of significant mediation for CRP and the lack of significant associations with depression for TNF-α and IL-8 could have been due to the number of covariates that

were included in the model. As previously stated, based on recommendations from O'Connor et al. (2009), age, biological sex, SES, SSRI use, exercise, alcohol use, waist-hip ratio, cancer history, and antihypertensive use were all used as covariates in analyses, because of their known influence on pro-inflammatory biomarkers. However, there is evidence that controlling for these factors has the potential to cancel significant findings. For example, a meta-analysis showed that after controlling for physical activity, body mass index, and smoking, there was no significant difference in IL-6 between participants with major depressive disorder vs. control participants (Ting et al., 2020). Given that several of the covariates included in analyses were not significantly related to main study variables at the bivariate level, it is possible that including these (despite being recommended) may have added noise to the data, decreasing the accuracy of coefficient estimates.

Alternatively, it is possible that differences in pro-inflammatory biomarkers could have been seen had the participants undergone some type of stressor before blood samples were obtained. For example, other studies have used the Trier Social Stress Test (Carpenter et al., 2010; Pace et al., 2006) to invoke a stress response from participants before samples were collected. The Trier Social Stress test is a prosocial experiment where participants perform role play, public speaking and math tasks in front of a confederate judge panel (Kirschbaum et al., 1993). Since CRP, IL-8, and TNF-α are released during the early phases of an inflammatory response perhaps having a stressor activity before would have yielded different results. Similarly, if biomarkers had been collected in closer proximity to the childhood maltreatment, inflammation may have been

more directly associated with maltreatment, relative to in the current sample when it was collected in adulthood, often many years after their reported childhood maltreatment.

Limitations

Results from the current study need to be interpreted within the context of several limitations. First, is the lack of diversity in the sample. MIDUS is a national longitudinal study in the United States with the main aim of investigating the health and well-being of Americans. Despite efforts to recruit Black, Indigenous, and People of Color participants (e.g., through a 2004 subsample targeting Black individuals), there is still a lack of racial representation (i.e., the current sample is 80.4% white). This limits the generalizability of the findings, given racial differences in inflammation (Lam et al., 2021; Schmeer & Tarrence, 2018) and research suggesting that ethnicity and culture influence the exposure and impact of traumatic events (McLaughlin et al., 2019).

Another limitation of this study was the retrospective report of childhood maltreatment. Although, the CTQ is a reliable and highly used measure when assessing childhood maltreatment, it still relies on recall from the participants, often many years later given that the mean age of the current sample was 51 years. Research has shown that memories fade and are reconstructed in our minds as time passes, especially if trauma is involved. For example, after a traumatic event people will remember more trauma than was actually experienced known as “memory amplification” (Strange & Takarangi, 2015). Relatedly, since the average age of the participants in this study was early 50s, the impact of childhood maltreatment (i.e., trauma that occurred prior to the age of 18) on their pro-inflammatory biomarkers may have been reduced over the years since the trauma occurred, resulting in the minimal associations between childhood maltreatment and pro-inflammatory biomarkers and mediational relations observed in the

current study.

Conclusions and Future Directions

Despite these limitations, this study confirmed that not only is childhood maltreatment a consistent predictor of adult depression, but inflammation, particularly IL-6, mediates this association. Results suggest that IL-6 is worthy of further investigation. Future studies should explore soluble IL-6R and soluble gp130 when examining the association of childhood maltreatment to depression because IL-6 has both pro and anti-inflammatory pathways in the body that work in sync with other cells. Specifically, IL-6 binds to the receptor (IL-6R) to form the IL-6-IL-6R complex. IL-6R can either be bound to the glycoprotein 130 (gp130) or soluble (i.e., unbound floating in the serum). In the classical signaling pathway (i.e., anti-inflammatory), IL-6 binds to the IL-6R that is membrane bound, which is found only on gp130 on particular cells such as macrophages, hepatocytes, and a subset of T-cell. IL-6 can only bind to the gp130 via the IL-6R receptor, which means that IL-6 cannot bind to gp130 without IL-6R. It is important to note that gp130 is expressed on all cell types, but only certain cells with the gp130 (i.e., macrophages, hepatocytes, and certain T-cells) have the IL-6R (under normal circumstances). Alternatively, in the trans-signaling pathway (i.e., pro-inflammatory) the IL-6-R receptor is cleaved from the cell surface by the disintegrin and metalloprotease domain-containing protein 17 (ADAM 17), generating a soluble IL-6R (sIL-6R). The sIL-6R is able to bind IL-6 in the serum and this IL-6-sIL-6R complex can now bind to any gp130 in the body, which means that cells that were normally unresponsive to IL-6 alone are now activated because it is connected to the sIL-6R (McElvaney et al, 2021) leading to complication throughout the body.

Previous research has suggested that sIL-6R has many functions including extending the half-life of IL-6. For example, Schöbitz and colleagues (1995) found that when rats were treated with IL-6 they had a decrease in food intake and locomotory activity and an increase in body temperature, which were prolonged when they were injected with sIL-6R. This demonstrates that it is important to distinguish between biological processes that occur with IL-6 alone and with the sIL-6R. Furthermore, it is important look at the interaction of soluble gp130 with sIL-6R since soluble gp130 inhibit the trans-signaling (pro-inflammatory) pathway of sIL-6R (Hong et al., 2016). Examining this interaction between sIL-6R and soluble gp130 could explain IL-6 mediational role with childhood maltreatment and depression.

It is also critical that future research examine the role of maltreatment in the development of inflammation and depression in child and adolescent samples. Ehrlich et al. (2021) found higher levels of inflammation in girls that had experienced childhood maltreatment between 0-12 years, with levels being especially high for girls that had experienced maltreatment before the age of 5 years old. This study highlights that inflammation can be evaluated during childhood and could provide more information on the onset and duration of inflammation after an exposure to maltreatment. Examining such inflammation, particularly via IL-6, in children that have experienced maltreatment could help identify which children are most at risk for developing depression later in life. Such insight can help inform intervention approaches, such as utilizing diet, exercise, or pharmacology to reduce inflammation, in addition to traditional evidence-based treatments for depression such as cognitive behavioral therapy (Hofmann et al., 2012) or interpersonal psychotherapy (Cuijpers et al., 2016).

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Table 1

Participant Demographics

	Mean or N	SD or Percent
Age	51.61	13.61
Biological Sex		
Female	372	50.3%
Male	368	49.7%
Race		
White	595	80.4%
African American	55	7.4%
Native American	16	2.2%
Asian	12	1.6%
Native Hawaiian	2	0.3%
Other	55	7.4%
Don’t Know	3	0.4%
No Response	2	0.3%
Wage		
Less than $0 - $0	170	23.0%
$1 - $19,999	118	15.9%
$20,000 - $39,999	101	13.6%
$40,000 - $59,999	104	14.1%
$60,000 - $79,999	69	9.3%
$80,000 - $99,999	35	4.7%
$100,000 or More	81	10.9%
Missing	62	8.4%

Table 2

Correlations Between Variables of Interest and Covariates

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. IL-6	--																	
2. IL-8	.30**	--																
3. CRP	.41**	.11**	--															
4.TNF-∝	.13**	.23**	.07	--														
5. PA	.10**	-.02	.14**	-.01	--													
6. EA	.09*	.03	.12**	-.03	.61**	--												
7. SA	.13**	0	.10**	0	.38**	.45**	--											
8. PN	.10**	-.02	.09*	.02	.49**	.50**	.25**	--										
9. EN	.06	-.02	.07	-.04	.44**	.64**	.34**	.62**	--									
10. Dep	.15**	0	.09*	-.01	.20**	.30**	.20**	.23**	.28**	--								
11. Sex	-.04	.11**	.14**	-.01	.04	.16**	.27**	0	.04	.09*	--							
12. Age	.34**	.27**	-.00	.02	-.03	-.06	-.02	-.02	-.02	-.19**	-.10**	--						
13. WH Ratio	.29**	.11**	.02	.06	.04	-.06	-.12**	.06	.05	-.02	-.62**	.29**	--					
14. Wages	-.20**	-.17**	-.03	-.01	-.08	-.11*	-.12*	-.06	-.09*	-.07	-.15**	-.20**	-.03	--				
15. SSRI	-.06	-.03	-.08*	.01	-.01	-.09*	-.03	-.03	-.07	-.13**	-.06	.01	-.01	-.09	--			
16. AHU	-.27**	-.23**	-.06	-.01	-.04	0	-.02	-.01	-.03	.02	.08*	-.40**	-.31**	.17**	-.026	--		
17. Exer.	.15**	.01	.06	.01	.02	.01	.01	.02	.04	.13**	0	-.01	.13**	-.06	-.078*	-.016	--	
18.Cancer	-.08*	-.08*	.02	.03	-.01	-.06	-.02	-.05	-.03	.07	-.02	-.20**	-.03	.05	-.030	.081*	.056	--
19. A/D	-.07	-.09*	-.04	-.06	-.03	-.04	-.01	-.05	0	-.05	.06	.02	-.08*	.04	.078	.026	-.045	-.011
M (SD)	2.71 (2.35)	12.26 (6.34)	2.78 (5.27)	2.19 (1.60)	6.96 (3.13)	8.12 (4.01)	6.50 (3.87)	6.71 (2.57)	9.93 (4.56)	8.67 (7.37)	--	51.61 (13.61)	--	--	--	--	--	--

Note. PA = physical abuse, SA = sexual abuse, EA = emotional abuse, PN = physical neglect, EN = emotional neglect, Dep = depression symptoms as measured on the CES-D, WH Ratio = waist-to-hip ratio, SSRI= current selective serotonin reuptake inhibitor use, AHU = current antihypertensive use, Cancer = cancer history, Exer.=exercise, A/D Hx= alcohol/drug problem within the past year

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 3
Analyses Examination Moderation for Biological Sex

Variable	*b*	*p*
Emotional Abuse	.451	.049
Sex	.567	.653
Emotional Abuse*Sex	.019	.885
Physical Abuse	.097	.733
Sex	-.204	.882
Physical Abuse*Sex	.191	.259
Sexual Abuse	.124	.786
Sex	.016	.992
Sexual Abuse*Sex	.109	.646
Emotional Neglect	.273	.137
Sex	.228	.861
Emotional Neglect*Sex	.086	.442
Physical Neglect	.388	.229
Sex	.227	.881
Physical Neglect*Sex	.149	.456

Note. Coefficients for covariates included in the model (age, biological sex, socioeconomic status, selective serotonin reuptake inhibitor use, exercise, alcohol use, waist-hip ratio, cancer history, and antihypertensive use) are not shown in the table for readability.

Appendix A: Glossary of Terminology Used in Master's Thesis

Term	Description
Anterior insula	Located in the insula and is responsible for awareness of sensations, time perception, and cognitive choices
Brainstem autonomic control nuclei	The bottom portion of the brain consisting of the pons, medulla oblongata, and midbrain. Regulates functions such as heart rate, balance, and breathing
Dendritic cells	A type of phagocyte found in the immune system that presents antigens on it's own surface to other immune cells
Dorsal anterior cingulate cortex	Responsible for various executive functions such as cognitive control, response detection, and working memory
Hypothalamus	Produces hormones that are released to the pituitary gland, which regulate the actions of the autonomic nervous system
Leukocytes	A white blood cell found in lymph nodes and blood
Lymphocytes	A white blood cell that can be divided into two types: B and T. B lymphocytes produce antibodies and T lymphocytes produce antibodies and T lymphocytes destroy tumor cells.
Microglia	Small cells that can be found throughout the central nervous system that help regulate brain development, maintain neuronal networks, and assist with injury repair
Monocytes	White blood cells that are developed in the bone marrow and travels to connective tissue where it transforms to a macrophage
Macrophages	White blood cell that removes dead cells and kills mircoorganisms
Neutrophils	A white blood cell that help to fight infections by ingesting bacteria and viruses
Natural killer cells	A type of white blood cell that contains small granules that kill viruses
Pro-inflammatory biomarkers	A protein that can detect inflammation in the body

Appendix B: Childhood Trauma Questionnaire – Short Form

9) These questions ask about some of your experiences growing up as a child and a teenager. Although some of the questions are of a personal nature, please try to answer as honestly as you can. For each question, circle the number under the response that best describes how you feel. [RA4Q9A] to [RA4Q9BB]

When I was growing up…		Never True	Rarely True	Sometimes True	Often True	Very Often True
a.	I didn't have enough to eat.	1	2	3	4	5
b.	I knew that there was someone to take care of me and protect me.	1	2	3	4	5
c.	People in my family called me things like "stupid," "lazy," or "ugly."	1	2	3	4	5
d.	My parents were too drunk or high to take care of me.	1	2	3	4	5
e.	There was someone in my family who helped me feel that I was important or special.	1	2	3	4	5
f.	I had to wear dirty clothes.	1	2	3	4	5
g.	I felt loved.	1	2	3	4	5
h.	I thought that my parents wished I had never been born.	1	2	3	4	5
i.	I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	1	2	3	4	5
j.	There was nothing I wanted to change about my family.	1	2	3	4	5
k.	People in my family hit me so hard that it left me with bruises or marks.	1	2	3	4	5
l.	I was punished with a belt, a board, a cord, or some other hard object.	1	2	3	4	5
m.	People in my family looked out for each other.	1	2	3	4	5
n	People in my family said hurtful or insulting things to me.	1	2	3	4	5
o.	I believe that I was physically abused.	1	2	3	4	5
p.	I had the perfect childhood.	1	2	3	4	5

Continued…		Never True	Rarely True	Sometimes True	Often True	Very Often True
q.	I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	1	2	3	4	5
r.	I felt that someone in my family hated me.	1	2	3	4	5
s.	People in my family felt close to each other.	1	2	3	4	5
t.	Someone tried to touch me in a sexual way, or tried to make me touch them.	1	2	3	4	5
u.	Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	1	2	3	4	5
v.	I had the best family in the world.	1	2	3	4	5
w.	Someone tried to make me do sexual things or watch sexual things.	1	2	3	4	5
x.	Someone molested me.	1	2	3	4	5
y.	I believe that I was emotionally abused.	1	2	3	4	5
z.	There was someone to take me to the doctor if I needed it.	1	2	3	4	5
aa.	I believe that I was sexually abused.	1	2	3	4	5
bb.	My family was a source of strength and support.	1	2	3	4	5

Appendix C: Center for Epidemiologic Studies Depression Scale

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.