CHILDHOOD MALTREATMENT, INFLAMMATION, AND MAJOR DEPRESSIVE SYMPTOMS: LONGITUDINAL ANALYSES EXPLORING THE EFFECTS OF MALTREATMENT TYPE AND THE INFLUENCE OF SEX AND GENDER

by

JAY DAVID O'SHIELDS

(Under the Direction of Orion Mowbray)

ABSTRACT

Experiences of childhood maltreatment are a substantial risk factor for the development of major depressive disorder in adulthood. Often, those who experience major depressive disorder and childhood maltreatment tend to have an overall worse prognosis, including a greater number of depressive symptoms, higher risk for death by suicide, and higher likelihood to not respond to treatments. Strong theoretical evidence suggests that experiences of childhood maltreatment may increase inflammatory signaling that targets the brain, creating depressive symptoms. This dissertation presents three studies that explore these associations with the goal of identifying novel treatment and prevention strategies for major depressive disorder related to childhood maltreatment. The first study presents a longitudinal, repeated measures model to assessing the association between the early life social environment, inflammation, and depressive symptoms across the first four decades of life using a nationally representative U.S. sample. Results from the first study indicate that reducing socioeconomic inequalities early in life could reduce the risk of childhood maltreatment while also reducing depressive symptoms and C-reactive protein in adulthood. Further, results from the first study indicate that a reduction in

depressive symptoms early in life could reduce adipose tissue as measured by body mass index which increases inflammation. The second study presents results from a longitudinal path model exploring the association between individual adverse childhood experiences, C-reactive protein, and depressive symptoms. Results from the second study indicate that the broad category of adverse childhood experiences can have complex differences in how they influence depressive symptoms and inflammation, particularly when sex and gender differences are considered. The third study explores how diagnosis timing of major depressive disorder affects the associations between childhood maltreatment, C-reactive protein, and depressive symptoms. Analyses from the third study indicate that the inflammatory effects associated with childhood maltreatment could be reduced through the identification of major depression by health care providers, underscoring the need for effective screening are referral to services. A chapter is devoted to each study within the dissertation. A final chapter concludes the dissertation with a summarization of findings and discussion of implications for social work research and practice.

INDEX WORDS: Depression, inflammation, childhood maltreatment, adverse childhood experiences, body mass index

CHILDHOOD MALTREATMENT, INFLAMMATION, AND MAJOR DEPRESSIVE SYMPTOMS: LONGITUDINAL ANALYSES EXPLORING THE EFFECTS OF MALTREATMENT TYPE AND THE INFLUENCE OF SEX AND GENDER

by

JAY DAVID O'SHIELDS

BS, Georgia Southern University, 2012

MSW, University of Georgia, 2015

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2024

CHILDHOOD MALTREATMENT, INFLAMMATION, AND MAJOR DEPRESSIVE SYMPTOMS: LONGITUDINAL ANALYSES EXPLORING THE EFFECTS OF MALTREATMENT TYPE AND THE INFLUENCE OF SEX AND GENDER

by

JAY DAVID O'SHIELDS

Major Professor:	Orion Mowbray
Committee:	Amy Baldwin
	Javier Boyas
	Rachel Fusco

Electronic Version Approved:

Ron Walcott
Vice Provost for Graduate Education and Dean of the Graduate School
The University of Georgia
August 2024

ACKNOWLEDGEMENTS

I want to first and foremost thank my wife, Becca, who has been a constant source of support. I love so much, and I could not imagine going through this process without you. Thank you for listening to me complain about lumpy data and R code. I cannot wait to do nothing but hang out and watch scary movies very soon.

I want to also thank my two children, Quinn and Coda, who have continued to remind me why I do this research. I hope that this work can make a better world for you both to grow up in.

To my dissertation chair, Dr. Orion Mowbray, I cannot begin to express my appreciation for the opportunities you have given me over the years. I do not know if I would have gone down this path had I not done that independent study with you a decade ago now. Thank you for all you have done over the years.

To the members of my committee, Drs. Rachel Fusco, Javier Boyas, and Amy Baldwin. I sincerely appreciate the time and energy you have put into helping me grow as a scholar. From attending a poultry sciences seminar, to thinking critically about the first four years of life, to learning more about medical sociology. I am a stronger scholar in my area of expertise because of the diverse paths you encouraged me to explore.

Last, I want to express my sincerest gratitude to the many faculty who welcomed me into their labs, volunteered their time, and gave me a chance to get experience. Drs. Theresa Yancey, Adriene Baldwin-White, Jeremy J. Gibbs, and George Slavich, thank you for giving me the opportunity to learn from you.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SUPPLEMENTARY TABLES

Page

CHAPTER 1

INTRODUCTION

Major depressive disorder (MDD) is a mood disorder defined by episodes of decreased mood and/or loss of interest in activities one would typically enjoy (American Psychiatric Association, 2023). Episodes are accompanied by a host of other symptoms including sleep disturbance, lethargy, inappropriate feelings of guilt, appetite disturbance, and at times, suicidal ideations or actions (American Psychiatric Association, 2013). Under the definition provided by the Diagnostic and Statistics Manual of Mental Disorders (DSM-5-TR), MDD has significant heterogeneity in its symptom presentation, with conservative calculations identifying 1,497 different symptom combinations (American Psychiatric Association, 2023; Ostegaard, et al., 2011).

- MDD is common, costly, and frequently disabling. Past year global estimates of MDD prevalence suggests a 4-5% incidence rate (Marx et al., 2023). The impact of MDD shows significant variation, with high income countries reporting the greatest prevalence of MDD over the past 30 years (Marx et al., 2023). A 2017 report from the World Health Organization showed that the United States (U.S.) had the highest past-year incidence at 5.9% of the population, tied with Estonia and Australia. Specific to the U.S., MDD is one of the most disabling mental health problems, accounting for 2.7 million disability-adjusted life years, a combined measure of years of life lost and years lived with disability (The U.S. Burden of Disease Collaborators et al., 2018). Underscoring the impact of MDD's disability on the U.S. population, the overall economic burden of MDD from a 2019 estimate ranged between 254.4 and 418.6 billion U.S.

dollars (Greenberg et al., 2023). This estimate was up by 3.5% from 2018, indicating the growing economic impact of MDD (Greenberg et al., 2023).

Despite the pressing need for fast and effective MDD prevention and treatment, current approaches are lacking. Results from the Sequenced Treatment Alternative to Relieve Depression (STAR*D) identified that the initial treatment of MDD via selective serotonin reuptake inhibitor (SSRI) resulted in remission for only 36.8% of study participants (Rush et al., 2006). For those who did not respond to SSRI treatment, subsequent assignment to one of four conditions, including combined pharmacotherapy and cognitive therapy, only increased the remission rate to 67% of participants (Rush et al., 2006). However, it should also be considered that 26% of participants withdrew from the STAR*D trial before the initial SSRI treatment phase, and therefore remission rates from the study may be inflated (Rush et al., 2006). Additionally, meta-analytic results from 81 studies identified that pharmacotherapy for MDD has a relatively small effect size (0.30; Gibertini et al., 2012). Thus, even under the best conditions, at least one in three persons who present and patriciate in the treatment of MDD will not achieve remission. Unfortunately, the lack of fast and effective treatments has reverberating consequences across the full spectrum of an individual's health. MDD is commonly comorbid with several physical health problems including diabetes, heart disease, stroke and trans-ischemic attack, and several forms of cancer (Gold et al., 2020). Untreated symptoms of MDD may lead to difficulty in the management of these health problems, leading to an increased risk of health complications and hospitalizations (Gold et al., 2020).

One method for improving treatment outcomes for those who experience MDD is to focus on substantive subgroups with poor outcomes. A significant subgroup includes individuals who have experienced childhood maltreatment. Experiences of childhood maltreatment have

been repeatedly identified as strong predictors of MDD in adulthood, with around 46% of those who have MDD reporting a history of childhood maltreatment (Nelson et al., 2017). Broadly defined, childhood maltreatment refers to experiences such as emotional abuse, physical abuse, sexual abuse, emotional neglect, and/or physical neglect prior to the age of 18 (Teicher et al., 2022). Within this framework, childhood maltreatment is typically demarcated by the perpetrator being a parent or other trusted adult, distinguishing it within the broad scope of adverse childhood experiences (Teicher et al., 2022). Individuals who experience MDD and have a history of childhood maltreatment are known to have a greater number of depressive symptoms, are at a greater risk for chronic or recurrent episodes of depression and are at a higher risk for suicide (Nelson et al., 2017; Teicher et al., 2022). Additionally, those with the dual experience of MDD and childhood maltreatment have lower response and remission rates to common antidepressant treatment, underscoring the need for novel treatment and prevention efforts in this group (Williams et al., 2016).

Accumulating evidence suggests that an increase in inflammation may be a key pathway by which childhood maltreatment is associated with depressive symptoms. An upregulation of the immune system and inflammatory activity have been implicated in MDD and depressive symptoms since the late 1970s (Beurel et al., 2020). Since these initial investigations, meta-analytic results have provided support for the involvement of several inflammatory molecules, most commonly C-reactive protein (CRP), interleukin-6, tumor necrosis factor α (TNF-α). CRP, an acute phase protein commonly used as an index of overall inflammation has commonly been associated with increased depressive symptoms (Osimo et al., 2019; Osimo et al., 2020). Similarly, IL-6, a pro-inflammatory cytokine that stimulates the liver to release CRP, is also positively associated with depressive symptoms (Osimo et al., 2020). Tumor necrosis factor α

(TNF-α), a pro-inflammatory cytokine with several functions including allowing IL-6 to permeate the blood brain barrier, has more mixed evidence for its association with depressive symptoms (Mac Giollabhui et al., 2021; Osimo et al., 2020). Meta-analytic analyses specific to longitudinal studies have continued to support that CRP and IL-6 are prospectively associated with depressive symptoms (Mac Giollabhui et al., 2021; Valkanova et al., 2013). Although, TNF-α has only been supported cross-sectionally, potentially indicating that it may only be associated with a current depressive episode. Supporting a potential connection, a systematic review investigating the association between childhood maltreatment and each of these inflammatory markers identified robust associations with CRP (*n*=27) and mixed associations with IL-6 (*n*=24) (Kerr et al., 2021). No statistically significant association was noted between childhood maltreatment and TNF-α. (*n*=17). Further supporting this link, a structural meta-analysis identified that childhood maltreatment was associated with increases in body-mass-index, which was then associated with an increase in depressive symptoms through an increase in CRP and IL-6 (Zagaria et al., 2024). Similar to the prior meta-analysis, no significant association was observed for TNF-α (Zagaria et al., 2024).

Theoretical Framework

The Social Signal Transduction Theory of Depression (SSTTD) has been a leader in explaining how stressful life events, particularly early interpersonal stress, increases inflammation that then creates depressive symptoms (Slavich & Irwin, 2014). The SSTTD builds off our current understanding of stress physiology. When a threat is detected by the brain, the fight or flight reaction is initiated via the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus releases corticotropin releasing hormone that targets the pituitary gland, causing it to release adrenocorticotropic hormone. Adrenocorticotropic hormone then targets the adrenals,

causing the release of cortisol. In addition to HPA-axis activity, parallel signaling processes take place through the sympathetic nervous system (SNS) and the efferent vagus nerve. The SNS releases norepinephrine and signals the adrenals to release epinephrine, while the vagus nerve releases acetylcholine. Once in the periphery, cortisol, norepinephrine, epinephrine, and acetylcholine bind to several different types of immune cells: macrophages, T cells, and natural killer cells. Cortisol and acetylcholine binding to immune cells has a short-term anti-inflammatory effect, leading to immuno-suppression during the fight or flight response. However, norepinephrine and epinephrine activate the nuclear factor-κB pathway within the targeted immune cells, leading to an increase in the production of pro-inflammatory cytokines such as IL-6 and TNF-α that are elevated into the recovery period after the fight or flight response has subsided. These pro-inflammatory cytokines are known to target the brain in three different ways: 1) through activation of the afferent vagus nerve; 2) traveling through the blood brain barrier; and 3) through immune cell infiltration at weak or incomplete sections of the blood brain barrier (Miller & Raison, 2016). This increase in inflammatory signaling affects several areas of the brain implicated in mental and behavioral health including the ventromedial prefrontal cortex, amygdala, hippocampus, insula, basal ganglia, and the subgeneal and dorsal portions of the anterior cingulate cortex. These regions of the brain then work to induce sickness behavior, a combination of behavioral changes (social withdrawal, hypervigilance, fatigue, sleep disturbance, anxiety) that promote recovery after a potential wound that could increase the risk for infection (Miller & Raison, 2016; Slavich & Irwin, 2014).

The SSTTD builds on this framework to outline how early life adversity, particularly social adversity, is related to an increase in inflammation and depressive symptoms. First, SSTTD highlights that social threat, including actual or perceived experiences of social

evaluation, rejection, isolation, and exclusion can set off the body's fight or flight response (Slavich & Irwin, 2014). Second, the SSTTD points towards the conserved transcriptional response to adversity (CTRA) as a mechanism for upregulating inflammatory signaling in the context of social threats (Slavich & Cole, 2013; Slavich & Irwin, 2014). The repeated activation of pro-inflammatory signaling via immune cells causes internal physiologic recursion, a process by which earlier systems that are components of the body's fight or flight response become sensitized to activation (Slavich & Cole, 2013). Additionally, repeated activation of this pathway is known to cause the transcriptional embedding of social experiences, a process by which the production of cells that release pro-inflammatory cytokines are increased (Slavich & Cole, 2013). Thus, the SSTTD offers a plausible theoretical framework for understanding how the conversion of social treats can lead to increased depressive symptoms via a sensitized and exacerbated inflammatory response.

Since the initial outlining of the SSTTD, two additional theoretical developments have emerged. First, a follow up study explored the developments of sex-differences research and outlined how the SSTTD may apply to the long-observed sex differences in MDD (Slavich & Sacher, 2019). Briefly, the body has three major groups of sex-hormones that influence inflammatory signaling: estrogens, progesterone, and androgens. Among the four major types of estrogen, 17β-estradiol (E2) has been found to have the greatest impact, with low concentrations being associated with pro-inflammatory activity and higher concentrations being associated with anti-inflammatory activity. Conversely, progesterone and two different androgens (testosterone and dehydroepiandrosterone) have been found to have mainly immunosuppressive and anti-inflammatory effects, via reducing the activation of the nuclear factor-κB pathway. When sex-hormone differences are considered, in addition to other factors such as women being at greater

risk to experience social threats that are likely to signal the fight or flight response, the SSTTD offers a potential explanation for why women may have greater levels of pro-inflammatory cytokines that are associated with greater depressive symptoms (Slavich & Sacher, 2019).

The second major theoretical development in our understanding of how social threats are related to MDD through inflammation was the rise of Social Safety Theory (SST), which builds on the framework of the SSTTD. The core of SST rests on three principles: 1) humans evolved to foster social safety; 2) social safety is beneficial for human health and behavior; and 3) social threats are harmful for human health and behavior and include experiences of loneliness, social conflict, isolation, rejection, devaluation, and exclusion (Slavich, 2020; Slavich et al. 2023). While the biological mechanisms associated with social threats are explained by the SSTTD, SST expands this understanding through the inclusion of social safety, or friendly and inclusive social bonds. Experiences of social threat and safety influence the development of cognitive schemas around the social self, social world, and social future (Slavich et al., 2023). These schemas are thought to be most malleable in early life, allowing for individuals to shape their behavioral and inflammatory response for an expected environment in adulthood (Slavich et al., 2023). Thus, SST highlights the development of cognitive schemas based on prior experiences, social safety, and threats. These elements shape social stressors in determining if the flight or fight response is activated, which shapes inflammatory signaling.

Current Gaps in Research

Our current understanding of the associations between childhood maltreatment, inflammation, and MDD have made significant strides in the past few decades. Despite this, many pressing questions remain. First, the field has been largely shaped by a handful of studies using data from the Dunedin (New Zealand) Municipality Cohort Study (Danese et al., 2007;

Danese et al., 2008; Danese et al., 2009). However, the U.S. is unique in that it has one of the highest rates of MDD in the world, leading to questions of how well the results from the Dunedin cohort can be generalized to the U.S. population (Marx et al., 2023). Further, of the studies able to evaluate the associations between childhood maltreatment, inflammation, and MDD, few have been able to incorporate longitudinal research designs, and even fewer have been able to incorporate repeated measures. Among the two studies that utilize repeated measures, analyses faced several limitations including small or non-nationally representative samples, a lack of childhood maltreatment assessment, and weakened the models based on the inclusion of BMI as a covariate rather than a potential pathway. In addition, models that do account for the effects of childhood maltreatment have included socioeconomic variables as control variables, with current recommendations for the inclusion of participant income or participant educational attainment as indicators of socioeconomic status (Horn et al., 2018). However, these variables are unable to indicate developmental trajectories due to their collection in adulthood. This has led some to develop household level (such as composites of parental occupation, household income, and public assistance receipt) and neighborhood level (such as composites of proportion of households below the poverty threshold, adults with below high school educational attainment and current unemployment) measures of socioeconomic status in childhood and adolescence that can be used to predict health related outcomes in adulthood (Belsky et al., 2018; Belsky et al., 2019). Despite this, studies have yet to incorporate these developmental approaches to socioeconomic measurement as predictors of risk factors for the development of health problems such as childhood maltreatment, making it difficult to understand developmental pathways.

Second, while a wealth of research has focused on how experiences of childhood maltreatment are associated with inflammation and MDD, considerably less work has focused on

how other adverse experiences may influence these associations. The initial framing of the "adverse childhood experiences" (ACEs) study recognized this issue, and therefore measured aspects of household dysfunction (Felitti et al., 1998). This broader approach to understanding the influence of the early social environment on long term health made important strides in understanding risk factors for the development of MDD in adulthood (Chapman et al., 2004; Mao & Tan, 2023). However, few studies have evaluated how inflammation may be related to the association between ACEs and MDD, and what work has been done under the "ACEs" framework is limited by overly focusing on childhood maltreatment (Zagaria et al., 2024). Additionally, much of the work in this area has focused on indexing ACEs, using the justification that experiences of ACEs are thought to be highly interrelated. While this approach has identified a robust finding that experiencing a greater number of ACEs is associated with a graded risk for the development of MDD, the few studies that explore the effects of individual ACEs have pointed towards differing associations between individual ACEs and MDD. Although, several studies have revealed that ACEs may have unique effects or that some may no longer be significant when tested conjointly in multivariate models. This is highly relevant when considering how sex differences may be relevant to associations between individual ACEs, inflammation, and MDD. Research focusing on sex-differences in childhood maltreatment, inflammation, and MDD has seen a strong growth, but with limited exploration on sex-differences in the broader context of ACEs (Iob et al., 2022; Kim et al., 2019).

Third, although the SST proposes several intervention and prevention approaches, understanding how the timing of interventions is related to inflammation and MDD is still unclear (Slavich, 2020). For instance, evidence from 56 randomized control trials suggests that psychosocial interventions or combined psychosocial and pharmacotherapy could reduce

inflammatory signaling (Shields et al., 2020). One mechanism by which this may take place is by increasing experiences of social safety, changing social schemas that influence the interpretation of social events and related inflammatory signaling (Slavich et al., 2023). Despite this, it should also be considered that the timing of an MDD diagnosis and its subsequent treatment may be a critical factor improving inflammatory health. Indeed, early treatment could reduce down-stream inflammatory signaling via a reduction in psychological recursion that sensitizes inflammatory signaling pathways (Slavich & Cole, 2013). However, it should also be noted that biological and social differences between men and women may be inherent in the association between childhood maltreatment, inflammation, and MDD. For instance, women have been found to be more likely to engage in help seeking behaviors, and therefore more likely to enter care after the experience of childhood maltreatment (Rushovich et al., 2023). Further, because women are more likely to enter care for MDD they may also be more likely to be treated with an antidepressant which could carry the risk of increased adipose tissue that then increases inflammatory signaling (Fava, 2000). To date, no study has investigated how the diagnosis timing of MDD could affect the association between childhood maltreatment, inflammation, and depressive symptoms.

Dissertation Structure

The dissertation will follow the three-article style with a focus on how early life experiences shape inflammation and depressive symptoms in adulthood. Each of the studies uses data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative panel study with five waves of data, beginning in late adolescence and concluding when participants were in their early 40s. The panel design of the Add Health data set allows for the longitudinal modeling of early life adversity on inflammation and depressive

symptoms. The first study (Chapter 2) presents results from the first nationally representative model of the United States to explore the associations between childhood maltreatment, CRP, and affective symptoms of depression. The use of panel data along with repeated measures allows for significant improvements in our understanding of how these factors are associated, allowing for the development of novel treatment targets. The second study (Chapter 3) expands on the first study, exploring a broader range of early life experiences under the adverse childhood experiences framework is associated with CRP and affective depressive symptoms while also exploring potential sex differences in the associations. The third study (Chapter 4) focuses in on how experiences of childhood maltreatment prior to the age of 12 are associated with CRP and affective depressive symptoms while also exploring how the early detection of MDD could be relevant to improving mental and inflammatory related health. As with the second study, potential sex differences in the associations were explored. This collective body of work offers key insights into new targets for intervention development as well as the policy level changes that can be used as preventative measures to improve mental and physical health in the U.S. for those who currently experience the worst outcomes.

Relevance to Social Work

Social workers make up most social services providers in the U.S., and around 60% of those who graduate with a Master of Social Work degree will provide mental health services for at least 50% of their clients (Mullan Institute, 2014). Despite being one of the most common and disabling mental health problems, evidence suggests that treatment options for those who experience MDD in adulthood with a history of childhood maltreatment are those most likely to not respond to treatment (Teicher et al., 2022). The present dissertation aims to provide insights on future intervention and prevention strategies to improve treatment outcomes for those who

experience MDD by focusing on the role of inflammation. Effective targeting of this pathway is critical for interrupting hypothesized bi-directional associations between inflammation and MDD, as well as attenuating the risk for common physical health problems such as heart disease and diabetes that have an inflammatory etiological component and are commonly co-occurring with MDD (Furman et al., 2019; Gold et al., 2020). Through this, the research presented in this work will address three of social work's Grand Challenges: ensuring healthy development for youth, closing the health gap, and advancing long and productive lives (Uehara et al., 2013).

References

American Psychiatric Association. (2023). *Diagnostic and statistics manual of mental disorders* (5th ed., text rev.).

Belsky, D. W., Caspi, A., Arseneault, L., Corcoran, D. L., Domingue, B. W., Harris, K. M., Houts, R. M., Mill, J. S., Moffitt, T. E., Prinz, J., Sugden, K., Wertz, J., Williams, B., & Odgers, C. L. (2019). Genetics and the geography of health, behaviour and attainment. *Nature Human Behavior*, *3*(6), 576-586. https://doi.org/10.1038/s41562-019-0562-1

Belsky, D. W., Domingue, B. W., Wedow, R., Arseneault, L., Boardman, J. D., Caspi, A., Conley, D., Fletcher, J. M., Freese, J., Herd, P., Moffitt, T. E., Poulton, R., Sicinski, K., Wertz, J., & Harris, K. M. (2018). Genetic analysis of social-class mobility in five longitudinal studies. *Proceedings of the National Academy of Sciences*, *115*(31), E7275-E7284. https://doi.org/doi:10.1073/pnas.1801238115

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The bidirectional relationship of depression and inflammation: Double trouble. *Neuron*, *107*(2), 234-256. https://doi.org/https://doi.org/10.1016/j.neuron.2020.06.002

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *Journal of Affective Disorders*, *82*(2), 217-225. https://doi.org/https://doi.org/10.1016/j.jad.2003.12.013

The US Burden of Disease Collaborators (2018). The state of US health, 1990-2016: Burden of diseases, injuries, and risk factors among US states. *JAMA*, *319*(14), 1444-1472. https://doi.org/10.1001/jama.2018.0158

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M., Poulton,

R., & Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatric & Adolescent Medicine*, *163*(12), 1135-1143. https://doi.org/10.1001/archpediatrics.2009.214

Danese, A., Moffitt, T. E., Pariante, C. M., Ambler, A., Poulton, R., & Caspi, A. (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of General Psychiatry*, *65*(4), 409-415. https://doi.org/10.1001/archpsyc.65.4.409

Danese, A., Pariante, C. M., Caspi, A., Taylor, A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences, 104*(4), 1319-1324. https://doi.org/doi:10.1073/pnas.0610362104

Fava, M. (2000). Weight gain and antidepressants. *Journal of Clinical Psychiatry*, *61 Suppl 11*, 37-41.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, *14*(4), 245-258.

Gibertini, M., Nations, K. R., & Whitaker, J. A. (2012). Obtained effect size as a function of sample size in approved antidepressants: A real-world illustration in support of better trial design. *International Clinical Psychopharmacology*, *27*(2). https://journals.lww.com/intclinpsychopharm/fulltext/2012/03000/obtained_effect_size_as_a_function_of_sample_size.4.aspx

Gold, S. M., Köhler-Forsberg, O., Moss-Morris, R., Mehnert, A., Miranda, J. J., Bullinger, M., Steptoe, A., Whooley, M. A., & Otte, C. (2020). Comorbid depression in medical diseases. *Nature Reviews Disease Primers*, *6*(1), 69. https://doi.org/10.1038/s41572-020-0200-2

Greenberg, P., Chitnis, A., Louie, D., Suthoff, E., Chen, S. Y., Maitland, J., Gagnon-Sanschagrin, P., Fournier, A. A., & Kessler, R. C. (2023). The economic burden of adults with major depressive disorder in the United States (2019). *Advances in Therapy*, *40*(10), 4460-4479. https://doi.org/10.1007/s12325-023-02622-x

Horn, S. R., Long, M. M., Nelson, B. W., Allen, N. B., Fisher, P. A., & Byrne, M. L. (2018). Replication and reproducibility issues in the relationship between C-reactive protein and depression: A systematic review and focused meta-analysis. *Brain, Behavior, and Immunity*, *73*, 85-114. https://doi.org/10.1016/j.bbi.2018.06.016

Iob, E., Lacey, R., Giunchiglia, V., & Steptoe, A. (2022). Adverse childhood experiences and severity levels of inflammation and depression from childhood to young adulthood: A longitudinal cohort study. *Molecular Psychiatry*, *27*(4), 2255-2263. https://doi.org/10.1038/s41380-022-01478-x

Kerr, D. M., McDonald, J., & Minnis, H. (2021). The association of child maltreatment and systemic inflammation in adulthood: A systematic review. *PLoS One*, *16*(4), e0243685. https://doi.org/10.1371/journal.pone.0243685

Kim, S., Watt, T., Ceballos, N., & Sharma, S. (2019). Adverse childhood experiences and neuroinflammatory biomarkers-The role of sex. *Stress Health*, *35*(4), 432-440. https://doi.org/10.1002/smi.2871

Mac Giollabhui, N., Ng, T. H., Ellman, L. M., & Alloy, L. B. (2021). The longitudinal

associations of inflammatory biomarkers and depression revisited: Systematic review, meta-analysis, and meta-regression. *Molecular Psychiatry*, *26*(7), 3302-3314. https://doi.org/10.1038/s41380-020-00867-4

Marx, W., Penninx, B. W. J. H., Solmi, M., Furukawa, T. A., Firth, J., Carvalho, A. F., & Berk, M. (2023). Major depressive disorder. *Nature Reviews Disease Primers*, *9*(1), 44. https://doi.org/10.1038/s41572-023-00454-1

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22-34. https://doi.org/10.1038/nri.2015.5

Nelson, J., Klumparendt, A., Doebler, P., & Ehring, T. (2017). Childhood maltreatment and characteristics of adult depression: Meta-analysis. *British Journal of Psychiatry*, *210*(2), 96-104. https://doi.org/10.1192/bjp.bp.115.180752

World Health Organization (2017). *Depression and other common mental disorders: Global health estimates*. https://iris.who.int/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B., & Khandaker, G. M. (2019). Prevalence of low-grade inflammation in depression: A systematic review and meta-analysis of CRP levels. *Psychological Medicine*, *49*(12), 1958-1970. https://doi.org/10.1017/S0033291719001454

Osimo, E. F., Pillinger, T., Rodriguez, I. M., Khandaker, G. M., Pariante, C. M., & Howes, O. D. (2020). Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain, Behavior, and Immunity*, *87*, 901-909. https://doi.org/10.1016/j.bbi.2020.02.010

Ostergaard, S. D., Jensen, S. O., & Bech, P. (2011). The heterogeneity of the depressive syndrome: when numbers get serious. *Acta Psychiatrica Scandinavica*, *124*(6), 495-496. https://doi.org/10.1111/j.1600-0447.2011.01744.x

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., & Lebowitz, B. D. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, *163*(11), 1905-1917.

Rushovich, T., Gompers, A., Lockhart, J. W., Omidiran, I., Worthington, S., Richardson, S. S., & Lee, K. M. N. (2023). Adverse drug events by sex after adjusting for baseline rates of drug use. *JAMA Network Open*, *6*(8), e2329074-e2329074. https://doi.org/10.1001/jamanetworkopen.2023.29074

Shields, G. S., Spahr, C. M., & Slavich, G. M. (2020). Psychosocial interventions and immune system function: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*, *77*(10), 1031-1043. https://doi.org/10.1001/jamapsychiatry.2020.0431

Slavich, G. M. (2020). Social Safety Theory: A biologically based evolutionary perspective on fife stress, health, and behavior. *Annual Review of Clinical Psychology, 16*, 265-295. https://doi.org/https://doi.org/10.1146/annurev-clinpsy-032816-045159

Slavich, G. M., & Cole, S. W. (2013). The emerging field of human social genomics. *Clinical Psychological Science*, *1*(3), 331-348. https://doi.org/10.1177/2167702613478594

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin*, *140*(3), 774-815. https://doi.org/10.1037/a0035302

Slavich, G. M., Roos, L. G., Mengelkoch, S., Webb, C. A., Shattuck, E. C., Moriarity, D. P., &

Alley, J. C. (2023). Social Safety Theory: Conceptual foundation, underlying mechanisms, and future directions. *Health Psychology Review*, *17*(1), 5-59. https://doi.org/10.1080/17437199.2023.2171900

Slavich, G. M., & Sacher, J. (2019). Stress, sex hormones, inflammation, and major depressive disorder: Extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders. *Psychopharmacology (Berl)*, *236*(10), 3063-3079. https://doi.org/10.1007/s00213-019-05326-9

Tan, M., & Mao, P. (2023). Type and dose-response effect of adverse childhood experiences in predicting depression: A systematic review and meta-analysis. *Child Abuse & Neglect*, *139*, 106091. https://doi.org/10.1016/j.chiabu.2023.106091

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry*, *27*(3), 1331-1338. https://doi.org/10.1038/s41380-021-01367-9

Uehara, E., Flynn, M., Fong, R., Brekke, J., Barth, R. P., Coulton, C., Davis, K., DiNitto, D., Hawkins, J. D., & Lubben, J. (2013). Grand challenges for social work. *Journal of the Society for Social Work and Research*, *4*(3), 165-170.

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders*, *150*(3), 736-744. https://doi.org/https://doi.org/10.1016/j.jad.2013.06.004

Williams, L. M., Debattista, C., Duchemin, A. M., Schatzberg, A. F., & Nemeroff, C. B. (2016). Childhood trauma predicts antidepressant response in adults with major depression: Data from the randomized international study to predict optimized treatment for depression.

Translational Psychiatry, *6*(5), e799-e799. https://doi.org/10.1038/tp.2016.61

Zagaria, A., Fiori, V., Vacca, M., Lombardo, C., Pariante, C. M., & Ballesio, A. (2024). Inflammation as a mediator between adverse childhood experiences and adult depression: A meta-analytic structural equation model. *Journal of Affective Disorders*, *357*, 85-96. https://doi.org/https://doi.or

CHAPTER 2

THE LONGITUDINAL EFFECTS OF CHILDHOOD MALTREATMENT ON INFLAMMATION, BODY MASS INDEX, AND DEPRESSIVE SYMPTOMS IN EARLY ADULTHOOD

Introduction

Experiences of childhood maltreatment are widely recognized as a major risk factor for the development of depressive symptoms in adulthood (Marx et al., 2023; Teicher et al., 2022). Indeed, of those who experience depressive symptoms severe enough to qualify as having a major depressive episode, as many as 57.1% have reported a history of experiencing childhood maltreatment (Struck et al., 2020; Teicher et al., 2022). Further, individuals with the dual experience of childhood maltreatment and depressive symptoms tend to experience more recurrent, persistent depressive symptoms and a greater risk for death by suicide relative to those with no childhood maltreatment experiences (Angelakis et al., 2019; Angelakis et al., 2020; Teicher et al., 2022). Current meta-analytic results suggest that structured psychotherapy and/or antidepressant therapies for depressive symptoms are less effective for those who have experienced childhood maltreatment (Nanni et al., 2012). Thus, the identification of early prevention strategies that can prevent childhood maltreatment or mitigate the potential of developing later depressive symptoms, as well as novel targets for depressive symptoms interventions is a chief public health concern.

Leading theories suggest the experiences of childhood maltreatment are associated with a dysregulation of the body's inflammatory response that helps explain the increase in depressive

symptoms in adulthood (Teicher et al., 2022; Miller & Raison, 2016; Slavich & Irwin, 2014). The experience of a threat (such as abuse) results in the threat detection components of the brain initiating the body's fight or flight response, leading to an initial immuno-suppressive effect followed by an increase in inflammatory signaling (Miller & Raison, 2016; Slavich & Irwin, 2014). The inflammatory molecules released during this process are thought to affect the brain through four distinct routes: by targeting the afferent vagus nerve (the neural route), by traveling through the meningeal vein and permeating the tight junctions of the blood-brain barrier via tumor necrosis factor-α signaling (the humoral route), by blood brain barrier infiltration of immune cells, and by traveling through the meningeal lymphatic vessels (Miller & Raison, 2016; Slavich et al., 2020).

Important to understanding this dynamic, the targeting of the brain by inflammatory molecules in the context of acute illness is considered a healthy, protective response (Maes et al., 2012). However, the repeated activation of this response due to social threats is thought to transition the behavioral response to inflammation from benign (i.e. sickness behavior) to pathological (i.e. depressive symptoms) (Slavich & Irwin, 2014). The experience of social threats is thought to sensitize the threat detection circuits of the brain, leading to more frequent activation of the inflammatory response (Slavich & Irwin, 2014). Central to the complex effects of childhood maltreatment, experiences of neglect may also be associated with a prolonged stress response due to a state of hyper-arousal after experiencing or a threat or an inability to effectively cope with stressors (McLaughlin et al., 2014). Additionally, the repeated activation of inflammatory signaling due to social stressors has been associated with an epigenetic upregulation of inflammatory molecule release during the inflammatory response, the Conserved Transcriptional Response to Adversity (Slavich & Cole, 2013). These mechanisms coalesce to

push the body's inflammatory response to activate more frequently and at a greater magnitude to social threats in the context of a history of childhood maltreatment and help to explain the associated increase in depressive symptoms.

Support for our understanding of these epidemiological mechanisms has largely rested on results from the Dunedin Multidisciplinary Health and Development Study, an ongoing panel study of Dunedin, New Zealand, residents exploring biopsychosocial factors and how they relate to health (Poulton et al., 2015). Thus far, the study has illuminated several foundational findings: 1) experiences of childhood maltreatment are prospectively associated with an increase in inflammation (Danese et al., 2007); 2) childhood maltreatment is prospectively associated with the co-occurrence of depressive symptoms and chronic low-grade inflammation (Danese et al., 2008); 3) childhood maltreatment, socioeconomic disadvantage, and social isolation have independent prospective associations with increased inflammation (Danese et al., 2009). These findings have been supported by multiple observational studies identifying an association between experiences of childhood maltreatment and increased inflammation in adulthood (Baumeister et al., 2016; Coelho et al., 2014; Danese & Baldwin, 2017; Kerr et al., 2021), as well as between depressive symptoms and inflammation (Mac Giollabhui et al., 2021; Osimo et al., 2020). Despite this support, inflammation and increased depressive symptoms are thought to be bi-sustaining, and few studies have been able to measure the association between inflammation and depressive symptoms using repeated measures designs that can establish causality (Beurel et al., 2020; Copeland et al., 2012; Huang et al., 2019; Stewart et al., 2009). As such, no known studies have been able to test the effects of childhood maltreatment, or generalize to a population given, these methodological limitations.

However, it should be further considered that even if repeated measures studies had accounted for childhood maltreatment in the association between inflammation and depressive symptoms, this approach lacks a nuanced approach to social determinants of health. Results from the Dunedin Cohort study highlight how childhood maltreatment is an independent predictor of inflammation in adulthood relative to other stressors, particularly early socioeconomic disadvantage (Danese et al., 2009). This finding has been underscored by meta-analytic results from 35 studies, concluding that there is an association between inflammation and early SES measured under a variety of different measures of socioeconomic status (Milaniak & Jaffee, 2019). However, early SES disadvantage has also been found to put individuals at an increased risk for the experience of childhood maltreatment, precluding its inclusion as an independent causal factor in the association between childhood maltreatment, inflammation, and depressive symptoms (Hunter & Flores, 2021; Kim & Drake, 2018; Vogel et al., 2021). The Environmental Affordances model proposes that differences in health can be accounted for, in part by differences in the distribution of access to coping resources or stress buffering resources across different strata of SES, and that this difference in access to resources affects an individual's ability to shut off the stress response (Mezuk et al., 2014). For instance, individuals who experience childhood maltreatment may have a stronger stress response to abuse due to being unable to access school or community resources such as safe and free use public parks that can provide access to social socially supportive relationships (Mckenzie et al., 2014 Mezuk et al., 2014; Slavich 2020).

Furthermore, many studies have overlooked pathophysiological mechanisms that may be highly relevant to understanding these associations, namely adipose tissue frequently proxied via body mass index. Consistently, the inclusion of BMI as a covariate in studies exploring the

effects of inflammation and depressive symptoms has been found to either attenuate or nullify the association. Adipose tissue produces a substantive portion of pro-inflammatory cytokines, and the number of cytokines produced has a positive association with the amount of adipose tissue (Ouchi et al., 2011). Thus, elevated BMI as a proxy for greater adipose tissue may be an important risk factor for increased inflammatory signaling that is then associated with increased depressive symptoms, as has been supported by two recent studies (Karageorgiou et al., 2023; Moriarity et al., 2023). However, when considering the effects of childhood maltreatment, a study comparing 41-inflammatory molecules in current MDD patients vs non-MDD patient controls in the UK identified that childhood maltreatment was positively associated with BMI, but not inflammation (Palmos et al., 2019). Similar to the effects of childhood maltreatment, early life SES may also affect adulthood inflammation through BMI, with current evidence suggesting lower early life SES is associated with a greater risk for food insecurity (Bergmans et al., 2018), and that food insecurity is associated with both a greater risk for obesity (Carvajal-Aldaz et al., 2022) as well as an increase for the experience of mood symptoms, depressive symptoms included (McLaughlin et al., 2012).

Aims of the present study

Significant evidence suggests that experiences of childhood maltreatment are associated with an increase in depressive symptoms across the lifespan, and that inflammation may be a pathway through which this effect occurs. Despite this, treatment outcomes have remained poor, with childhood maltreatment indicating overall worse outcomes for those that experience depressive symptoms, including an increased risk for death by suicide. The present study aims to improve our understanding of how experiences of childhood maltreatment are associated with the relation between inflammation and depressive symptoms using nationally representative data

that can explore the mechanisms by which these associations may be occurring. To accomplish this, four objectives were established:

1) Use nationally representative data with a repeated measures approach to understand how depressive symptoms and inflammation are associated.
2) Understand how BMI as a proxy for adipose tissue may be associated with inflammation and depressive symptoms.
3) Explore how experiences of childhood maltreatment affect the relation between inflammation, depressive symptoms, and BMI.
4) Model the effects of early SES disadvantage on experiences of childhood maltreatment, inflammation, depressive symptoms, and BMI.

Method

Data Source and Sample

The present study draws data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative panel study of individuals in the United States (Harris et al., 2019). Data collection for the Add Health study began in 1994, collecting psychosocial information from 90,118 students in school, and then followed by home visits to 20,745 students to collect additional psychosocial data (Harris et al., 2019). Currently, the Add Health study has released five total waves of data, with wave-to-wave retention rates ranging from 71.8% to 88.6% (Harris et al., 2019). The present study utilizes data from the main Waves 1, 3, 4 & 5, as well as the biomarker sub-projects for Waves 4 and 5, resulting in a total sample size of 1,932 participants.

Measures

Early socioeconomic status was measured across two variables: family socioeconomic status and neighborhood socioeconomic disadvantage. Family socioeconomic status was based on the Social Origins scale, a composite of parent or adult caregivers self-reported education, occupation, household income, and household receipt of public assistance during an in-home interview at Wave 1. The measure was pre-calculated by the Add Health team via principal components analysis and was z-transformed to adhere to a normal distribution (Belsky et al., 2018). Thus, the measure can be interpreted as relatively average early socioeconomic status around mean, early socioeconomic disadvantage when below the mean, and early socioeconomic advantage when above the mean. Neighborhood socioeconomic disadvantage at Wave 1 was precalculated by the Add Health team. Scores were based on the proportion of five single items: female-headed households, individuals living below the poverty threshold, individuals receiving public assistance, adults with less than a high school education, and adults who were unemployed within the participant's census tract. Each of these items were scored on a scale of 1-10 and then summed. Thus, potential neighborhood socioeconomic disadvantage had a potential rage from 5-50 (Belsky et al., 2019).

Childhood maltreatment occurrence was measured via retrospective self-report and included the occurrence of five different types of maltreatment experience. Three experiences of abuse were measured at Wave 4 and included emotional abuse, physical abuse, or sexual abuse. Emotional abuse was defined as a parent or other adult caregivers saying things that really hurt a child's feelings or made them feel like they were not wanted or loved prior to their 18th birthday. Physical abuse was defined as a parent or adult caregiver hitting a child with a fist, kicking, or throwing them down on the flood, into a wall, or downstairs prior to their 18th birthday. Sexual

abuse was defined as a parent or other adult caregiver touching a child in a sexual way, force them to touch him or her in a sexual way, or force them to have sexual relations. Two experiences of neglect were measured at Wave 3 and included physical and social neglect. Social neglect was defined as the participant confirming that by the time you started 6th grade, their parents or other adult caregivers left them home alone when an adult should have been with them. Physical neglect was defined as the participant confirming their parents or other adult caregivers had not taken care of their basic needs, such as keeping them clean or providing food or clothing. For each type of childhood maltreatment participants were asked to report the occurrence of the event. Consistent with the work of Cammak and Hogue (2017) experiences of emotional abuse were considered present (1) if the event happened three or more times while experiences of physical abuse were considered present (1) if the event happened two or more times. Sexual abuse, physical neglect, and social neglect were considered present (1) if the event happened one or more times and absent (0) if the event never occurred.

Body mass index was measured at Waves 3, 4, & 5 through its typical formulation: weight in kilograms divided by squared height in meters. Participant height was measured to the nearest 0.05cm by an Add Health Field Interviewer while the participant standing upright with their head, shoulders, buttocks, and heels flat against a wall. Weight was measured to the nearest 0.1kg by an Add Health Field Interviewer via the participant standing unassisted on a digital scale with a maximum capacity of 200kg.

Depressive symptoms were measured at Waves 3, 4 & 5 using a modified version of the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1991). The modified CES-D assess affective symptoms of depression over the past 7 days via scale with potential responses ranging including 0 “rarely or none of the time (less than 1 day)”, 1 “some or a little of

the time (1-2 days)", 2 "occasionally or a moderate amount of the time (3-4 days)", or 3 "most or all of the time (5-7 days)". The three symptoms include not being able to shake off the blues even with friends and family, feeling depressed, feeling sad. Potential score ranged from 0-9.

Inflammation was measured at waves 4 and 5 using C-reactive protein (CRP) levels as an index of overall systemic inflammation. Wave 4 CRP levels were derived from capillary blood spot samples obtained via finger prick during an in-home visit. A single 3.2mm diameter punch was taken from each obtained blood spot and placed in a deep-well microtiter plate. Samples were assayed via sandwich enzyme-linked immunosorbent assay method (McDade et al., 2004). Sensitivity for Wave 4 CRP assay methods were 0.035 mg/L, with a within-assay coefficient of variation of 8.1% and a between assay coefficient variation of 11.0% (Whitsel et al., 2012). Wave 5 CRP samples were derived from plasma, collected through venous blood venipuncture by a phlebotomist as the final stage of an in-home visit. Serum samples were assayed via CRP-specific particle enhanced immunonephelometric assay via Siemens BNII/BN Prospec System (Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany). Sensitivity for Wave 5 CRP assay methods was dependent on the lower limit of the reference curve related, determined by the concentration of the protein in the N Rheumatology Standard SL (Whitsel et al., 2022). Wave 4 blood spot samples were converted to the same scale as Wave 5 plasma samples by the Add Health team (Whitsel et al., 2012). Comparison of dried blood spot and serum assay methods for CRP have not been found to differ in comparison studies, with the sole exception of serum levels being 1.6 times greater than dried blood spot levels (Brindle et al., 2010). Conversion of dried blood spot levels were handled internally by the Add Health team to allow for accurate comparisons between CRP levels at Waves 4 and 5 (Whitsel et al., 2022).

Repeated measure control variables included participant's self-reported cigarette smoking status, ongoing chronic health condition, past month binge drinking (5 alcoholic drinks or more during a single episode of drinking), antidepressant medication use, and anti-inflammatory medication use. Cigarette smoking status was measured at Waves 4 and 5 and included categorically: no history of cigarette smoking (0), history of cigarette smoking without current use (1), and current cigarette smoking (1). Binge drinking behavior was measured at Waves 4 and 5 and included categorically: binge drinking in the last 30 days (1) or no binge drinking in the past 30 days (0). The presence of a chronic health condition was measured at Waves 4 and 5, and included categorically as the presence of cardiovascular disease, diabetes mellitus, cancer, rheumatoid arthritis, and/or metabolic syndrome (1), or no presence (0). Antidepressant medication use was included as measured at Waves 4 and 5 and included categorically as the use of an antidepressant including SSRI, tricyclic, phenylpiperazine, tetracyclic, SSNRI, or other miscellaneous antidepressant agent as defined by Multum Lexicon codes (1), or no use (0). Anti-inflammatory medication use was included as measured at Waves 4 and 5 and included categorically as the past month use nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, inhaled corticosteroids, corticotropin/glucocorticoid medications, antirheumatic/antipsoriatic medications, and/or immunosuppressive medications (1), or no use (0).

Demographic control variables included participant's age, self-reported sex, self-reported racial/ethnic identity, occupational prestige score, and neighborhood socioeconomic disadvantage (Wave 4). Age was reported at Wave 1 and ranged from 12 years to 21 years. Sex was reported at Wave 1 and was included as a dichotomous measure: female (1) or male (0). Race/ethnicity was reported at Wave 1 and was included as non-Hispanic White (0), non-

Hispanic Black (1), Hispanic only identifying (1), and all other racial/ethnic categories including multi-racial identities (1). Occupational prestige score was measured at Wave 4 and is a composite of participant's scores on the Hauser & Warren Occupation Income and Occupational Education scales, pre-calculated by the Add Health team and used here as a proxy for socioeconomic status in adulthood (Belsky et al., 2018). Neighborhood socioeconomic disadvantage was measured a second time at Wave 4, but with the same measurement method. Therefore, neighborhood socioeconomic disadvantage at Wave 4 also had a potential score range of 5-50 (Belsky et al., 2019).

Ongoing physical illness symptoms were controlled for via the inclusion of a categorical variable as measured at Waves 4 and 5: current inflammatory symptoms (1), no current symptoms (0). This included the presence of flu-like symptoms, fever, night sweats, nausea or vomiting or diarrhea, blood in stool or feces or urine, frequent urination, and/or skin rash or abscess in the past two weeks. These symptoms were recorded during the same visit that blood spot or venous blood samples were acquired.

Analytic strategy

To assess how the effects of early life effects of childhood maltreatment types and socioeconomic status on depressive symptoms, inflammation, and BMI, three longitudinal structural equation models were estimated. First, a path model was used to estimate the associations between the repeated measures: depressive symptoms at Waves 3-5, CRP at Waves 4 and 5, and BMI at Waves 3-5. This path model controlled for the autoregressive effects between waves (i.e. CRP at Wave 4 on CRP at Wave 5). Consistent with the hypothesized bi-directional associations between inflammation and depressive symptoms, covariances were used to model the cross-sectional associations between CRP and depressive symptoms. Based on

findings that the inclusion of BMI could weaken the measured association between CRP and depressive symptoms, and that increased adipose tissue is a pathway by which inflammatory signaling is increased, BMI was included as a cross-sectional predictor of CRP, only (Moriarity et al., 2023). Based on this same logic, cross-lagged associations were measured only from depressive symptoms at Wave 3 to BMI at Wave 4, depressive symptoms at Wave 4 to BMI at Wave 5, and CRP at Wave 4 to depressive symptoms at Wave 5. The second model then tested the effects of early life socioeconomic status and childhood maltreatment types affect the established path model by modeling their effects on the Wave 3 depressive symptoms and BMI as well as on Wave 4 CRP. The third model then adjusted for the confounding effects of several covariates. Demographic control measures were applied cross-sectionally at the wave they were first measured at as well as longitudinally. All variables were entered into the tested models as observed variables.

Models were estimated in r (version 4.1.2; R Core Team, 2021). All models adjusted for the complex survey design of the Add Health study as recommended by the Add Health team (Chen & Harris, 2020). The Lavaan package (Rosseel, 2012) was used for structural equation modeling and adjusted for the complex survey design using the lavaan.survey package (Oberski, 2014).

Missing data analysis revealed 75.72% complete data for Model 1, 73.65% complete data for Model 2, and 70.34% complete data for Model 3. Wave 5 CRP was found to have the greatest source of missingness, followed by Wave 4 CRP, and Wave 3 BMI. Little's MCAR test indicated that data could not be treated as missing completely at random (χ^2= 2,049.0, p<0.001). Multiple imputation with chained equations was used to impute missing values, imputing continuous data via predictive mean matching and categorical data via logistic regression.

Variables in the substantive model were included in the imputation model to maintain congeniality. Additionally, waist circumference at Waves 4 and 5 as well as Epstein-Barr virus at Wave 4 were included as auxiliary variables. To account for the complex design the survey weight was included as a continuous predictor while the primary sampling unit and region weights were included as categorical predictors in the imputation model (He, 2022). Imputation was conducted using the MICE package and passed to the lavaan.survey package using the mitools package (Lumley, 2006; van Buuren & Groothuis-Oudshoorn, 2011).

Results

Sample description

The sample predominantly identified as female (68.79%) and non-Hispanic White (73.36%). Mean depressive symptoms were relatively low across but showed a slight trend upwards at Waves 3 (*M*=1.31, *SE*=0.07), 4 (*M*=1.42, *SE*=0.05) & 5 (*M*=1.50, *SE*=0.07); although, 15.89% of the sample reported use of an antidepressant at Wave 4 and 19.32% at Wave 5. Similarly, a slight trend in BMI was noted at Waves 3 (*M*=26.85, *SE*= 0.26), 4 (*M*=29.28, *SE*=0.31) & 5 (*M*=31.09, *SE*=0.35). CRP levels were higher at Wave 4 (*M*=6.07, *SE*=0.30) than Wave 5 (*M*=4.41, *SE*=0.21); however, anti-inflammatory use was relatively similar between Wave 4 (36.71%) and Wave 5 (37.05%). The most common form of childhood maltreatment was social neglect (39.25%), followed by emotional abuse (31.65%), and then physical abuse (14.44%). A full review of univariate statistics are in Table 2.1.

Table 2.1: Sample Description

	Mean (*SE*) or *N*	Range or %
Depressive Symptoms		
W5	1.50 (0.07)	0-9
W4	1.42 (0.05)	0-9
W3	1.31 (0.07)	0-9
C-reactive protein		
W5	4.41 (0.21)	0.15-44.20

W4	6.07 (0.30)	0.08-205.00
Body Mass index		
W5	31.09 (0.35)	16.40-79.60
W4	29.28 (0.31)	16.80-71.20
W3	26.85 (0.26)	13.80-54.41
Childhood Maltreatment		
Emotional Abuse	2,078,953	31.65%
Physical Abuse	950,384	14.44%
Sexual Abuse	372,690.90	5.66%
Physical Neglect	488,796.10	7.64%
Social Neglect	2,450,929	39.25%
SES		
Family SES W1	0.26 (0.07)	-4.66-3.35
Neighborhood SES W1	23.84 (0.94)	5-50
Adulthood SES W4	101.10 (1.82)	33.77-179.51
Neighborhood SES W4	19.86 (0.49)	5-47
Gender		
Male	2,062,018	31.21%
Female	4,545,047	68.79%
Race/Ethnicity		
Non-Hispanic White	4,840,914	73.36%
Non-Hispanic Black	738,957	11.20%
Hispanic	409874.50	6.21%
All other identities	608,305.20	9.21%
Age at W1	15.86	12-21
Smoking Status		
Current W5	1,436,849	21.74%
Past W5	1,558,028	23.61%
No history W5		54.65%
Current W4	2,107,035	31.89%
Past W4	868,086.90	13.13%
No history W4		54.98%
Past Month Binge Drinking		
W5	1,107,329	16.78%
W4	1,333,250	20.51%
Health Status		
Chronic Condition W5	1,852,300	28.45%
Chronic Condition W4	1,241,427	18.78%
Infection W5	2,402,458	36.42%
Infection W4	3,071,077	46.48%
Medication Use		
Antidepressant W5	1,276,637	19.32%
Inflammatory W5	2,448,076	37.05%
Antidepressant W4	1,049,858	15.89%
Inflammatory W4	2,425,786	36.71%
Auxiliary Imputation Variables		
EBV W4	157.09 (3.45)	26.00-819.00
Waist Circumference W5	98.98 (0.86)	50.00-180.00
Waist Circumference W4	98.22 (0.72)	50.00-190.00

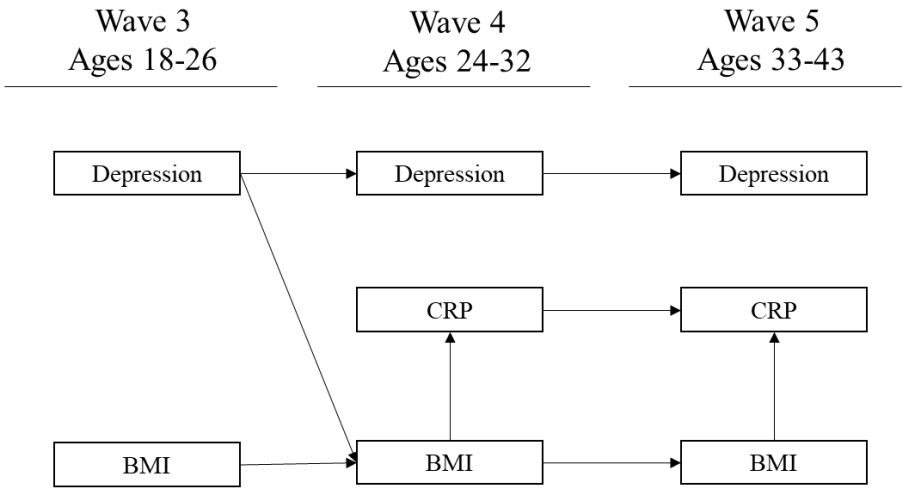
Path Model of BMI, CRP, and Depressive Symptoms

Model fit statistics indicated mixed results. Model chi-square (χ^2= 161.18, *df*= 14, *p*<0.001) and Tucker-Lewis Index (0.92) did not meet the threshold to indicate good model fit. However, the root mean square error approximation (0.07), comparative fit index (0.96) and standardized root mean square residuals (0.03) indicated good model fit. The path model identified several significant associations. One significant cross-lagged association was identified with depressive symptoms at Wave 3 being positively associated with BMI at Wave 4 (β=0.04, *SE*=0.07, *p*<0.05). Cross sectionally, BMI at Wave 4 was positively associated with CRP at Wave 4 (β=0.18, *SE*=0.03, *p*<0.001) and BMI at Wave 5 was positively associated with CRP at Wave 5 (β=0.35, *SE*=0.01, *p*<0.001). No significant association was identified between CRP and depressive symptoms. Table 2.2 reports all comparative fit indices for the model. Figure 2.1 displays significant associations between each of the main variables tested, including autoregressive associations. A complete report of standardized betas and standard errors for each association tested can be reviewed in Supplementary Table 2.1.

Table 2.2: Comparative Model Fit Indices

	Model 1	Model 2	Model 3
χ^2 (df)	161.18(14)***	447.65(56)***	1,485.78(242)***
χ^2/df	11.51	7.99	6.13
CFI	0.96	0.92	0.83
TLI	0.92	0.86	0.70
RMSEA	0.07	0.06	0.05
SRMR	0.03	0.04	0.04
AIC	67,655.00	116,438.89	115,708.29
BIC	67,794.16	116,878.62	116,866.08
Loglikelihood	-33,802.50	-58,140.44	-57,646.14

Figure 2.1: Path Model of Repeated Measures



All paths presented are significant at least at the $p<0.05$ level.
Positive pathways are denoted by a solid line while negative pathways are denoted by a dashed line.
All variables in the model are observed variables.

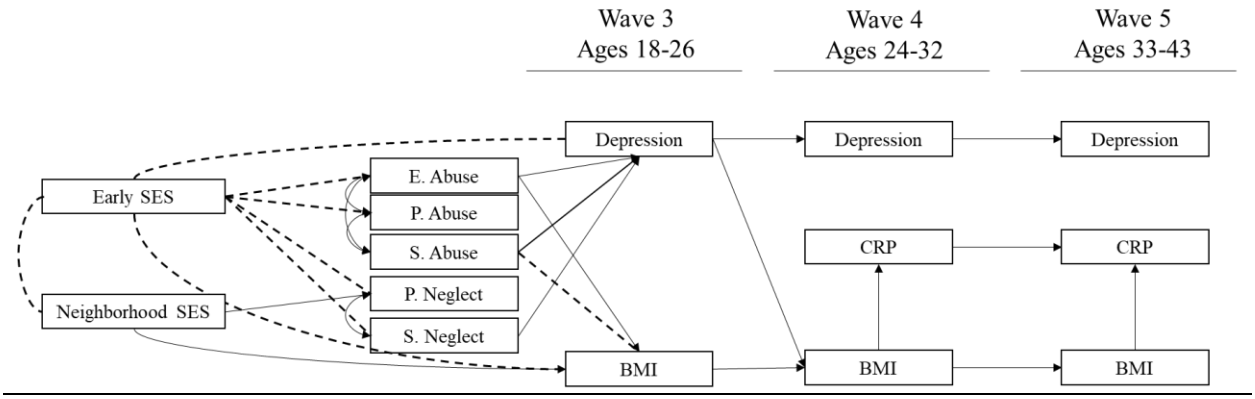
Effects of Early Life Environment and Adjusting for Covariates

Including the effects of early life adversity indicated some functional difference in model fit indices. Model chi-square (χ^2= 447.65, *df*= 56, $p<0.001$) and Tucker-Lewis Index (0.86) continued to indicate that the model was not a good fit. Additionally, the comparative fit index (0.86) no longer reached the threshold to indicate good fit. Although, the root mean square error approximation (0.06) and standardized root mean square residuals (0.04) continued to indicate good model fit.

Several significant associations were identified through the model. Family SES was negatively associated with emotional abuse (β= -0.05, *SE*=0.01, $p<0.05$), physical abuse (β= -0.10, *SE*=0.01, $p<0.001$), physical neglect (β= -0.05, *SE*=0.01, $p<0.05$), and social neglect (β= -0.08, *SE*=0.01, $p<0.001$). Further, family SES was negatively associated with depressive symptoms at Wave 3 (β= -0.07, *SE*=0.03, $p<0.01$) and BMI at Wave 3 (β= -0.15, *SE*=0.14, $p<0.001$). Neighborhood socioeconomic disadvantage was positively associated with physical

neglect (β= 0.11, *SE*=0.01, *p*<0.01) and Wave 3 BMI (β=0.07, *SE*=0.01, *p*<0.001). Emotional abuse was positively associated with depressive symptoms at Wave 3 (β=0.05, *SE*=0.10, *p*<0.05) and BMI at Wave 3 (β=0.05, *SE*=0.40, *p*<0.05). Social neglect was positively associated with depressive symptoms at Wave 3 (β=0.07, *SE*=0.08, *p*<0.01). Sexual abuse was positively associated with depressive symptoms at Wave 3 (β=0.07, *SE*=0.18, *p*<0.001) but negatively associated with BMI at Wave 3 (β= -0.04, *SE*=0.72, *p*<0.05). A figure displaying the significant associations can be reviewed in Figure 2.2 and a table displaying all significant standardized betas and standard errors for the tested associations can be reviewed in Supplementary Table 2.2.

Figure 2.2: Path Model Adjusted for Early Life

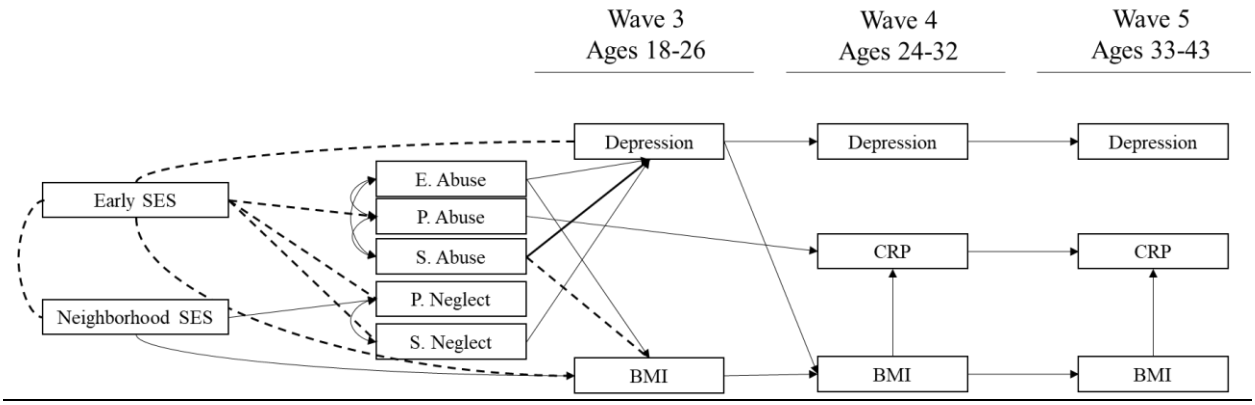


All paths presented are significant at least at the *p*<0.05 level.
Positive pathways are denoted by a solid line while negative pathways are denoted by a dashed line.
All variables in the model are observed variables.

Adjusting the model for control variables did not result in a functional difference for model fit statistics. Reviewing the associations between variables, two relevant differences were noted. First, physical abuse was positively associated with CRP at Wave 4 (β=0.05, *SE*=0.98, *p*<0.05). Second, there was no longer a significant association between family SES and emotional abuse (*p*=0.09). Adjusting the model did not result in any additional change in the significance or directionality of associations. A figure displaying the significant associations can be reviewed in Figure 2.3 and a table displaying all significant standardized betas and standard

errors for the tested associations can be reviewed in Supplementary Table 2.3. Supplementary Table 2.4 reports the variance explained among each endogenous variable included in the model.

Figure 2.3: Path Model Adjusted for Early Life and Controls



All paths presented are significant at least at the $p<0.05$ level.
Positive pathways are denoted by a solid line while negative pathways are denoted by a dashed line.
All variables in the model are observed variables.

Discussion

The present study aimed to improve our understanding of how childhood maltreatment is related to inflammation and depressive symptoms, with the goal of identifying novel intervention targets. Keeping with this aim, the effects of socioeconomic disadvantage and adipose tissue approximated via BMI were also included to better elucidate potential pathway from the social environment to mental and physical health. To do this, analyses used data from the Add Health study, taking advantage of repeated measures as well as the breadth of sociological, biological, and psychological measures. Results indicate that socioeconomic conditions are associated with an increased risk to experience multiple types of childhood maltreatment, and these experiences of childhood maltreatment are associated with BMI, CRP, and depressive symptoms. Further, socioeconomic conditions also affect depressive symptoms and BMI directly, underscoring the critical role of early socioeconomic conditions. Interestingly, depressive symptoms at Wave 3 were positively associated with BMI at Wave 4 and BMI at Wave 4 was cross-sectionally

associated with CRP. Thus, results also point towards a critical inroad to reducing inflammatory signaling via a reduction in BMI through the early treatment of depressive symptoms.

Implications

Findings for the present study build on the paucity of prior studies also able to implement repeated measures designs to test the association between inflammation and depressive symptoms (Copeland et al., 2012; Huang et al., 2019; Stewart et al., 2009). Both Stewert et al. (2009) and Huang et al. (2019) employed CLPM designs, assessing the longitudinal associations between inflammatory signaling and depressive symptoms across a six-year and seven-year follow up, respectively. Contrary to established findings, results did not replicate the significant cross-sectional or longitudinal association between CRP and depressive symptoms as identified by Huang et al. (2019), nor the trend towards a significant longitudinal association identified by Stewart et al. (2009). Interestingly, Stuart et al. and Huang et al. both utilized cohorts of adults at least age 50 and up; however, Copeland et al. (2012) did not identify a significant longitudinal association between CRP and depressive symptoms in a nine-wave cohort study of children followed up to age 21. In context of the present study, these results suggest that the association between CRP and depressive symptoms in a general community sample does not arise until at least after the first four decades of life.

When considering the effects of childhood maltreatment, which prior repeated measures studies were not able to model, results indicate that early intervention of depressive symptoms among those who have experienced childhood maltreatment may provide a pathway for preventing many of the health morbidities associated with childhood maltreatment. Indeed, meta-analytic results from 40 publications identified that experiences of childhood maltreatment were associated with an increased risk for cardiovascular disease, diabetes, and hypertension (Basu et

al., 2017). Each of these conditions has a high degree of co-occurrence with major depressive disorder, and increased inflammation signaling is thought to play a pathophysiological role in each of these disorders, depression included (Furman et al., 2019; Gold et al., 2021). Prior studies have found that depressive symptoms have a positive association with BMI, with the increase in inflammatory signaling due to greater adipose tissue being hypothesized as a connecting mechanism. Although, results from this study indicate that experiences of childhood maltreatment are more closely associated with depressive symptoms that are then associated with an increase in adipose tissue that explains a coinciding increase in inflammation. This helps to illuminate the findings of Prak and colleagues (2022) identified that after removing individuals with physical health problems, there was no association between depressive symptoms and 29 inflammatory molecules in a sample of adults aged 50-80.

Interventions aimed at attenuating the long-term related sequalae of childhood maltreatment via the targeting of depressive symptoms is of high concern for the U.S. population. Concerningly, the greatest incidence of major depressive episodes for the U.S. adult population is among those ages 18-25, with 18.6% of adults in this demographic reporting a past-year major depressive episode (National institute of Mental Health, 2021). Given the high prevalence of childhood maltreatment among this subpopulation and the overlapping health risks associated with both depressive symptoms and childhood maltreatment, this paints a worrying outlook for the health of adults in the U.S. as they age. Optimistically though, results from the present study indicate that the treatment of depressive symptoms for those aged 18-26 could provide a critical off-ramp, reducing both depressive symptoms as well as the risk for developing associated health morbidities via a reduction in adipose tissue that then increases inflammatory signaling. Current effective therapeutic options for the reduction of depressive symptoms among

those who have experienced childhood maltreatment are few; although, some evidence suggests Cognitive Behavioral Analysis System of Psychotherapy (CBASP) may be an effective option (Nemeroff et al., 2003; Teicher et al., 2022). The increased use of CBASP for those that experience childhood maltreatment and depressive symptoms within the first three decades of life may be able to make a substantial improvement in long-term health; however, studies that can assess these long-term effects are still needed. Similarly, limited evidence suggests intravenous ketamine infusion may be helpful for those with a history of childhood maltreatment that are also experiencing treatment resistant depressive symptoms, with a single infusion being found to effectively reduce symptoms (O'Brien et al., 2019). However, further evidence is needed to understand if ketamine infusion is effective for treatment-naive patients with a history of childhood maltreatment and the potential for long-term health outcomes. Testing of both CBASP and ketamine infusion for those ages18-25 could provide valuable insights for attenuating the sequalae of childhood maltreatment and making a substantive improvement in the health trajectory of the U.S. population.

Another consideration for the prevention of related health problems would be to focus on a reduction of adipose tissue. Several studies have identified an association between BMI and depressive symptoms, with some identifying that inflammation is a mediator. Despite not identifying an association between depressive symptoms and CRP, the effective targeting of CRP through a reduction of BMI is still of worthy consideration given the wide number of health problems associated with increased inflammatory signaling. To this end, a focus on interventions aimed at the reduction of adipose tissue is a natural extension; however, it should be considered that this approach is not without risks. For instance, sports that focus on a lean physique or weight control may carry an increased risk for the development of disordered eating and body

dysmorphia (Anderson et al., 2016; Cerea et al., 2018; Holm-Denoma et al., 2008; Satterfield & Stutts, 2021). Additionally, media that glorifies a thin physical appearance or large muscles has been found to have a similar effect (Cramblitt & Pritchard, 2013; Rodgers & Melioli, 2015; Yang et al., 2005). While results from the present study should not be taken as an indicator to stop encouraging a healthy lifestyle, results do indicate that reducing SES disparities may be associated with a reduction in BMI in adulthood. It should be noted though, to the author's knowledge, no studies have assessed policy level interventions to reduce BMI in adulthood via the alleviation of early SES disparities (Hillier-Brown et al., 2014). Despite this, there have been calls for policies aimed at the reduction of food insecurity, which is hypothesized to mediate the association between SES disparities and increased BMI in adulthood (Hartline-Grafton & Hassink, 2021; Miller & Thomas, 2020). Future studies could assess how direct policy interventions, such as food assistance programs, or indirect policy interventions, such as work programs that increase a household's spending power, are related to BMI in adulthood, potentially reducing the incidence of related health problems (Hartline-Grafton & Hassink, 2021; Miller & Thomas, 2020).

Strengths

The present study has several compelling strengths that support the novelty and breadth of the claims stated here. First, the present study is the first to provide a longitudinal model based on nationally representative data of the U.S. population. Few data sets are available to model the complex associations between the social environment and biometric data that can also be generalized to the U.S. population, meaning that our understanding for how childhood maltreatment is related to inflammation and depressive symptoms has rested on findings from the Dunedin Cohort studies. Second, analyses explored how BMI as a proxy for adipose may be

a substantive variable in the complex relationship between the social environment, inflammation, and depressive symptoms. Studies have recently highlighted how BMI should be explored in greater depth, rather than relegating it as a factor to be controlled for, and these results underscore this development in the literature. Third, the use of a cross-lagged panel model approach highlights key points for where intervention and prevention efforts should be focused. Fourth, to produce nationally representative results, modeling focused on the inclusion of statistical controls rather than exclusion of participants. Historically, participants have been excluded based on CRP levels above 10 mg/L; however, studies have found that these elevated CRP levels may be meaningful to those experiencing major depressive disorder (Moriarity et al., 2021). Taking advantage of the Add Health study's acquisition of inflammatory symptom data at the time of biomarker collection, results are more aligned with the reality faced by health practitioners in clinics, particularly those in collaborative care settings.

Limitations

Although results for the present study provide important insights, findings should be considered within the context of some limitations. First, the Add Health study assessed depressive symptoms using a modified version of the CES-D that focuses on affective symptoms. While affective symptoms such as decreased mood are a hallmark symptom of a major depressive episode, it should be considered that depressive symptoms can take a broad and varied presentation (Fried, 2017). Second, despite the use of strong statistical control, other factors such as exposure to environmental pollutants, dietary considerations, and physical activity should be considered in future studies (Horn et al., 2018). Third, while the analytic strategy employed here improves the causal inference between constructs through longitudinal design and modeling cross-lagged associations, additional work is still needed to improve causal

inference. Fourth, the present study takes advantage of recent recommendations to better assess the associations between CRP and depressive symptoms by treating BMI as a pathway for increasing inflammation rather than a covariate. Although, it could be considered that BMI considered that BMI and depressive symptoms have bi-directional associations that could have been tested cross-sectionally, such as in cases of atypical depressive episodes or comorbid eating disorders. Last, fit indices for the multivariate models here presented mixed results. While the relevance of which fit indices to use and the specification of cut points has seen wide discussion, future studies may consider model building approaches aimed at improving fit indices (Fan & Sivo, 2007; Kline, 2016).

Conclusion

The present study aimed to identify novel targets to improve outcomes for those with a history of childhood maltreatment that also experience depressive symptoms in adulthood. Nationally representative data was used to model how childhood maltreatment affects inflammation and depressive symptoms in adulthood, while also accounting for other critical factors such as early SES and BMI. For those that experience childhood maltreatment, the treatment of related depressive symptoms between the ages of 18-26 may be a critical window for the improvement of overall health across the lifespan. Further, policy level interventions aimed at decreasing SES disparities experienced early in life could provide a multi-pronged preventative approach, decreasing the odds of experiencing childhood maltreatment, which is associated with depressive symptoms while also decreasing BMI, which is associated with increased inflammation.

References

Anderson, L. M., Reilly, E. E., Gorrell, S., & Anderson, D. A. (2016). Running to win or to be thin? An evaluation of body dissatisfaction and eating disorder symptoms among adult runners. *Body Image, 17*, 43-47. https://doi.org/https://doi.org/10.1016/j.bodyim.2016.02.003

Angelakis, I., Austin, J. L., & Gooding, P. (2020). Association of childhood maltreatment with suicide behaviors among young people: A systematic review and meta-analysis. *JAMA Network Open*, *3*(8), e2012563-e2012563. https://doi.org/10.1001/jamanetworkopen.2020.12563

Angelakis, I., Gillespie, E. L., & Panagioti, M. (2019). Childhood maltreatment and adult suicidality: a comprehensive systematic review with meta-analysis. *Psychological Medicine*, *49*(7), 1057-1078. https://doi.org/10.1017/s0033291718003823

Basu, A., McLaughlin, K. A., Misra, S., & Koenen, K. C. (2017). Childhood maltreatment and health impact: The examples of cardiovascular disease and type 2 diabetes mellitus in adults. *Clinical Psychology: Science and Practice*, *24*(2), 125-139. https://doi.org/10.1037/h0101742

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Molecular Psychiatry*, *21*(5), 642-649. https://doi.org/10.1038/mp.2015.67

Belsky, D. W., Caspi, A., Arseneault, L., Corcoran, D. L., Domingue, B. W., Harris, K. M., Houts, R. M., Mill, J. S., Moffitt, T. E., Prinz, J., Sugden, K., Wertz, J., Williams, B., & Odgers, C. L. (2019). Genetics and the geography of health, behaviour and attainment.

Nature Human Behavior, *3*(6), 576-586. https://doi.org/10.1038/s41562-019-0562-1

Belsky, D. W., Domingue, B. W., Wedow, R., Arseneault, L., Boardman, J. D., Caspi, A., Conley, D., Fletcher, J. M., Freese, J., Herd, P., Moffitt, T. E., Poulton, R., Sicinski, K., Wertz, J., & Harris, K. M. (2018). Genetic analysis of social-class mobility in five longitudinal studies. *Proceedings of the National Academy of Sciences*, *115*(31), E7275-E7284. https://doi.org/doi:10.1073/pnas.1801238115

Bergmans, R. S., Palta, M., Robert, S. A., Berger, L. M., Ehrenthal, D. B., & Malecki, K. M. (2018). Associations between food security status and dietary inflammatory potential within lower-income adults from the United States National Health and Nutrition Examination Survey, cycles 2007 to 2014. *Journal of the Academy of Nutrition and Dietetics*, *118*(6), 994-1005. https://doi.org/https://doi.org/10.1016/j.jand.2017.12.003

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The bidirectional relationship of depression and inflammation: Double trouble. *Neuron*, *107*(2), 234-256. https://doi.org/https://doi.org/10.1016/j.neuron.2020.06.002

Brindle, E., Fujita, M., Shofer, J., & O'Connor, K. A. (2010). Serum, plasma, and dried blood spot high-sensitivity C-reactive protein enzyme immunoassay for population research. *Journal of Immunological Methods*, *362*(1-2), 112-120. https://doi.org/10.1016/j.jim.2010.09.014

Carvajal-Aldaz, D., Cucalon, G., & Ordonez, C. (2022). Food insecurity as a risk factor for obesity: A review. *Frontiers in Nutrition*, *9*, 1012734. https://doi.org/10.3389/fnut.2022.1012734

Cerea, S., Bottesi, G., Pacelli, Q. F., Paoli, A., & Ghisi, M. (2018). Muscle dysmorphia and its associated psychological features in three groups of recreational athletes. *Scientific*

Reports, *8*(1), 8877. https://doi.org/10.1038/s41598-018-27176-9

Chen, P., & Harris, K. M. (2020). Add Health documentation: Guidelines for analyzing Add Health data. *Carolina Population Center*. https://doi.org/10.17615/C6BW8W

Yang, C.-F. J., Gray, P., & Pope, H. G. (2005). Male body image in Taiwan versus the West: Yanggang Zhiqi meets the Adonis Complex. *American Journal of Psychiatry*, *162*(2), 263-269. https://doi.org/10.1176/appi.ajp.162.2.263

Coelho, R., Viola, T. W., Walss-Bass, C., Brietzke, E., & Grassi-Oliveira, R. (2014). Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatrica Scandinavica*, *129*(3), 180-192. https://doi.org/https://doi.org/10.1111/acps.12217

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A., & Costello, E. J. (2012). Cumulative depression episodes predict later C-reactive protein levels: A prospective analysis. *Biological Psychiatry, 71*(1), 15-21. https://doi.org/https://doi.org/10.1016/j.biopsych.2011.09.023

Cramblitt, B., & Pritchard, M. (2013). Media's influence on the drive for muscularity in undergraduates. *Eating Behaviors, 14*(4), 441-446. https://doi.org/https://doi.org/10.1016/j.eatbeh.2013.08.003

Danese, A., & Baldwin, J. R. (2017). Hidden wounds? Inflammatory links between childhood trauma and psychopathology. *Annual Reviews in Psychology, 68*, 517-544. https://doi.org/10.1146/annurev-psych-010416-044208

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M., Poulton, R., & Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics & Adolescent Medicine, 163*(12), 1135-1143.

https://doi.org/10.1001/archpediatrics.2009.214

Danese, A., Moffitt, T. E., Pariante, C. M., Ambler, A., Poulton, R., & Caspi, A. (2008). Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Archives of General Psychiatry, 65*(4), 409-415. https://doi.org/10.1001/archpsyc.65.4.409

Danese, A., Pariante, C. M., Caspi, A., Taylor, A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences*, *104*(4), 1319-1324. https://doi.org/doi:10.1073/pnas.0610362104

Fried, E. I. (2017). The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *Journal of Affective Disorders*, *208,* 191-197. https://doi.org/10.1016/j.jad.2016.10.019

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N., & Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine*, *25*(12), 1822-1832. https://doi.org/10.1038/s41591-019-0675-0

Gold, S. M., Köhler-Forsberg, O., Moss-Morris, R., Mehnert, A., Miranda, J. J., Bullinger, M., Steptoe, A., Whooley, M. A., & Otte, C. (2020). Comorbid depression in medical diseases. *Nature Reviews Disease Primers*, *6*(1), 69. https://doi.org/10.1038/s41572-020-0200-2

Harris, K. M., Halpern, C. T., Whitsel, E. A., Hussey, J. M., Killeya-Jones, L. A., Tabor, J., & Dean, S. C. (2019). Cohort profile: The National Longitudinal Study of Adolescent to

Adult Health (Add Health). *International Journal of Epidemiology*, *48*(5), 1415-1415k. https://doi.org/10.1093/ije/dyz115

Hartline-Grafton, H., & Hassink, S. G. (2021). Food insecurity and health: Practices and policies to address food insecurity among children. *Academic Pediatrics*, *21*(2), 205-210. https://doi.org/10.1016/j.acap.2020.07.006

He, Y. (2022). *Multiple imputation of missing data in practice : basic theory and analysis strategies* [Bibliographies Online Non-fiction Electronic document]. A Chapman & Hall Book, CRC Press. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=cat06564a&AN=uga.9949531239902959&site=eds-live&custid=uga1 https://galileouga.primo.exlibrisgroup.com/openurl/01GALI_UGA/01GALI_UGA:UGA?u.ignore_date_coverage=true&rft.mms_id=9949531239902959

Hillier-Brown, F. C., Bambra, C. L., Cairns, J. M., Kasim, A., Moore, H. J., & Summerbell, C. D. (2014). A systematic review of the effectiveness of individual, community and societal-level interventions at reducing socio-economic inequalities in obesity among adults. *International Journal of Obesity (Lond)*, *38*(12), 1483-1490. https://doi.org/10.1038/ijo.2014.75

Holm-Denoma, J. M., Scaringi, V., Gordon, K. H., Van Orden, K. A., & Joiner Jr., T. E. (2009). Eating disorder symptoms among undergraduate varsity athletes, club athletes, independent exercisers, and nonexercisers. *International Journal of Eating Disorders*, *42*(1), 47-53. https://doi.org/https://doi.org/10.1002/eat.20560

Horn, S. R., Long, M. M., Nelson, B. W., Allen, N. B., Fisher, P. A., & Byrne, M. L. (2018). Replication and reproducibility issues in the relationship between C-reactive protein and

depression: A systematic review and focused meta-analysis. *Brain, Behavior, and Immunity*, *73*, 85-114. https://doi.org/10.1016/j.bbi.2018.06.016

Huang, M., Su, S., Goldberg, J., Miller, A. H., Levantsevych, O. M., Shallenberger, L., Pimple, P., Pearce, B., Bremner, J. D., & Vaccarino, V. (2019). Longitudinal association of inflammation with depressive symptoms: A 7-year cross-lagged twin difference study. *Brain, Behavior, and Immunity*, *75*, 200-207. https://doi.org/https://doi.org/10.1016/j.bbi.2018.10.007

Hunter, A. A., & Flores, G. (2021). Social determinants of health and child maltreatment: a systematic review. *Pediatric Research*, *89*(2), 269-274. https://doi.org/10.1038/s41390-020-01175-x

Karageorgiou, V., Casanova, F., O'Loughlin, J., Green, H., McKinley, T. J., Bowden, J., & Tyrrell, J. (2023). Body mass index and inflammation in depression and treatment-resistant depression: a Mendelian randomisation study. *BMC Medicine*, *21*(1), 355. https://doi.org/10.1186/s12916-023-03001-7

Kerr, D. M., McDonald, J., & Minnis, H. (2021). The association of child maltreatment and systemic inflammation in adulthood: A systematic review. *PLoS One*, *16*(4), e0243685. https://doi.org/10.1371/journal.pone.0243685

Kim, H., & Drake, B. (2018). Child maltreatment risk as a function of poverty and race/ethnicity in the USA. *International Journal of Epidemiology*, *47*(3), 780-787. https://doi.org/10.1093/ije/dyx280

Kline, R. B. (2016). *Principles and practice of structural equation modeling, 4th ed*. Guilford Press.

Lumley, T. (2006). mitools: Tools for multiple imputation of missing data. *URL http://CRAN. R-*

project. org.

Luning Prak, E. T., Brooks, T., Makhoul, W., Beer, J. C., Zhao, L., Girelli, T., Skarke, C., & Sheline, Y. I. (2022). No increase in inflammation in late-life major depression screened to exclude physical illness. *Translational Psychiatry*, *12*(1), 118. https://doi.org/10.1038/s41398-022-01883-4

Mac Giollabhui, N., Ng, T. H., Ellman, L. M., & Alloy, L. B. (2021). The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. *Molecular Psychiatry*, *26*(7), 3302-3314. https://doi.org/10.1038/s41380-020-00867-4

Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Gałecki, P., & Leonard, B. (2012). Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Medicine*, *10*, 66. https://doi.org/10.1186/1741-7015-10-66

Marx, W., Penninx, B. W. J. H., Solmi, M., Furukawa, T. A., Firth, J., Carvalho, A. F., & Berk, M. (2023). Major depressive disorder. *Nature Reviews Disease Primers*, *9*(1), 44. https://doi.org/10.1038/s41572-023-00454-1

McDade, T. W., Burhop, J., & Dohnal, J. (2004). High-sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. *Clinical Chemistry*, *50*(3), 652-654. https://doi.org/10.1373/clinchem.2003.029488

McKenzie, T. L., Moody, J. S., Carlson, J. A., Lopez, N. V., & Elder, J. P. (2013). Neighborhood income matters: Disparities in community recreation facilities, amenities, and programs. *Journal of Park and Recreation Administration*, *31*(4), 12-22.

McLaughlin, K. A., Green, J. G., Alegría, M., Jane Costello, E., Gruber, M. J., Sampson, N. A., & Kessler, R. C. (2012). Food insecurity and mental disorders in a national sample of

U.S. adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(12), 1293-1303. https://doi.org/https://doi.org/10.1016/j.jaac.2012.09.009

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience & Biobehavioral Reviews*, *47*, 578-591. https://doi.org/10.1016/j.neubiorev.2014.10.012

Mezuk, B., Abdou, C. M., Hudson, D., Kershaw, K. N., Rafferty, J. A., Lee, H., & Jackson, J. S. (2013). "White Box" epidemiology and the social neuroscience of health behaviors: The Environmental Affordances model. *Society and Mental Health*, *3*(2). https://doi.org/10.1177/2156869313480892

Milaniak, I., & Jaffee, S. R. (2019). Childhood socioeconomic status and inflammation: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, *78*, 161-176. https://doi.org/https://doi.org/10.1016/j.bbi.2019.01.018

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22-34. https://doi.org/10.1038/nri.2015.5

Miller, D. P., & Thomas, M. M. C. (2020). Policies to reduce food insecurity: An ethical imperative. *Physiology & Behavior*, *222*, 112943. https://doi.org/10.1016/j.physbeh.2020.112943

Moriarity, D. P., Horn, S. R., Kautz, M. M., Haslbeck, J. M. B., & Alloy, L. B. (2021). How handling extreme C-reactive protein (CRP) values and regularization influences CRP and depression criteria associations in network analyses. *Brain, Behavior, and Immunity*, *91*, 393-403. https://doi.org/https://doi.org/10.1016/j.bbi.2020.10.020

Moriarity, D. P., Mengelkoch, S., & Slavich, G. M. (2023). Incorporating causal inference perspectives into psychoneuroimmunology: A simulation study highlighting concerns about controlling for adiposity in immunopsychiatry. *Brain, Behavior, and Immunity, 113*, 259-266. https://doi.org/https://doi.org/10.1016/j.bbi.2023.06.022

Muscatell, K. A., Brosso, S. N., & Humphreys, K. L. (2020). Socioeconomic status and inflammation: A meta-analysis. *Molecular Psychiatry*, *25*(9), 2189-2199. https://doi.org/10.1038/s41380-018-0259-2

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, A. J., Schatzberg, A. F., Ninan, P. T., McCullough, J. P., Weiss, P. M., Dunner, D. L., Rothbaum, B. O., Kornstein, S., Keitner, G., & Keller, M. B. (2003). Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proceedings of the National Academy of Sciences*, *100*(24), 14293-14296. https://doi.org/doi:10.1073/pnas.2336126100

Oberski, D. (2014). lavaan.survey: An R package for complex survey analysis of structural equation models. *Journal of Statistical Software, 57*(1), 1 - 27. https://doi.org/10.18637/jss.v057.i01

O'Brien, B., Lijffijt, M., Wells, A., Swann, A. C., & Mathew, S. J. (2019). The impact of childhood maltreatment on intravenous ketamine outcomes for adult patients with treatment-resistant depression. *Pharmaceuticals (Basel), 12*(3). https://doi.org/10.3390/ph12030133

Osimo, E. F., Pillinger, T., Rodriguez, I. M., Khandaker, G. M., Pariante, C. M., & Howes, O. D. (2020). Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain, Behavior, and Immunity*, *87*, 901-

909. https://doi.org/10.1016/j.bbi.2020.02.010

Ouchi, N., Parker, J. L., Lugus, J. J., & Walsh, K. (2011). Adipokines in inflammation and metabolic disease. *Nature Reviews Immunology, 11*(2), 85-97. https://doi.org/10.1038/nri2921

Palmos, A. B., Watson, S., Hughes, T., Finkelmeyer, A., McAllister-Williams, R. H., Ferrier, N., Anderson, I. M., Nair, R., Young, A. H., Strawbridge, R., Cleare, A. J., Chung, R., Frissa, S., Goodwin, L., Hotopf, M., Hatch, S. L., Wang, H., Collier, D. A., Thuret, S., . . . Powell, T. R. (2019). Associations between childhood maltreatment and inflammatory markers. *BJPsych Open*, *5*(1), e3. https://doi.org/10.1192/bjo.2018.80

Poulton, R., Moffitt, T. E., & Silva, P. A. (2015). The Dunedin Multidisciplinary Health and Development Study: Overview of the first 40 years, with an eye to the future. *Social Psychiatry and Psychiatric Epidemiology, 50*(5), 679-693. https://doi.org/10.1007/s00127-015-1048-8

Radloff, L. S. (1991). The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *Journal of Youth and Adolescence*, *20*(2), 149-166.

Rodgers, R. F., & Melioli, T. (2016). The relationship between body image concerns, eating disorders and internet use, part I: A review of empirical support. *Adolescent Research Review, 1*(2), 95-119. https://doi.org/10.1007/s40894-015-0016-6

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, *48*(2), 1 - 36. https://doi.org/10.18637/jss.v048.i02

Satterfield, N. A., & Stutts, L. A. (2021). Pinning down the problems and influences: Disordered eating and body satisfaction in male wrestlers. *Psychology of Sport and Exercise, 54*, 101884. https://doi.org/https://doi.org/10.1016/j.psychsport.2021.101884

Slavich, G. M. (2020). Social Safety Theory: A Biologically Based Evolutionary Perspective on Life Stress, Health, and Behavior. *Annual Review of Clinical Psychology*, *16*, 265-295. https://doi.org/https://doi.org/10.1146/annurev-clinpsy-032816-045159

Slavich, G. M., & Cole, S. W. (2013). The emerging field of human social genomics. *Clinical Psychological Science*, *1*(3), 331-348. https://doi.org/10.1177/2167702613478594

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, *140*(3), 774-815. https://doi.org/10.1037/a0035302

Stewart, J. C., Rand, K. L., Muldoon, M. F., & Kamarck, T. W. (2009). A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain, Behavior, and Immunity*, *23*(7), 936-944. https://doi.org/https://doi.org/10.1016/j.bbi.2009.04.011

Struck, N., Krug, A., Yuksel, D., Stein, F., Schmitt, S., Meller, T., Brosch, K., Dannlowski, U., Nenadić, I., Kircher, T., & Brakemeier, E.-L. (2020). Childhood maltreatment and adult mental disorders – The prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Research*, *293*, 113398. https://doi.org/https://doi.org/10.1016/j.psychres.2020.113398

R Core Team (2021). *R: A language and environment for statistical computing*. In R Foundation for Statistical Computing.

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry*, *27*(3), 1331-1338. https://doi.org/10.1038/s41380-021-01367-9

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course

of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry*, *169*(2), 141-151. https://doi.org/10.1176/appi.ajp.2011.11020335

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(3), 1 - 67. https://doi.org/10.18637/jss.v045.i03

Vogel, S. C., Perry, R. E., Brandes-Aitken, A., Braren, S., & Blair, C. (2021). Deprivation and threat as developmental mediators in the relation between early life socioeconomic status and executive functioning outcomes in early childhood. *Developmental Cognitive Neuroscience*, *47*, 100907. https://doi.org/10.1016/j.dcn.2020.100907

Whitsel, E. A., Angel, R., O'Hara, R., Qu, L., Carrier, K., & Harris, K. M. (2022). Add Health Wave V documentation: Inflammation and immune function. *Carolina Population Center*. https://doi.org/10.17615/99s8-5w6210.17615.99s8-5w62

Whitsel, E. A., Cuthbertson, C. C., Tabor, J. W., Potter, A. J., Wener, M. H., Killeya-Jones, L. A., & Harris, K. M. (2012). Add Health Wave IV documentation: Measures of inflammation and immune function. *Carolina*

Supplementary Materials

Supplementary Table 2.1: Parameter Estimates for Path Model of Repeated Measures								
	1	2	3	4	5	6	7	8
1	-							
2	0.02 (0.22)	-						
3	-	**0.35 (0.01)**	-					
4	**0.36 (0.02)**	0.00 (0.06)	0.01 (0.06)	-				
5	-0.01 (0.00)	**0.15 (0.01)**	-	0.03 (0.54)	-			
6	-	**-**	**0.77 (0.01)**	-	**0.18 (0.03)**	-		
7	-	-	-	**0.28 (0.02)**	-	**0.04 (0.07)**	-	
8	-	-	-	**-**	**-**	**0.67 (0.01)**	-	-
1: Wave 5 Depressive Symptoms; 2: Wave 5 CRP; 3: Wave 5 BMI; 4: Wave 4 Depressive Symptoms; 5: Wave 4 CRP; 6: Wave 4 BMI; 7: Wave 3 Depressive Symptoms; 8: Wave 3 BMI Coefficients are presented as standardized betas (standard error) Significance at least at the $p<0.05$ signified by **bold** print								

Supplementary Table 2.2: Parameter Estimates for Path Model Adjusted for Early Life

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	-														
2	0.02 (0.21)	-													
3	-	**0.34 (0.01)**	-												
4	**0.36 (0.02)**	0.01 (0.01)	0.01 (0.07)	-											
5	-0.01 (0.01)	**0.15 (0.01)**	-	0.03 (0.53)	-										
6	-	-	**0.77 (0.01)**	-	**0.17 (0.03)**	-									
7	-	-	-	**0.26 (0.02)**	-	**0.04 (0.07)**	-								
8	-	-	-	-	-	**0.66 (0.01)**	-	-							
9	-	-	-	**-**	-0.01 (0.75)	-	**0.05 (0.10)**	**0.05 (0.40)**	-						
10	-	-	-	**-**	0.04 (0.98)	**-**	-0.00 (0.13)	0.04 (0.52)	**0.44 (0.01)**	-					
11	-	-	-	-	-0.01 (1.34)	-	**0.07 (0.18)**	**-0.04 (0.72)**	**0.22 (0.01)**	**0.16 (0.01)**	-				
12	-	-	-	-	-0.03 (1.10)	-	0.02 (0.14)	-0.01 (0.59)	-	-	-	-			
13	-	-	-	-	0.02 (0.65)	-	**0.07 (0.08)**	-0.01 (0.35)	-	-	-	**0.27 (0.01)**	-		
14	-	-	-	**-**	0.02 (0.26)	-	**-0.07 (0.03)**	**-0.15 (0.14)**	**-0.05 (0.01)**	**-0.10 (0.01)**	-0.03 (0.01)	**-0.05 (0.01)**	**-0.08 (0.01)**	-	
15	-	-	-	**-**	0.03 (0.03)	**-**	-0.02 (0.01)	**0.11 (0.01)**	-0.02 (0.01)	-0.01 (0.01)	0.04 (0.01)	**0.07 (0.01)**	0.01 (0.01)	**-0.42 (0.36)**	-

1: Wave 5 Depressive Symptoms; 2: Wave 5 CRP; 3: Wave 5 BMI; 4: Wave 4 Depressive Symptoms; 5: Wave 4 CRP; 6: Wave 4 BMI; 7: Wave 3 Depressive Symptoms; 8: Wave 3 BMI; 9: Emotional Abuse; 10: Physical Abuse;11: Sexual Abuse; 12: Physical Neglect; 13: Social Neglect; 14: Early family SES; 15: Neighborhood Socioeconomic Disadvantage

Coefficients are presented as standardized betas (standard error)

Significance at least at the $p<0.05$ signified by **bold** print

Supplementary Table 2.3: Parameter Estimates for Path Model Adjusted for Early Life and Controls															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	-														
2	0.01 (0.20)	-													
3	-	**0.34 (0.01)**	-												
4	**0.31 (0.02)**	-0.01 (0.06)	-0.01 (0.07)	-											
5	-0.01 (0.01)	**0.14 (0.01)**	-	0.03 (0.52)	-										
6	-	-	**0.75 (0.01)**	-	**0.18 (0.03)**	-									
7	-	-	-	**0.26 (0.02)**	-	**0.03 (0.07)**	-								
8	-	-	-	-	-	**0.65 (0.01)**	-	-							
9	-	-	-	**-**	-0.01 (0.74)	-	**0.05 (0.10)**	**0.05 (0.40)**	-						
10	-	-	-	**-**	**0.05 (0.98)**	**-**	-0.01 (0.13)	0.04 (0.53)	**0.44 (0.01)**	-					
11	-	-	-	-	-0.03 (1.35)	-	**0.07 (0.18)**	**-0.04 (0.73)**	**0.21 (0.01)**	**0.15 (0.01)**	-				
12	-	-	-	-	-0.03 (1.10)	-	0.02 (0.15)	-0.01 (0.60)	-	-	-	-			
13	-	-	-	-	-0.02 (1.10)	-	**0.06 (0.08)**	-0.01 (0.35)	-	-	-	**0.26 (0.01)**	-		
14	-	-	-	**-**	0.02 (0.65)	-	**-0.06 (0.03)**	**-0.16 (0.14)**	-0.04 (0.01)	**-0.09 (0.01)**	-0.01 (0.01)	**-0.05 (0.01)**	**-0.07 (0.01)**	-	
15	-	-	-	**-**	0.03 (0.03)	**-**	-0.03 (0.01)	**0.11 (0.01)**	-0.02 (0.01)	-0.01 (0.01)	0.05 (0.01)	**0.07 (0.01)**	-0.01 (0.01)	**-0.36 (0.31)**	-
16	**0.04 (0.11)**	0.01 (0.34)	-0.01 (0.36)	**-**	-	**-**	-	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
17	0.15 (0.10)	0.01 (0.33)	-0.01 (0.35)	**-**	-	**-**	-	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
18	-0.01 (0.09)	0.01 (0.30)	0.02 (0.32)	**-**	-	**-**	-	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
19	0.02 (0.08)	-0.02 (0.25)	0.01 (0.27)	**-**	-	**-**	-	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
20	0.14 (0.10)	0.01 (0.31)	0.02 (0.32)	**-**	-	**-**	-	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

21	0.09 (0.08)	0.04 (0.25)	0.01 (0.27)	-	-	-	-	-	-	-	-	-	-	-	-
22	0.03 (0.08)	0.01 (0.27)	0.02 (0.28)	-	-	-	-	-	-	-	-	-	-	-	-
23	**-0.07 (0.01)**	0.01 (0.01)	-0.02 (0.01)	**-0.07 (0.01)**	0.01 (0.01)	**-0.04 (0.01)**	-	-	-	-	-	-	-	-	-
24	**0.05 (0.05)**	**0.06 (0.01)**	**0.06 (0.01)**	0.03 (0.01)	-0.04 (0.04)	**0.03 (0.01)**	-	-	-	-	-	-	-	-	-
25	-	-	-	-0.02 (0.10)	0.01 (0.79)	0.02 (0.35)	-	-	-	-	-	-	-	-	-
26	-	-	-	**0.08 (0.09)**	0.01 (0.73)	**-0.06 (0.32)**	-	-	-	-	-	-	-	-	-
27	-	-	-	0.01 (0.12)	0.04 (0.95)	0.01 (0.42)	-	-	-	-	-	-	-	-	-
28	-	-	-	-0.01 (0.08)	0.02 (0.65)	0.02 (0.29)	-	-	-	-	-	-	-	-	-
29	-	-	-	**0.11 (0.10)**	0.01 (0.85)	**0.03 (0.38)**	-	-	-	-	-	-	-	-	-
30	-	-	-	0.01 (0.07)	-0.01 (0.62)	0.01 (0.27)	-	-	-	-	-	-	-	-	-
31	-	-	-	**0.07 (0.10)**	0.01 (0.79)	**0.07 (0.35)**	-	-	-	-	-	-	-	-	-
32	0.04 (0.08)	**0.13 (0.27)**	-0.01 (0.28)	0.01 (0.08)	**0.10 (0.69)**	-0.02 (0.30)	0.03 (0.09)	-0.04 (0.37)	**0.05 (0.02)**	-0.02 (0.01)	**0.13 (0.01)**	-0.06 (0.01)	-0.01 (0.02)	-0.04 (0.06)	0.01 (0.50)
33	-0.02 (0.13)	-0.02 (0.40)	**0.03 (0.43)**	**0.08 (0.13)**	0.03 (1.14)	**0.04 (0.46)**	0.01 (0.14)	0.01 (0.59)	-0.01 (0.03)	0.01 (0.02)	0.01 (0.01)	0.02 (0.02)	**0.05 (0.03)**	**-0.23 (0.09)**	**0.42 (0.74)**
34	**0.08 (0.16)**	0.01 (0.51)	0.01 (0.53)	0.02 (0.16)	0.01 (1.33)	**0.04 (0.58)**	0.02 (0.17)	**-0.05 (0.71)**	-0.01 (0.04)	0.02 (0.03)	0.01 (0.02)	-0.01 (0.02)	0.03 (0.04)	**-0.16 (0.11)**	**0.12 (0.96)**
35	0.01 (0.13)	**-0.05 (0.42)**	0.01 (0.44)	**0.08 (0.13)**	**0.04 (1.08)**	-0.01 (0.48)	0.02 (0.14)	0.01 (0.58)	0.03 (0.03)	**0.08 (0.02)**	0.01 (0.01)	**0.05 (0.02)**	0.04 (0.03)	**-0.08 (0.09)**	**0.10 (0.80)**
36	**0.05 (0.02)**	-0.03 (0.06)	-0.01 (0.07)	0.01 (0.02)	0.01 (0.17)	-0.01 (0.07)	0.17 (0.02)	0.01 (0.09)	0.03 (0.01)	**-0.04 (0.01)**	-0.01 (0.01)	-0.01 (0.01)	-0.02 (0.01)	**-0.04 (0.01)**	**0.05 (0.13)**

1: Wave 5 Depressive Symptoms; 2: Wave 5 CRP; 3: Wave 5 BMI; 4: Wave 4 Depressive Symptoms; 5: Wave 4 CRP; 6: Wave 4 BMI; 7: Wave 3 Depressive Symptoms; 8: Wave 3 BMI; 9: Emotional Abuse; 10: Physical Abuse;11: Sexual Abuse; 12: Physical Neglect; 13: Social Neglect; 14: Early family SES; 15: Neighborhood Socioeconomic Disadvantage; 16: Wave 5 Binge Drinking; 17: Wave 5 Current Smoking; 18: Wave 5 Prior Smoking; 19: Wave 5 Anti-inflammatory Medication; 20: Wave 5 Antidepressant Medication; 21: Wave 5 Infection Symptoms; 22: Wave 5 Chronic Health Problem; 23: Wave 4 Occupational Prestige Score; 24: Neighborhood Socioeconomic Disadvantage; 25: Wave 4 Binge Drinking; 26: Wave 4 Current Smoking; 27: Wave 4 Prior Smoking; 28: Wave 4 Anti-inflammatory Medication; 29: Wave 4 Antidepressant Medication; 30: Wave 4 Infection Symptoms; 31: Wave 4 Chronic Health Problem; 32: Female Sex; 33: Non-Hispanic Black Racial/Ethnic Identity; 34: Hispanic Only Racial/Ethnic Identity; 35: All Other Racial/Ethnic Identities; 36: Age at Wave 1

Coefficients are presented as standardized betas (standard error)
Significance at least at the $p<0.05$ signified by **bold** print

Supplementary Table 2.4: Variance Explained Across Endogenous Variables				
	Wave 1	Wave 3	Wave 4	Wave 5
Depressive symptoms	-	0.02	0.12	0.22
CRP	-	-	0.03	0.09
BMI	-		0.49	0.60
Emotional abuse	-	-	0.01	-
Physical abuse	-	-	0.01	-
Sexual abuse	-	-	0.02	-
Social neglect	-	0.01	-	-
Physical neglect	-	0.02	-	-
Family SES	0.08	-	-	-
Neighborhood SES	0.19	-	-	-
Coefficients represent the variance explained across each endogenous variable in the multivariate model adjusted for sociodemographic and control variables. Note that endogenous variables utilize different predictor matrices and comparisons should be made with care.				

CHAPTER 3

EXPLORING SEX DIFFERENCES IN HOW ADVERSE CHILDHOOD EXPERIENCES AFFECT INFLAMMAITION AND DEPRESSIVE SYMPOTMS

Introduction

Adverse childhood experiences (ACEs) are considered a major risk factor for the development of depressive symptoms in adulthood (Chapman et al., 2004; Tan & Mao, 2023). Broadly, ACEs expanded on the widely understood association between childhood maltreatment and common medical problems by assessing how household dysfunction in addition to maltreatment contributed to long-term health behaviors and health outcomes (Felitti et al., 1998). Evidence suggests that the experience of ACEs are associated with greater depressive symptoms starting in childhood and continuing into adulthood relative to those who have not experienced ACEs (Desch et al., 2023). Additionally, evidence also indicates that a greater number of ACEs are associated with a dose-response increase in the risk for lifetime major depressive disorder (Chapman et al., 2004; Tan & Mao, 2023). As much as 62% of those who experience major depressive episode have a history of at least one ACE, and the experience of ACEs place has been found to place individuals at increased risk for suicide (Dube et al., 2001; Thompson et al., 2018).

One of the pathways through which ACEs may be related to depressive symptoms is through an increase in inflammation. Experiences of early life events calibrate the body's threat detection and complimentary stress response systems (Slavich et al., 2023). ACEs can prime the body to initiate a fight or flight response more frequently or for a more prolonged period relative

to unaffected individuals, leading to initial immunosuppression that is followed by an increase in inflammatory signaling (Slavich et al., 2023). This increase in inflammatory signaling is thought to target key areas of the brain that are associated with mental health problems such as major depressive disorder. The repeated activation of the stress response, to a true threat or a cognitive appraisal of a threat, creates epigenetic changes at the cellular level that increase the inflammatory activity associated with the stress response (Slavich & Cole, 2013; Slavich et al., 2023). Inflammatory activity and depressive symptoms are thought to be bi-sustaining mechanisms, with inflammatory molecules affecting regions of the brain that initiate depressive symptoms, while negative mood states can lead to the activation of cognitive schemas that induce an inflammatory response (Beurel et al., 2020; Messay et al., 2012; Slavich et al., 2023). Thus, an understanding of how different ACEs conjointly affect inflammation and depression could provide new insights into how interventions can be more effectively initiated and structured.

Understanding the relationship between ACEs, inflammation, and depressive symptoms is difficult due to a tendency for the field to collapse ACEs into a simplified index. Some of the earliest studies reporting associations between ACEs and depressive symptoms have justified this approach by emphasizing the interrelatedness of ACEs (Chapman et al., 2004). However, some evidence suggests that individuals ACEs may have differential effects. For example, a history of family mental illness and sexual abuse emerged as the only significant ACE associated with depressive symptoms in adulthood among other individual ACEs (Giano et al., 2021). Meta-analytic results exploring ACEs, inflammation, and depressive symptoms have offered similarly conflicting results. A meta-analysis of 22 studies showed that ACEs were positively associated with C-reactive protein (CRP) and interleukin-6 (IL-6) (common measures of

inflammation) and depressive symptoms, and that CRP and IL-6 were associated with an increase in depressive symptoms (Zagaria et al., 2024). However, at least eight of the studies measured ACEs using a version of the Childhood Trauma Questionnaire, which is a measure of childhood maltreatment, not household dysfunction, as initially conceptualized in ACEs measurement (Chapman et al., 2004; Felitti et al., 1998). Further, the meta-analytic results pointed towards BMI as an intermediary between ACEs and inflammation that helped sequentially explain the association between inflammation and depressive symptoms. Although this line of research has shown significant promise in understanding the effects of childhood maltreatment, inflammation, and depressive symptoms (Kerr et al., 2021), ACEs in the broader sense have been only weakly associated with obesity, which is defined by a BMI of 30.00 or greater (Hughes et al., 2017).

Further complicating the association between different ACEs, inflammation, and depressive symptoms is the multidimensional role of sex differences. While the onset of puberty is marked by a significant increase in the onset of major depression, adolescent females show twice the increase in incidence of major depression as adolescent males (Nolen Hoeksema, 1984; Nolen-Hoeksema & Girgus, 1994; Slavich & Sacher, 2019). The onset timing of this difference has led to numerous investigations into the role of sex hormones. For example, estradiol can have non-linear effects on inflammation depending on the concentration and exogenous sex hormones can have protective effects in for individuals with low estrogen levels (Lombardo et al., 2021; Slavich & Sacher, 2019). Additionally, females have been found to report greater rates of ACEs such as verbal abuse, physical abuse, and sexual abuse that have been dually associated with increases in inflammation and depressive symptoms (Derry et al., 2015; Keyes et al., 2012). Despite these hypothesized differences, sex-differences in ACEs, inflammation, and depressive

symptoms have not been widely investigated except for two prior studies. First, in a study of 85 U.S. college students, Kim et al. (2019) identified that collapsing ACEs into measures of abuse, neglect, and family dysfunction revealed a positive association between family dysfunction and CRP that was stronger in female students. Second, in a longitudinal study following English participants from ages 9 to 23, Iob et al (2022) found that sexual abuse was associated with increased CRP trajectories for males but not for females.

Aims of the present study

Increases in the number of ACEs have been associated with increases in depressive symptoms in adulthood (Mao & Tan, 2023; Chapman et al., 2004). However, some evidence suggests that some ACEs have a greater effect on depressive symptoms than others, and therefore collapsing ACEs into an index may eliminate important information from a model (Iob et al., 2023). Additionally, individual ACEs may have differing effects on inflammatory signaling, which is a key pathway thought to influence depressive symptoms (Iob et al., 2023; Slavich et al., 2023). Increased inflammation signaling and depressive symptoms are hypothesized to be bi-sustaining although no models have tested how individual ACEs are related to both inflammation and depressive symptoms (Beurel et al., 2020; Slavich et al., 2023). Further, males and females may have significant differences in these associations, but understanding these potential sex-differences has gone under-investigated (Iob et al., 2022; Kim et al., 2019; Slavich & Sacher et al., 2019). Thus, the present study has two objectives:

1. To understand how individual ACEs are related to both inflammation and depressive symptoms in a nationally representative sample of the U.S. population.
2. To understand if there are sex differences in the associations between individual ACEs, inflammation, depressive symptoms.

Method

Data Source and Sample:

The present study utilized data from the National Study of Adolescent to Adult Health (Add Health), a nationally representative panel study of the U.S. (Harris et al., 2019). The Add Health study began in 1994, sampling over 90,118 adolescents, grades 7-12, through an in-school survey. From this initial pool of participants, 20,745 participants were administered an in-home survey, forming the primary sampling frame for follow-up home surveys. Five waves of data are currently available for analysis, and a sixth wave is forthcoming. Analyses for this study used data from Waves 1 (1994-1995), 3 (2001-2002), and 4 (2008-2009), as well as the survey of parents at Wave 1 and the biomarker collection portion of Wave 4. After combining relevant data frames for Waves 1, 3, 4 there were 4,900 participants in the data frame. After compiling data frames, 272 participants were removed due to not having a relevant survey weight. From the remaining 4,628 participants, 27 were removed due to parents of the participants not participating in the parent portion of the Wave 1 survey leaving a final analytic sample of 4,601 participants.

Measures:

Adverse Childhood Experiences were measured similar to prior studies that have explored the effects of ACEs within Add Health data (Brumley et al., 2016; Schwartz et al., 2019; Testa & Jackson, 2020). Ten different events were included categorically: emotional abuse, physical abuse, sexual abuse, physical neglect, emotional neglect, parental incarceration, parental separation, substance use in the home, community violence, and exposure to suicide. The occurrence of each individual ACE was accounted for categorically as occurring (1) or not occurring (0). Emotional abuse, sexual abuse, physical abuse, and parental incarceration were

assessed via participant self-report at Wave 4. Physical neglect was assessed via participant self-report at Wave 3. Community violence, emotional neglect, and exposure to family or friend suicide were assessed via participant self-report at Wave 1. Parental marital status was assessed via parent self-report at Wave 1. In home substance use was assessed via a combination of participant and parent self-report at Wave 1. ACEs measures are described in Supplementary Table 4.1.

Depressive Symptoms were measured at Wave 4 using a 10-item, modified version of the Center for Epidemiological Studies-Depression scale (CES-D 10). The modified CES-D 10 covered affective, cognitive, somatic, and interpersonal aspects of depressive symptoms. Each item asked the respondent to rate their experience of the symptom as 0 "rarely or none of the time (less than 1 day)," 1 "some or a little of the time (1-2 days)," 2 "occasionally or a moderate amount of the time (3-4 days)," or 3 "most or all of the time (5-7 days)." Items were summed to create a potential score range of 0-30 with greater scores indicating a greater experience of past week depressive symptoms. Cronbach's alpha calculated based on the analytic sample for the present study was 0.85, indicating good internal consistency. A complete list of the items used to measure depressive symptoms can be reviewed in Supplementary Table 4.2.

C-reactive protein level at Wave 4 was used as an overall index of systemic inflammation. CRP levels were derived from capillary blood spot samples obtained via finger prick during an in-home visit. A single 3.2mm diameter punch was taken from each obtained blood spot and placed in a deep-well microliter plate. Samples were then assayed via sandwich enzyme-linked immunosorbent assay method (McDade et al., 2024). Sensitivity for assayed CRP was 0.035mg/L. Within-assay coefficient of variation was 8.1%. Between assay coefficient variation was 11.0% (Whitsel et al., 2012).

Sex was assessed by participant self-report at Wave 1. Participants reported their sex as either female (1) or male (0).

Control variables included those known to affect the relationship between CRP and depressive symptoms: body mass index (BMI) at Wave 4, current tobacco cigarette smoking status at Wave 4, presence of a physical health condition at Wave 4, antidepressant use at Wave 4, anti-inflammatory use at Wave 4, exogenous sex hormone use at Wave 4, and depressive symptoms at Wave 1. Wave 4 BMI was included as continuous variable, calculated through its typical formulation of kilograms divided by meters squared. Tobacco cigarette smoking status at Wave 4 was included categorically as current smoking status (1) or current non-smoking status (0). Presence of a physical health condition was included categorically as the presence (1) or absence (0) of heart disease, high blood cholesterol, high triglycerides, high lipids, or evidence of current diabetes (HbA1c > 6.5.%, fasting glucose $\geq$ 200mg/dl, or antidiabetic medication use). Antidepressant use (SSRI, tricyclics, phenylpiperazine, tetracyclic, SSNRI, or miscellaneous antidepressant) at Wave 4 was included categorically as any antidepressant use (1) or no use (0). Anti-inflammatory use (NSAID and salicylates, cox-2 inhibitors, inhaled corticosteroid, corticotropin/glucocorticoid, antirheumatic/antipsoriatic, or immunosuppressives) at Wave 4 was included categorically as any anti-inflammatory use (1) or no use (0). Exogenous sex hormone use (contraceptives, androgens and anabolic steroids, estrogens, gonadotropins, progestins, sex hormone combinations, or miscellaneous sex hormones) at Wave 4 was included categorically as any sex hormone use (1) or no use (0).

Demographic variables included age at Wave 1, racial identity, ethnic identity, and four measures of socioeconomic status: Social Origins Score at Wave 1, Occupational Prestige score at Wave 4, and Neighborhood Socioeconomic Disadvantage score at Waves 1 and 4. Age at

Wave 1 was included as a continuous variable with a potential range of 12-21 years. Racial identity was included categorically as White (0), Black (1), Asian and/or Pacific Islander (1), Native American (1), other racial identity (1), or multi-racial identity (1). Ethnic identity was included categorically as Hispanic (1), or non-Hispanic (0). Social Origins scores were pre-calculated by the Add Health team, using principal components analysis to create a composite measure of parental education, parental occupation, household income, and household receipt of public assistance. Social Origins scores were *z*-transformed by the Add Health team and included in the present study as a continuous measure (Belsky et al., 2018). Occupational Prestige precalculated by the Add Health team via an average of the Hauser and Warren Occupational Income and Occupational Education Scales. This created a socioeconomic index, with greater scores indicating greater socioeconomic status (Belsky et al., 2018). Neighborhood Socioeconomic Disadvantage at Waves 1 and 4 were based on the proportion of five items: female-headed households, individuals living below the poverty threshold, individuals receiving public assistance, adults with less than a high school education, and adults who were unemployed within the participant's census tract. Each of these items were then scored on a scale of 1-10 and summed, resulting in a potential range of 5-50 (Belsky et al., 2019).

Analytic Strategy

To understand the effects of individual ACEs on both depressive symptoms and CRP, two non-recursive path models were estimated. The first model included each ACE as an individual predictor of depressive symptoms and CRP, while also allowing depressive symptoms and CRP to covary. Self-reported sex, control variables, and demographic variables were included as covariates in the model, predicting depressive symptoms and CRP. Notably, BMI was constrained to predicting CRP, but not depressive symptoms per findings by Moriarity et al.

(2023) that the inclusion of BMI as a covariate predicting depressive symptoms with CRP may increase the risk for false negative results when testing for associations between inflammation and depressive symptoms. To account for the interrelatedness of ACEs, covariances were assigned among each individual ACE. Additionally, because ACEs have been frequently associated with socioeconomic conditions covariances were assigned between social origins score and neighborhood socioeconomic conditions at Wave 1 and individual ACEs. Last, the use of model fit indices were used to add covariances between social origins score and neighborhood socioeconomic conditions at Wave 1, social origins score and occupational prestige score, and occupational prestige score and neighborhood socioeconomic conditions at Wave 4. The second phase of analyses began by first disaggregating the sample by self-reported sex, and then rerunning the non-recursive model as two separate males only and female only models. Covariates for the sex-disaggregated models included control variables and demographic variables as previously implemented but did not include sex as a covariate. Covariances between ACEs and socioeconomic conditions were also retained for sex-disaggregated models. Univariate sample statistics for the total sample as well as the sex-disaggregated samples were calculated to provide further context for the multivariate models. Additionally, *t*-tests and chi-square tests were utilized to better understand how potential bivariate differences may contribute to the sex-disaggregated multivariate models.

To control for the effects of acute infection while retaining participants with baseline CRP levels greater than 10, which may be relevant for depressive symptoms, participants with CRP levels greater than 10mg/L and at least one acute infection symptom within 2 weeks prior to blood sample collection were removed from the sample (Moriarity et al., 2021). Infections symptoms included flu symptoms, fever, night sweats, diarrhea, nausea, vomiting, bloody stool,

polyuria, or skin rash. Among the remaining 3,615 participants in the analytic sample, 3,003 (83.07%) provided complete data. The greatest source of missingness was CRP (*n*=189, 5.22%). *T*-tests and chi-square analyses were utilized to assess the potential biasing effects of CRP missingness on the multivariate model. No association was noted between missing values for CRP and depressive symptoms at Wave 4, ACE, sex, race, or ethnic identity. Therefore, all missing data was treated as missing at random.

All analyses were conducted in R version 4.2.3 (R Core Team). All analyses accounted for the complex survey design elements of the Add Health data set as recommended by the Add Health team (Chen & Mullan-Harris, 2020). Univariate and bivariate analyses were conducted using the survey package recommended by Lumley et al. (2024). Multivariate analyses were conducted using the Lavaan and lavaan.survey packages (Oberski, 2014; Rosseel, 2012). Multivariate models were estimated using the robust maximum likelihood estimation method, accounting for the expected skew in community samples of depressive symptoms and CRP.

Results

Sample Description

The sample primarily identified as White (78.16 %), non-Hispanic (9.27 %), and female (64.63 %). Mean depressive symptoms for the sample were relatively low (*M*=6.48, *SE*=0.16). Mean CRP levels (*M*=4.66, *SE*=0.16) were above the threshold of 3mg/L for low-grade inflammation with a strong right skew; although, median CRP levels were 2.56. The most common ACE experienced by the sample was emotional abuse (48.59%) followed by in home substance use (17.15%), while the least common was suicide exposure (3.77%). Most of the sample experienced at least 1 ACE, although 30.14% experienced no ACEs. A complete review of the total sample statistics can be reviewed in Table 3.1.

Table 3.1: Sample Descriptive Statistics

	Mean (*SE*) or %
Dependent Variables	
Depressive Symptoms Wave 4	6.48 (0.11)
CRP Wave 4	4.66 (0.16)
ACE	
Emotional abuse	48.59%
Physical abuse	17.04%
Sexual abuse	5.33%
Physical neglect	9.75%
Emotional neglect	15.40%
Parental separation	16.99%
In home substance use	17.15%
Parental incarceration	10.37%
Suicide exposure	3.77%
Community violence	9.39%
Control Variable	
Depressive symptoms at Wave 1	10.82 (0.17)
Physical Health Problem at Wave 4	18.30%
Antidepressant at Wave 4	15.18%
Anti-inflammatory at Wave 4	38.63%
Exogenous sex hormone at Wave 4	27.89%
Current tobacco cigarette smoking at Wave 4	33.28%
BMI at Wave 4	28.85 (0.22)
Demographics	
Age at Wave 1	15.92 (0.11)
Race: White	78.16%
Race: Black	10.28%
Race: Asian/Pacific Islander	1.79%
Race: Native American	0.49%
Race: Other racial identity	5.35%
Race: Multi racial identity	3.90%
Ethnicity: Hispanic	9.27%
Sex: female	64.63%
Social Origins Score	0.15 (0.07)
Occupational Prestige Score	99.51 (1.24)
Neighborhood at Wave 1	23.87 (0.85)
Neighborhood at Wave 4	20.01 (0.39)

When exploring sex differences, male and female samples did not differ in their mean depressive symptoms (p=0.62); however, the female sample had higher mean CRP levels

($t(127)= 7.43$, $p<0.001$). Regarding ACEs, the female sample was more likely to report experiencing emotional abuse (Female: 51.73%; Male: 42.85%), sexual abuse (Female: 6.77%; Male: 2.69%), and emotional neglect (Female: 18.01%; Male: 10.65%). The male sample was more likely to report experiencing physical neglect (Female: 7.15%; Male: 14.61%) and community violence (Female: 7.12%; Male: 13.55%). There was no significant difference in the mean number of ACEs experienced between males and females ($p=0.91$). A complete review of mean and frequency comparisons across male and female samples can be reviewed in Table 3.2.

Table 3.2: Mean and frequency comparisons across female and male participants

	Female Mean (*SE*) or *n*	Male Mean (*SE*) or *n*	Test statistic (*df*)
Dependent Variables			
Depressive Symptoms (Wave 4)	6.52 (0.13)	6.41 (0.20)	0.49 (127)
CRP (Wave 4)	5.42 (0.21)	3.27 (0.20)	7.43 (127)***
ACE			
Emotional abuse	2,218,138	1,005,428	14.29 (128)***
Physical abuse	699,864.4	430,586.8	0.80 (128)
Sexual abuse	290,454.77	63,325.35	10.89 (128)**
Physical neglect	298,999.8	326,808.3	19.24 (128)***
Emotional neglect	764,319.9	246,861.2	14.35 (128)***
Parental separation	734,983.9	392,617.5	0.06 (128)
In home substance use	718,088.0	405,546.4	0.06 (128)
Parental incarceration	423,638.6	264,271.6	1.01 (128)
Suicide exposure	179,073.74	71,452.74	1.94 (128)
Community violence	303,416.8	314,669.2	14.84 (128)***
Control Variables			
Depressive symptoms (Wave 1)	11.26 (0.23)	10.03 (0.23)	3.72 (127)***
Physical Health Problem (Wave 4)	681,947.1	532,289.8	9.61 (128)**
Antidepressant (Wave 4)	662,274.1	344,824.2	0.19 (128)
Anti-inflammatory (Wave 4)	1,651,193.8	912,081.8	0.02 (128)
Exogenous sex hormone (Wave 4)	1,943,090.807	7,614.795	258.07 (128)***
Current tobacco cigarette smoking (Wave 4)	1,365,387.7	842,338.6	34.92 (128)***
BMI (Wave 4)	28.46 (0.28)	29.58 (0.31)	-2.84 (127)**
Demographics			
Age (Wave 1)	15.79 (0.12)	16.15 (0.13)	-3.42 (127)***
Race: White	3,355,559.1	1,824,542.5	1.08 (124)
Race: Black	457,546.9	223,811.2	
Race: Asian/Pacific Islander	87,395.06	31,345.67	
Race: Native American	19,162.24	13,872.68	
Race: Other racial identity	214,500.4	140,514.8	
Race: Multi racial identity	146,534	112,225.3	

Ethnicity: Hispanic	355,852.7	259,440.3	3.97 (128)*
Ethnicity: non-Hispanic	3,931,676.7	2,086,853.8	
Social Origins Score	0.18 (0.07)	0.09 (0.09)	1.13 (127)
Occupational Prestige Score	102.66 (1.22)	93.75 (2.10)	4.48 (126)***
Neighborhood (Wave 1)	23.80 (0.86)	23.99 (1.02)	-0.27 (127)
Neighborhood (Wave 4)	19.72 (0.40)	20.56 (0.50)	-2.06 (127)*

*p<0.05, **p<0.01, ***p<0.001

Multivariate analysis

Table 3.3: Comparative Model Fit indices for Multivariate Models

	Total Sample (*N*=6,633,824)	Female Sample (*N*=4,287,530)	Male Sample (*N*=2,346,294)
χ^2(df)	2414.57 (233)***	1873.92 (219)***	816.95 (219)***
χ^2/df	10.36	8.55	3.73
CFI	0.66	0.64	0.71
TLI	0.48	0.44	0.55
RMSEA	0.05	0.06	0.05
SRMR	0.05	0.05	0.05
AIC	134,229.18	94,521.64	38,472.66
BIC	135,184.35	95,409.76	39,224.53
Loglikelihood	-66,955.59	-47,103.82	-19,079.33

*p<0.05, **p<0.01, ***p<0.001

Model fit indices for the total sample model showed mixed results. The RMSEA (0.05) and SRMR (0.05) both showed excellent fit. However, model χ^2 (2414.57, *df*=233), CFI (0.66), and TLI (0.48) each indicated a poor fit. Among ACE's there were several differences between significant predictors of depressive symptoms and significant predictors CRP. Emotional abuse (β= 0.08, *SE*=0.16, *p*<0.001) had a significant positive association with depressive symptoms; however, emotional abuse (β= -0.05, *SE*=0.24, *p*<0.001) had a significant negative association with CRP. Sexual abuse (β= 0.05, *SE*=0.34, *p*<0.01) and emotional neglect (β=0.03, *SE*=0.22, *p*<0.05) each had a significant positive association with depressive symptoms, but neither had an association with CRP. Physical neglect (β= -0.03, *SE*=0.27, *p*<0.05) had a significant negative association with depressive symptoms, but no association with CRP. Parental incarceration (β=0.08, *SE*=0.40, *p*<0.001) was associated with an increase in CRP but was not associated with

depressive symptoms. Exposure to suicide (β= 0.05, *SE*=0.39, *p*<0.01) was associated with an increase in depressive symptoms but was not associated with CRP. There was no significant covariance between depressive symptoms and CRP (*p*=0.961). Covariances between ACEs were widely significant; although, exposure to suicide showed the weakest covariance associations among ACEs. Most notably, the only significant covariances associated with suicide exposure were emotional abuse (β= 0.06, *SE*= 0.01, *p*<0.001), physical abuse (β= 0.05, *SE*= 0.01, *p*<0.01), and emotional neglect (β= 0.05, *SE*=0.01, *p*<0.01). The strongest covariance associations among ACEs were noted between emotional abuse and physical abuse (β=0.35, *SE*=0.01, *p*<0.001), emotional abuse and emotional neglect (β=0.20, *SE*= 0.01, *p*<0.001), and in home substance use and parental incarceration (β=0.24, *SE*=0.01, *p*<0.001). A complete report of all model fit indices can be reviewed in Table 3.3. Associations between ACEs and depressive symptoms and CRP can be reviewed in Table 3.4. A matrix of covariance associations for the total model can be reviewed in Supplementary Table 3.3.

Table 3.4: Standardized Coefficients for non-Recursive path Model of Different ACEs Predicting Depressive Symptoms and CRP

	Total Sample	
	Depressive Symptoms	CRP
ACE	β (*SE*)	β (*SE*)
Emotional abuse	0.08 (0.16)***	-0.05 (0.24)***
Physical abuse	0.02 (0.22)	-0.01 (0.32)
Sexual abuse	0.05 (0.34)**	-0.01 (0.50)
Physical neglect	-0.03 (0.27)*	-0.01 (0.39)
Emotional neglect	0.03 (0.22)*	-0.01 (0.33)
Parental separation	0.01 (0.21)	-0.02 (0.31)
In home substance use	0.01 (0.22)	0.02 (0.32)
Parental incarceration	-0.01 (0.27)	0.08 (0.40)***
Suicide exposure	0.05 (0.39)**	0.01 (0.43)
Community violence	-0.01 (0.27)	-0.01 (0.40)

ACE: adverse childhood experience; CRP: C-reactive protein
* *p*<0.05, ** *p*<0.01, *** *p*<0.001

When considering model fit indices for the female only and male only models, model fit indices showed similar mixed findings. The RMSEA (female: 0.06; male:0.05) and SRMR (female: 0.05; male: 0.05) both indicated excellent model fit. However, model χ^2 (female: χ^2 =1873.92, *df*=219; male: χ^2 = 816.95, *df*=219), CFI (female: 0.64; male: 0.71), and TLI (female: 0.44; male: 0.55) each indicated a poor fit. Among ACEs, there were several significant differences between the male only and the female only models. Emotional abuse (female: β= 0.07, *SE*=0.20, *p*<0.001; male: β=0.09, *SE*=0.29, *p*<0.001) was positively associated with depressive symptoms across both models; however, emotional abuse (female: β= -0.06, *SE*=0.34, *p*<0.01; male: β= -0.08, 0.24, *p*<0.01) was negatively associated with CRP across both models. Similarly, parental incarceration (female: β= 0.08, *SE*= 0.55, *p*<0.001; male: β=0.77, *SE*= 0.40, *p*<0.05) was positively associated with CRP in both models. Physical abuse (β=0.05, *SE*=0.27, *p*<0.01) and sexual abuse (β= 0.06, *SE*=0.37, *p*<0.01) were both positively associated with depressive symptoms in only the female model; although, sexual abuse (β= 0.12, *SE*=0.69, *p*<0.001) was positively associated with CRP in only the male model. In the female model, emotional neglect (β= 0.05, *SE*=0.25, *p*<0.01) was positively associated with depressive symptoms, while physical neglect (β= -0.04, *SE*=0.38, *p*<0.05) was negatively associated with depressive symptoms. Exposure to suicide (β= 0.19, *SE*=0.72, *p*<0.001) was the strongest predictor across all models and was positively associated with depressive symptoms only in the male model. There was no significant covariance between CRP and depressive symptoms in the female only model (*p*=0.80) or male only model (*p*=0.22). As with the total sample model, suicide exposure showed the weakest covariance associations between other ACEs in the female model, being only associated with emotional abuse (β=0.04, *SE*=0.01, *p*<0.05) and community violence (β=0.14, *SE*=0.01, *p*<0.001). Also similar to the total model, emotional abuse and

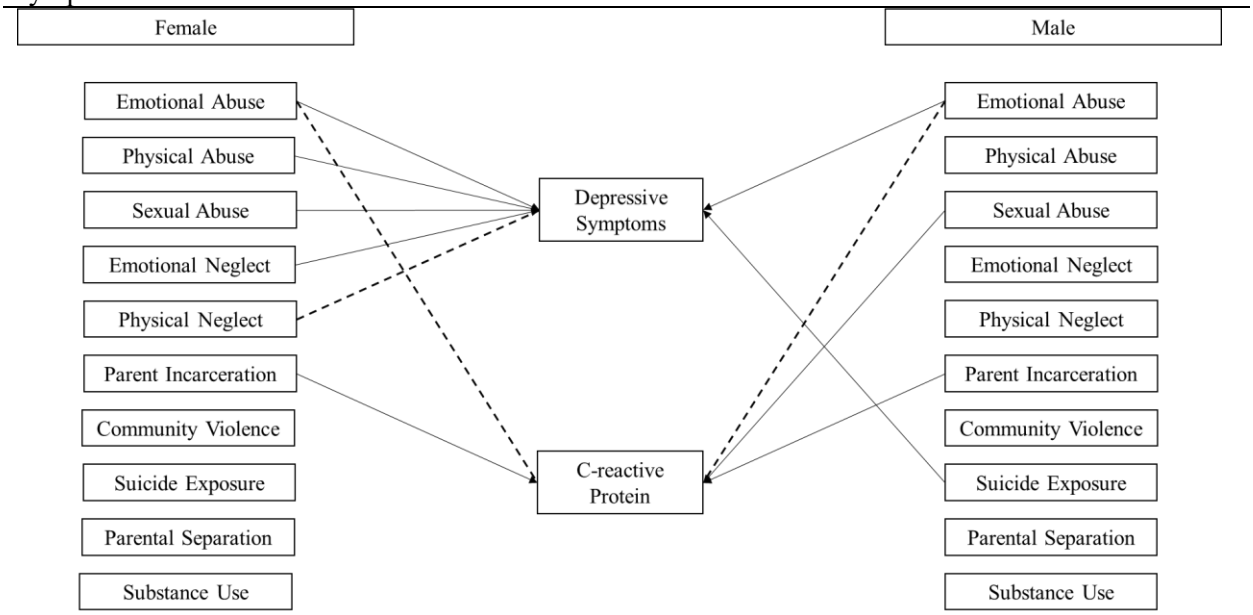
physical abuse (female: β= 0.35, *SE*= 0.01, *p*<0.001; male: β= 0.35, *SE*=0.01, *p*<0.001) had the greatest covariance association among ACEs for both the male model and female model. However, the male model found particularly strong covariance associations between in home substance use and parental incarceration (β=0.32, *SE*=0.01, *p*<0.001) and in home substance use and parental separation (β= 0.28, *SE*= 0.01, *p*<0.001). Associations between all substantive variables and depressive symptoms and CRP can be reviewed in Table 3.5. A graphical representation of the sex-differences model can be reviewed in Figure 3.1. A matrix of covariance associations can be reviewed in Supplementary Tables 3.4 and 3.5.

Table 3.5: Standardized Coefficients for non-Recursive Path Model of Different ACEs Predicting Depressive Symptoms and CRP Across Females and Males

	Female		Male	
	Depressive Symptoms	CRP	Depressive Symptoms	CRP
ACE	β (*SE*)	β (*SE*)	β (*SE*)	β (*SE*)
Emotional abuse	0.07 (0.20)***	-0.06 (0.34)**	0.09 (0.29)**	-0.08 (0.24)**
Physical abuse	0.05 (0.27)**	-0.01 (0.46)	-0.05 (0.36)	-0.01 (0.31)
Sexual abuse	0.06 (0.37)**	-0.01 (0.62)	0.01 (0.81)	0.12 (0.69)***
Physical neglect	-0.04 (0.38)*	-0.03 (0.63)	-0.04 (0.39)	0.05 (0.33)
Emotional neglect	0.05 (0.25)**	0.01 (0.43)	-0.01 (0.43)	-0.04 (0.36)
Parental separation	0.01 (0.26)	-0.02 (0.43)	-0.01 (0.37)	0.01 (0.32)
In home substance use	0.01 (0.26)	0.03 (0.43)	0.01 (0.40)	0.04 (0.34)
Parental incarceration	-0.02 (0.32)	0.08 (0.55)***	0.04 (0.47)	0.7 (0.40)*
Suicide exposure	-0.01 (0.46)	0.01 (0.77)	0.19 (0.72)***	-0.01 (0.61)
Community violence	-0.01 (0.38)	-0.01 (0.64)	-0.01 (0.40)	-0.01 (0.34)

ACE: adverse childhood experience; CRP: C-reactive protein
* *p*<0.05, ** *p*<0.01, *** *p*<0.001

Figure 3.1: Graphical representation ACEs and their associations between CRP and depressive symptoms



Only significant paths are presented. Positive associations are depicted by a solid line. Negative associations are depicted with a dashed line. Covariances are omitted for clarity. Betas and standard errors can be reviewed in Table 3.5.

Discussion

The present study utilized nationally representative data to understand the longitudinal effects of individual ACEs on depressive symptoms and CRP in adulthood using a non-recursive path model. Doing so highlights distinct differences in which ACEs are predictors of depressive symptoms vs CRP. Additionally, significant heterogeneity emerged between predictors when models were disaggregated by sex. Analyses indicate that while emotional abuse and parental incarceration have consistent associations between depressive symptoms and CRP among males and females, experiences of abuse, neglect, and exposure to suicide shows significant differences.

The present study adds to the small but growing number of studies supporting differences in the associations between ACEs, inflammation, and depressive symptoms across males and

females (Iob et al., 2022; Kim et al., 2019; Lacey et al., 2020). Most notably, Iob et al. (2022) had also tested the associations between individual ACEs, CRP, and depressive symptoms in a longitudinal study of English identifying children, following them until age 23. Analyses here support a Iob et al.'s (2022) finding that sexual abuse seems to be associated with a significant later increase in CRP, extending the findings by replicating the association in males in the U.S. between the ages of 24-32. These findings stand in contrast to Lacey et al. (2020) who did not find an association between sexual abuse and CRP in a 1958 British birth cohort study although the sample was aged 44-45 years at the time CRP was assessed, but sex differences were not investigated. Interestingly, these findings were not replicated by Kim et al. (2019) either who also assessed the effects of ACEs on depressive symptoms and CRP in a sample of 85 undergraduate students but collapsed abuse into a single broad category. Results for the present study join with the work of Iob et al. (2020), which demonstrates that individual types of abuse may have different effects on inflammation; however, if studies are limited in their ability to interrogate specific abuse subtypes or sex differences, then the association may be missed.

In turning to depressive symptoms, models confirm prior work that has broadly identified experiences of emotional abuse as being highly relevant for depressive symptoms, and this finding was replicated in all models. However, several notable differences arose among other predictors, namely that other forms of childhood maltreatment had a significant association with depressive symptoms only in females, but that exposure to suicide was associated with depressive symptoms only in males. Critically, analyses accounted for early depressive symptoms and thus, the effects of ACEs can be considered as accounting for depressive symptom growth over time. In this context, experiences of physical neglect may be associated with a decline in depressive symptoms over time for females, while emotional abuse, physical

abuse, sexual abuse, and emotional neglect were associated with greater depressive symptom growth over time. Interestingly, Desch et al., (2023) identified that latent class analysis defined clusters of ACEs may have different growth trajectories over time also using the Add Health data set. The group with the greatest depressive symptom scores at Wave 1 of the Add Health study showed a decrease in depressive symptoms over time, while the group with a moderate degree of depressive symptoms at Wave 1 showed the greatest growth in depressive symptoms by Wave 4. Critically, the group with declining depressive symptoms had twice the frequency of physical neglect. Results presented here build on the work of Desch, et al. (2023) by demonstrating that the experience of physical neglect, particularly among females, may explain depressive symptom decline over time. However, it should be made clear that results from the present study identified several significant covariance associations with emotional abuse, physical abuse, and emotional neglect, each of which was associated with greater depressive symptoms at Wave 4. Thus, physical neglect should not be considered a protective factor, so much as a developmental clue for understanding different trajectories in depressive symptoms.

An additional critical finding is the strong association between exposure to suicide and the increase in depressive symptoms among males. While the total sample model did demonstrate an association between exposure to suicide and depressive symptoms, the standardized beta grew nearly four times when considering the effects for males only and was no longer significant when considering the effects with females. One potential explanation for the association is that there is a familial risk for suicide that is being transmitted to offspring and that this transmission may coincide with more severe depression (Ranning et al., 2022). However, this explanation would hold for both males and females, and does not explain the sex differences observed here. Further, the exposure to suicide variable qualifies suicide exposure among either

friends and/or family, meaning that a genetic risk is likely not the sole factor. A complimentary explanation could also be that exposure to suicide reduces the size of an individual's social network at a critical time in its formation, predisposing them to greater isolation over the life course (Umberson et al., 2011).

Beyond comparison to other ACEs studies, the decision to keep ACEs as individual events rather than collapsing them into an index allows for meaningful comparisons to other studies that have focused on a single stressful event. Of relevance is the effect of parental incarceration on inflammation. Recent findings from Add Health data have already identified that parental incarceration has a lasting effect on CRP (Tung et al, 2023). However, this prior finding did not control for other ACEs outside of collapsing several forms of physical abuse, sexual abuse, and neglect into a single indicator of childhood maltreatment. By adopting the ACEs measures already implemented by other Add Health researchers and using a path model to test covariances among ACEs, analyses from the present study were able to confirm that parental incarceration is indeed associated with higher CRP even when controlling for a broader scope of ACEs. The present study also highlights that parental incarceration had the strongest covariance association with in-home substance use. Thus, while the present study echoes the key message of Tung et al. (2023) that parental incarceration has lasting effects on inflammation, the present study points towards a need for the reduction of carceral approaches to dealing with substance use problems. At present the U.S. has the highest incarceration rate in the world and around 1 in 5 of those who are arrested have a drug related offense (Ohringer et al., 2020; Sawyer & Wagner, 2024). Policy level changes such as the decriminalization of cannabis have resulted in lower drug related charges without any increase in the prevalence of cannabis use, and the wide adoption of

such policies could lead to improved health outcomes for inflammatory related disease in the U.S. (Grucza et al., 2018).

Another larger consideration beyond comparisons ACEs related studies is the lack of association between CRP and depressive symptoms. Theoretical reasoning seems to support that an increase in CRP should be associated with depressive symptoms. However, Iob et al. (2022) also identified a non-significant association between CRP and depressive symptoms in their cohort study of adolescents into young adulthood. Iob et al. (2022), concluded that a potential reason for this lack of association may be due to the cohort being too young for the association to emerge. However, the present study was still unable to identify such an association despite following participants into their 30s. One reason for this may be that the present study did not account for the effects of recent life stress at the time that depressive symptoms and CRP were being assessed. Evidence from Metcalf et al. (2023) identified that females who experienced greater recent stress and had a history of experiencing more ACEs had a significant association between CRP and depressive symptoms. Alternatively, individuals with a current major depressive episode in the context of a history of childhood maltreatment, as opposed to depressive symptoms, have been found to have greater CRP than those without a current major depressive episode (Danese et al., 2009). Thus, CRP may show more utility as a marker of caseness in the context of combined ACE and higher levels of depressive symptoms that qualify as a major depressive episode, while other inflammatory molecules such as IL-6 may be better linear indicators of depressive symptoms. Last, and most relevant for the present study, the use of antidepressants and anti-inflammatory medications in the context of ACEs may have complex effects. Nearly 40% of the sample for the present study reported recently using some form of anti-inflammatory medication, and thus it may be difficult to assess the association between

ACEs with particularly high incidences such as emotional abuse and CRP, as well as the association between CRP and depressive symptoms.

Limitations

While the analyses presented here offer several insights on the associations between individual ACEs, inflammation, and depressive symptoms, interpretations should be considered in light of several limitations. First, the analytic strategy utilized here focused on identifying mechanisms that are associated with inflammation and depressive symptoms. However, repeated measures approaches are needed to extend our understanding on what this means for the overall trajectory of inflammation and depressive symptoms in the context of ACEs. Second, although CRP has been widely used as an index for overall inflammation, has been associated with major depression, and is indicative of wider inflammation activity such as IL-6 secretion, analyses here are limited using a single inflammatory marker. Future research could build on the present study by extending analyses to other relevant inflammatory markers (e.g. IL-6 or TNF-α) as well as those associated with stress responsivity as has been done in allostatic load studies. Third, while the present study utilized many control variables and longitudinal data from a representative cohort study of the U.S. population, true causal inference must be based in experimental design. Future studies may be able to build on the present study using stress responsivity testing to understand how inflammation is related to ACE affected currently depressed individuals relative to control conditions. Last, although the present study is consistent with the framework of prior ACEs studies in evaluating the effects of the occurrence of an adverse event prior to age 18, other aspects such as intensity, frequency, and onset timing are worth consideration. Future studies could address this shortcoming through use of measures such as the Stress and Adversity

Inventory to better understand how these various qualities of ACEs are related to inflammation and depressive symptoms (Slavich & Shields, 2018).

Conclusion

Adverse childhood experiences have been identified as a major risk factor for depressive symptoms in adulthood, potentially though an increase in inflammatory signaling. While results from the present study could not confirm an association between inflammation and depressive symptoms, complex differences were identified between individual ACEs, depressive symptoms, and CRP as an index of overall inflammation. Further, sex-disaggregated models point towards commonalities in the effects of emotional abuse and parental incarceration while also highlighting the sex-specific effects of other forms of childhood maltreatment and exposure to suicide.

References

Belsky, D. W., Caspi, A., Arseneault, L., Corcoran, D. L., Domingue, B. W., Harris, K. M., Houts, R. M., Mill, J. S., Moffitt, T. E., Prinz, J., Sugden, K., Wertz, J., Williams, B., & Odgers, C. L. (2019). Genetics and the geography of health, behaviour and attainment. *Nature Human Behavior*, *3*(6), 576-586. https://doi.org/10.1038/s41562-019-0562-1

Belsky, D. W., Domingue, B. W., Wedow, R., Arseneault, L., Boardman, J. D., Caspi, A., Conley, D., Fletcher, J. M., Freese, J., Herd, P., Moffitt, T. E., Poulton, R., Sicinski, K., Wertz, J., & Harris, K. M. (2018). Genetic analysis of social-class mobility in five longitudinal studies. *Proceedings of the National Academy of Sciences*, *115*(31), E7275-E7284. https://doi.org/doi:10.1073/pnas.1801238115

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The Bidirectional relationship of depression and inflammation: Double trouble. *Neuron*, *107*(2), 234-256. https://doi.org/https://doi.org/10.1016/j.neuron.2020.06.002

Brumley, L. D., Jaffee, S. R., & Brumley, B. P. (2017). Pathways from childhood adversity to problem behaviors in young adulthood: The mediating role of adolescents' future expectations. *Journal of Youth and Adolescence, 46*(1), 1-14. https://doi.org/10.1007/s10964-016-0597-9

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *Journal of Affective Disorders*, *82*(2), 217-225.

Chen, P., & Harris, K. M. (2020). Add Health documentation: Guidelines for analyzing Add Health data. *Carolina Population Center*. https://doi.org/10.17615/C6BW8W

Derry, H. M., Padin, A. C., Kuo, J. L., Hughes, S., & Kiecolt-Glaser, J. K. (2015). Sex

differences in depression: Does inflammation play a role? *Current Psychiatry Reports*, *17*(10), 78. https://doi.org/10.1007/s11920-015-0618-5

Desch, J., Mansuri, F., Tran, D., Schwartz, S. W., & Bakour, C. (2023). The association between adverse childhood experiences and depression trajectories in the Add Health study. *Child Abuse and Neglect*, *137*, 106034. https://doi.org/10.1016/j.chiabu.2023.106034

Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., & Giles, W. H. (2001). Childhood Abuse, Household Dysfunction, and the Risk of Attempted Suicide Throughout the Life SpanFindings From the Adverse Childhood Experiences Study. *JAMA*, *286*(24), 3089-3096. https://doi.org/10.1001/jama.286.24.3089

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, *14*(4), 245-258.

Giano, Z., Ernst, C. W., Snider, K., Davis, A., O'Neil, A. M., & Hubach, R. D. (2021). ACE domains and depression: Investigating which specific domains are associated with depression in adulthood. *Child Abuse & Neglect*, *122*, 105335. https://doi.org/https://doi.org/10.1016/j.chiabu.2021.105335

Grucza, R. A., Vuolo, M., Krauss, M. J., Plunk, A. D., Agrawal, A., Chaloupka, F. J., & Bierut, L. J. (2018). Cannabis decriminalization: A study of recent policy change in five U.S. states. *International Journal of Drug Policy*, *59*, 67-75. https://doi.org/10.1016/j.drugpo.2018.06.016

Harris, K. M., Halpern, C. T., Whitsel, E. A., Hussey, J. M., Killeya-Jones, L. A., Tabor, J., & Dean, S. C. (2019). Cohort profile: The National Longitudinal Study of Adolescent to

Adult Health (Add Health). *International Journal of Epidemiology*, *48*(5), 1415-1415k. https://doi.org/10.1093/ije/dyz115

Hughes, K., Bellis, M. A., Hardcastle, K. A., Sethi, D., Butchart, A., Mikton, C., Jones, L., & Dunne, M. P. (2017). The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *The Lancet Public Health*, *2*(8), e356-e366. https://doi.org/10.1016/S2468-2667(17)30118-4

Iob, E., Lacey, R., Giunchiglia, V., & Steptoe, A. (2022). Adverse childhood experiences and severity levels of inflammation and depression from childhood to young adulthood: a longitudinal cohort study. *Molecular Psychiatry*, *27*(4), 2255-2263. https://doi.org/10.1038/s41380-022-01478-x

Iob, E., Lacey, R., & Steptoe, A. (2020). The long-term association of adverse childhood experiences with C-reactive protein and hair cortisol: Cumulative risk versus dimensions of adversity. *Brain, Behavior, and Immunity*, *87*, 318-328. https://doi.org/https://doi.org/10.1016/j.bbi.2019.12.019

Kerr, D. M., McDonald, J., & Minnis, H. (2021). The association of child maltreatment and systemic inflammation in adulthood: A systematic review. *PLoS One*, *16*(4), e0243685. https://doi.org/10.1371/journal.pone.0243685

Keyes, K. M., Eaton, N. R., Krueger, R. F., McLaughlin, K. A., Wall, M. M., Grant, B. F., & Hasin, D. S. (2012). Childhood maltreatment and the structure of common psychiatric disorders. *British Journal of Psychiatry*, *200*(2), 107-115. https://doi.org/10.1192/bjp.bp.111.093062

Kim, S., Watt, T., Ceballos, N., & Sharma, S. (2019). Adverse childhood experiences and neuroinflammatory biomarkers-The role of sex. *Stress and Health*, *35*(4), 432-440.

https://doi.org/10.1002/smi.2871

Lacey, R. E., Pinto Pereira, S. M., Li, L., & Danese, A. (2020). Adverse childhood experiences and adult inflammation: Single adversity, cumulative risk and latent class approaches. *Brain, Behavior, and Immunity*, *87*, 820-830. https://doi.org/https://doi.org/10.1016/j.bbi.2020.03.017

Lombardo, G., Mondelli, V., Dazzan, P., & Pariante, C. M. (2021). Sex hormones and immune system: A possible interplay in affective disorders? A systematic review. *Journal of Affective Disorders*, *290*, 1-14. https://doi.org/https://doi.org/10.1016/j.jad.2021.04.035

Messay, B., Lim, A., & Marsland, A. L. (2012). Current understanding of the bi-directional relationship of major depression with inflammation. *Biology of Mood & Anxiety Disorders*, *2*(1), 4. https://doi.org/10.1186/2045-5380-2-4

Moriarity, D. P., Horn, S. R., Kautz, M. M., Haslbeck, J. M. B., & Alloy, L. B. (2021). How handling extreme C-reactive protein (CRP) values and regularization influences CRP and depression criteria associations in network analyses. *Brain, Behavior, and Immunity*, *91*, 393-403. https://doi.org/https://doi.org/10.1016/j.bbi.2020.10.020

Moriarity, D. P., Mengelkoch, S., & Slavich, G. M. (2023). Incorporating causal inference perspectives into psychoneuroimmunology: A simulation study highlighting concerns about controlling for adiposity in immunopsychiatry. *Brain, Behavior, and Immunity*, *113*, 259-266. https://doi.org/https://doi.org/10.1016/j.bbi.2023.06.022

Nolen-Hoeksema, S. (1987). Sex differences in unipolar depression: evidence and theory. *Psychological Bulletin*, *101*(2), 259.

Nolen-Hoeksema, S., & Girgus, J. S. (1994). The emergence of gender differences in depression during adolescence. *Psychological Bulletin*, *115*(3), 424-443.

https://doi.org/10.1037/0033-2909.115.3.424

Oberski, D. (2014). lavaan.survey: An R package for complex survey analysis of structural equation models. *Journal of Statistical Software, 57*(1), 1 - 27. https://doi.org/10.18637/jss.v057.i01

Ohringer, A. R., Ezer, T., & Serota, D. P. (2020). Prison-based harm reduction services are needed to address the dual substance use disorder and infectious disease epidemics in US prisons. *eClinicalMedicine, 22*. https://doi.org/10.1016/j.eclinm.2020.100367

Pinto Pereira, S. M., Stein Merkin, S., Seeman, T., & Power, C. (2019). Understanding associations of early-life adversities with mid-life inflammatory profiles: Evidence from the UK and USA. *Brain, Behavior, and Immunity*, *78*, 143-152. https://doi.org/https://doi.org/10.1016/j.bbi.2019.01.016

Ranning, A., Madsen, T., Hawton, K., Nordentoft, M., & Erlangsen, A. (2022). Transgenerational concordance in parent-to-child transmission of suicidal behaviour: A retrospective, nationwide, register-based cohort study of 4,419,642 individuals in Denmark. *The Lancet Psychiatry*, *9*(5), 363-374. https://doi.org/10.1016/S2215-0366(22)00042-6

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software, 48*(2), 1 - 36. https://doi.org/10.18637/jss.v048.i02

Schwartz, J. A., Wright, E. M., & Valgardson, B. A. (2019). Adverse childhood experiences and deleterious outcomes in adulthood: A consideration of the simultaneous role of genetic and environmental influences in two independent samples from the United States. *Child Abuse & Neglect, 88,* 420-431. https://doi.org/https://doi.org/10.1016/j.chiabu.2018.12.022

Slavich, G. M., & Cole, S. W. (2013). The Emerging Field of Human Social Genomics. *Clinical Psychological Science*, *1*(3), 331-348. https://doi.org/10.1177/2167702613478594

Slavich, G. M., Roos, L. G., Mengelkoch, S., Webb, C. A., Shattuck, E. C., Moriarity, D. P., & Alley, J. C. (2023). Social Safety Theory: Conceptual foundation, underlying mechanisms, and future directions. *Health Psychology Review*, *17*(1), 5-59. https://doi.org/10.1080/17437199.2023.2171900

Slavich, G. M., & Shields, G. S. (2018). Assessing lifetime stress exposure using the Stress and Adversity Inventory for Adults (Adult STRAIN): An overview and initial validation. *Psychosomatic Medicine, 80*, 17-27. doi: 10.1097/PSY.0000000000000534

Slavich, G. M., & Sacher, J. (2019). Stress, sex hormones, inflammation, and major depressive disorder: Extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders. *Psychopharmacology (Berl)*, *236*(10), 3063-3079. https://doi.org/10.1007/s00213-019-05326-9

Tan, M., & Mao, P. (2023). Type and dose-response effect of adverse childhood experiences in predicting depression: A systematic review and meta-analysis. *Child Abuse & Neglect*, *139*, 106091. https://doi.org/10.1016/j.chiabu.2023.106091

Team, R. C. (2021). *R: A language and environment for statistical computing*. In R Foundation for Statistical Computing.

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry*, *27*(3), 1331-1338. https://doi.org/10.1038/s41380-021-01367-9

Testa, A., & Jackson, D. B. (2020). Adverse childhood experiences and food insecurity in

adulthood: Evidence from the national longitudinal study of adolescent to adult health. *Journal of Adolescent Health*, *67*(2), 218-224. https://doi.org/https://doi.org/10.1016/j.jadohealth.2020.02.002

Thompson, M. P., Kingree, J. B., & Lamis, D. (2019). Associations of adverse childhood experiences and suicidal behaviors in adulthood in a U.S. nationally representative sample. *Child: Care, Health and Development*, *45*(1), 121-128. https://doi.org/https://doi.org/10.1111/cch.12617

Tung, E. L., Wroblewski, K. E., Makelarski, J. A., Glasser, N. J., & Lindau, S. T. (2023). Childhood parental incarceration and adult-onset hypertension and cardiovascular risk. *JAMA Cardiology*, *8*(10), 927-935. https://doi.org/10.1001/jamacardio.2023.2672

Umberson, D., Crosnoe, R., & Reczek, C. (2010). Social relationships and health behavior across life course. *Annual Reviews in Sociology*, *36*, 139-157. https://doi.org/10.1146/annurev-soc-070308-120011

Whitsel, E. A., Cuthbertson, C. C., Tabor, J. W., Potter, A. J., Wener, M. H., Killeya-Jones, L. A., & Harris, K. M. (2012). Add Health Wave IV documentation: Measures of inflammation and immune function. *Carolina Population Center*. https://doi.org/10.17615/C60M2R

Zagaria, A., Fiori, V., Vacca, M., Lombardo, C., Pariante, C. M., & Ballesio, A. (2024). Inflammation as a mediator between adverse childhood experiences and adult depression: A meta-analytic structural equation model. *Journal of Affective Disorders*, *357*, 85-96. https://doi.org/https://doi.org/10.1016/j.jad.2024.04.072

Supplementary Materials

Supplementary Table 3.1: ACEs Coding Scheme

ACE	Prompt	Coding Scheme	Wave	Source
Emotional abuse	"Before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?"	Any instance of emotional abuse=1 No history of emotional abuse=0	4	Participant
Physical abuse	"Before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or down stairs?"	Any instance of physical abuse=1 No history of physical abuse=0	4	Participant
Sexual abuse	"Before your 18th birthday how often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?"	Any instance of sexual abuse=1 No history of sexual abuse=0	4	Participant
Emotional neglect	"Most of the time, your [mother/father] is warm and loving toward you" "Overall, you are satisfied with your relationship with your [mother/father]" "You are satisfied with the way your [mother/father] and you communicate with each other."	Likert scale response for each item ranged from 1 (strongly agree)-5 (strongly disagree). Responses were averaged for mother and father and then summed. Scores of greater than or equal to 8=1 Scores lower than 8=0	1	Participant
Physical neglect	"How often had your parents or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing?"	Any instance of physical neglect =1 No history of physical neglect=0	3	Participant

Parental incarceration	"(Has/did) your [biological mother/ biological father/mother figure/father figure] ever (spent/spend) time in jail or prison?"	Any time in jail or prison=1 No time in jail or prison=0	Parent	Participant
Parental separation	"What is your current marital status"	Divorced or separated=1 Single (never married), married, widowed=0	Parent	Parent
Substance use in the home	"Does respondent's biological mother currently have the following health problem: Alcoholism" "Does respondent's biological father currently have the following health problem: Alcoholism" "Are illegal drugs easily available to you in your home"	Any parental report of alcoholism or self-report access to drugs in the home=1 No parental report of alcoholism or self-report access to drugs in the home=0	Parent/1	Parent
Community violence	"During the past 12 months, how often did you see someone shoot or stab another person?" "During the past 12 months, how often did someone pull a knife or gun on you?" "During the past 12 months, how often did someone shoot or stab you?" "During the past 12 months, how often did someone cut or stab you?"	Any history of community violence in the past 12 months=1 No history of community violence in the past 12 months=0	1	Participant
Exposure to suicide	"Have any of your friends tried to kill themselves during the past 12 months?" "Have any of them succeeded?"	Attempt and death by suicide in the past 12 months=1 No death by suicide in the past 12 months=0	1	Participant

Supplementary Table 3.2: Depressive Symptoms as Measured by the CES-D and Availability of Each Question per Add Health Wave

Item	Prompt	Wave	
		1	4
1	You were bothered by things that usually don't bother you	X	X
2	You did not feel like eating; your appetite was poor	X	
3	You felt that you could not shake off the blues even with help from your family or friends	X	X
4	You felt you were just as good as other people	X	X
5	You had trouble keeping your mind on what you were doing	X	X
6	You felt depressed	X	X
7	You felt that you were too tired to do things	X	X
8	You felt hopeful about the future	X	
9	You thought your life had been a failure	X	
10	You felt fearful	X	
11	My sleep was restless		
12	You were happy	X	X
13	You talked less than usual	X	
14	You felt lonely	X	
15	People were unfriendly	X	
16	You enjoyed life	X	X
17	You had crying spells		
18	You felt sad	X	X
19	You felt that people dislike you	X	X
20	It was hard to get started doing things	X	
21	You felt life was not worth living	X	

Items 11 and 17 are typically included in the 20-item version of the CES-D but were not implemented in the Add Health version.
Item 21 is not typically included in the 20-item version of the CES-D but was included for Add Health
Waves 1 & 2 are 19 items, Wave 3 is 10 items, Wave 4 is 9 items, and Wave 5 is 5 items

Supplementary Table 3.3: Covariances for Total Sample Multivariate Model																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Depression	1	-															
CRP	2	0.01 (0.48)	-														
Emotional abuse	3	-	-	-													
Physical abuse	4	-	-	**0.35 (0.01)**	-												
Sexual abuse	5	-	-	**0.14 (0.01)**	**0.16 (0.01)**	-											
Physical neglect	6	-	-	**0.05 (0.01)**	**0.10 (0.01)**	0.02 (0.01)	-										
Emotional neglect	7	-	-	**0.20 (0.01)**	**0.14 (0.01)**	**0.09 (0.01)**	0.03 (0.01)	-									
Parental separation	8	-	-	**0.09 (0.01)**	**0.08 (0.01)**	**0.05 (0.01)**	**0.06 (0.01)**	**0.04 (0.01)**	-								
In home substance use	9	-	-	**0.12 (0.01)**	**0.07 (0.01)**	**0.08 (0.01)**	**0.07 (0.01)**	**0.07 (0.01)**	**0.20 (0.01)**	-							
Parental incarceration	10	-	-	**0.11 (0.01)**	**0.10 (0.01)**	**0.08 (0.01)**	**0.14 (0.01)**	**0.14 (0.01)**	**0.14 (0.01)**	**0.24 (0.01)**	-						
Suicide exposure	11	-	-	**0.06 (0.01)**	**0.05 (0.01)**	0.01 (0.01)	-0.03 (0.01)	**0.05 (0.01)**	0.01 (0.01)	0.01 (0.01)	-0.01 (0.01)	-					
Community violence	12	-	-	**0.06 (0.01)**	**0.09 (0.01)**	0.01 (0.01)	**0.09 (0.01)**	**0.06 (0.01)**	**0.13 (0.01)**	**0.08 (0.01)**	0.02 (0.01)	**0.14 (0.01)**	-				
Family SES	13	-	-	**-0.08 (0.01)**	**-0.12 (0.01)**	**-0.08 (0.01)**	**-0.08 (0.01)**	**-0.05 (0.01)**	**-0.23 (0.01)**	**-0.12 (0.01)**	**-0.23 (0.01)**	-0.01 (0.01)	**-0.13 (0.01)**	-			
Neighborhood	14	-	-	0.01 (0.09)	0.02 (0.07)	**0.06 (0.04)**	**0.05 (0.05)**	0.03 (0.06)	**0.08 (0.07)**	0.03 (0.06)	**0.11 (0.05)**	0.01 (0.03)	**0.11 (0.05)**	**-0.37 (0.25)**	-		
Occupational Prestige	15	-	-	-	-	-	-	-	-	-	-	-	-	**0.20 (0.75)**	-	-	
Neighborhood	16	-	-	-	-	-	-	-	-	-	-	-	-	-	**0.28 (1.44)**	**-0.14 (4.82)**	-
Standardized betas and standard errors for covariances in the multivariate model Bolded coefficients are significant at least at the p<0.05 level																	

Supplementary Table 3.4: Covariances for Male Sample Multivariate Model																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Depression	1	-															
CRP	2	0.04 (0.44)	-														
Emotional abuse	3	-	-	-													
Physical abuse	4	-	-	**0.35 (0.01)**	-												
Sexual abuse	5	-	-	**0.16 (0.01)**	**0.18 (0.01)**	-											
Physical neglect	6	-	-	0.05 (0.01)	0.05 (0.01)	0.07 (0.01)	-										
Emotional neglect	7	-	-	**0.17 (0.01)**	**0.16 (0.01)**	**0.09 (0.01)**	**0.06 (0.01)**	-									
Parental separation	8	-	-	**0.06 (0.01)**	0.01 (0.01)	-0.02 (0.01)	**0.10 (0.01)**	0.02 (0.01)	-								
In home substance use	9	-	-	**0.11 (0.01)**	**0.08 (0.01)**	**0.17 (0.01)**	**0.08 (0.01)**	**0.12 (0.01)**	**0.28 (0.01)**	-							
Parental incarceration	10	-	-	**0.14 (0.01)**	**0.08 (0.01)**	**0.08 (0.01)**	**0.21 (0.01)**	**0.08 (0.01)**	**0.21 (0.01)**	**0.32 (0.01)**	-						
Suicide exposure	11	-	-	**0.10 (0.01)**	**0.11 (0.01)**	0.04 (0.01)	-0.05 (0.01)	**0.15 (0.01)**	-0.01 (0.01)	0.01 (0.01)	-0.03 (0.01)	-					
Community violence	12	-	-	0.01 (0.01)	0.02 (0.01)	-0.01 (0.01)	**0.10 (0.01)**	**0.07 (0.01)**	**0.11 (0.01)**	**0.08 (0.01)**	-0.03 (0.01)	**0.14 (0.01)**	-				
Family SES	13	-	-	-0.05 (0.01)	**-0.14 (0.01**	-0.06 (0.01)	**-0.07 (0.01)**	-0.04 (0.01)	**-0.27 (0.01)**	**-0.20 (1.46)**	**-0.23 (0.01)**	0.01 (0.01)	**-0.12 (0.01)**	-			
Neighborhood	14	-	-	-0.01 (0.17)	-0.01 (0.13)	0.01 (0.05)	0.04 (0.12)	0.04 (0.11)	0.05 (0.13)	0.06 (0.12)	**0.09 (0.10)**	0.04 (0.06)	**0.18 (0.12)**	**-0.36 (0.47)**	-		
Occupational Prestige	15	-	-	-	-	-	-	-	-	-	-	-	-	**0.20 (1.46)**	-	-	
Neighborhood	16	-	-	-	-	-	-	-	-	-	-	-	-	-	**0.27 (2.64)**	**-0.16 (9.40)**	-
Standardized betas and standard errors for covariances in the multivariate model Bolded coefficients are significant at least at the p<0.05 level																	

Supplementary Table 3.5: Covariances for Female Sample Multivariate Model																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Depression	1	-															
CRP	2	-0.01 (0.67)	-														
Emotional abuse	3	-	-	-													
Physical abuse	4	-	-	**0.35 (0.01)**	-												
Sexual abuse	5	-	-	**0.13 (0.01)**	**0.16 (0.01)**	-											
Physical neglect	6	-	-	**0.08 (0.01)**	**0.13 (0.01)**	0.02 (0.01)	-										
Emotional neglect	7	-	-	**0.21 (0.01)**	**0.14 (0.01)**	**0.09 (0.01)**	0.03 (0.01)	-									
Parental separation	8	-	-	**0.10 (0.01)**	**0.12 (0.01)**	**0.08 (0.01)**	0.04 (0.01)	**0.05 (0.01)**	-								
In home substance use	9	-	-	**0.13 (0.01)**	**0.06 (0.01)**	**0.06 (0.01)**	**0.07 (0.01)**	**0.08 (0.01)**	**0.16 (0.01)**	-							
Parental incarceration	10	-	-	**0.10 (0.01)**	**0.10 (0.01)**	**0.08 (0.01)**	**0.09 (0.01)**	**0.04 (0.01)**	**0.10 (0.01)**	**0.20 (0.01)**	-						
Suicide exposure	11	-	-	**0.04 (0.01)**	0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	0.01 (0.01)	0.02 (0.01)	0.02 (0.01)	0.01 (0.01)	-					
Community violence	12	-	-	**0.11 (0.01)**	**0.14 (0.01)**	0.02 (0.01)	**0.05 (0.01)**	**0.07 (0.01)**	**0.15 (0.01)**	**0.08 (0.01)**	**0.05 (0.01)**	**0.14 (0.01)**	-				
Family SES	13	-	-	**-0.10 (0.01)**	**-0.11 (0.01)**	**-0.09 (0.01)**	**-0.08 (0.01)**	**-0.05 (0.01)**	**-0.21 (0.01)**	**-0.07 (0.01)**	**-0.23 (0.01)**	-0.01 (0.01)	**-0.14 (0.01)**	-			
Neighborhood Wave 1	14	-	-	0.01 (0.11)	**0.04 (0.08)**	**0.07 (0.05)**	**0.06 (0.05)**	0.02 (0.08)	**0.10 (0.08)**	0.01 (0.08)	**0.12 (0.06)**	-0.01 (0.04)	**0.07 (0.05)**	**-0.37 (0.29)**	-		
Occupational Prestige	15	-	-	-	-	-	-	-	-	-	-	-	-	**0.21 (0.86)**	-	-	
Neighborhood Wave 4	16	-	-	-	-	-	-	-	-	-	-	-	-	-	**0.30 (1.71)**	**-0.12 (5.49)**	-
Standardized betas and standard errors for covariances in the multivariate model Bolded coefficients are significant at least at the p<0.05 level																	

CHAPTER 4

HOW DIAGNOSIS TIMING OF MAJOR DEPRESSIVE DISORDER AFFECTS THE ASSOCIATIONS BETWEEN EARLY CHILDHOOD MALTREATMENT, INFLAMMATION, AND DEPRESSIVE SYMPTOMS

Introduction

Experiences of childhood maltreatment are a well-documented risk factor for the occurrence of major depressive disorder (MDD) in adulthood. Current evidence suggests that 46% of those who experience MDD report a history of childhood maltreatment and that a 10-25% reduction in childhood maltreatment could prevent millions of cases of MDD across the globe (Li et al., 2016; Lippard & Nemeroff, 2019). Regrettably, experiences of childhood maltreatment also indicate an overall worse course of illness marked by a greater number of depressive symptoms, increased risk for death by suicide, and a greater chance for treatment resistance to current front-line treatments (Medeiros et al., 2020; Nanni et al., 2012; Williams et al., 2016). Additionally, individuals with the dual experiences of childhood maltreatment and adulthood MDD are at a greater risk for several physical health conditions including heart disease, diabetes mellitus, stroke, and several forms of cancer (Chen et al., 2023; Gold et al., 2020; Hovdestad et al., 2020; Wen et al., 2024). Concerningly, documented rates of childhood maltreatment are among the highest in the world in North America, and the U.S. population has the highest incidence rate of MDD among all high-income nations (Moody et al., 2018).

When considering different aspects of childhood maltreatment and their different effects on MDD, the onset timing of childhood maltreatment has received increasing attention. Meta-

analytic results from 58 studies identified that childhood maltreatment exposure timing had different degrees of association with MDD, and that exposure to childhood maltreatment between the ages of 6-13 had a stronger association than ages 14-19 (Li et al., 2022). Critically, earlier onset of childhood maltreatment has been associated with lower response rates to antidepressant treatment and a lower likelihood to achieve remission in adults who experience MDD (Williams et al., 2016). One potential reason for this increased risk is that earlier exposure to childhood maltreatment is also associated with a more chronic course of childhood maltreatment, and therefore an earlier onset may partially be related to an increased risk through greater exposure (Cowell et al., 2015). Further, an earlier onset of childhood maltreatment that is chronic in nature could span multiple developmental windows, which has also been found to increase the risk for developing MDD (Russotti et al., 2021).

One explanation for the association between childhood maltreatment and MDD is an increase in inflammatory signaling that targets key areas of the brain associated with depressive symptoms. Social Safety Theory (SST) provides a framework for this pathway, based around three key tenets: 1) humans have evolved to foster socially supportive and friendly bonds (social safety), 2) experiences of social safety are beneficial to health, behavioral outcomes, and longevity, and 3) experiences of social threats are harmful to health, behavioral outcomes, and mortality (Slavich et al., 2023). The experience of socially safe and socially threatening situations influences cognitive schemas that have reciprocal effects with perceptions of social situations. Through these mechanisms, early life experiences of social safety and social threats calibrate stress detection and responsivity (Slavich, 2021). Thus, individuals who experience childhood maltreatment may have more frequent activation of the body's stress response than unaffected peers, leading to downstream increases in inflammatory signaling (Slavich & Irwin,

2014). Further, the repeated activations of the stress response are associated with a greater release of inflammatory molecules via epigenetic changes within immune cells (Slavich & Cole, 2013). This progressive increase in inflammatory signaling can target key areas of the brain associated with MDD, increasing the risk of experiencing depressive symptoms and subsequent episodes of MDD (Slavich & Irwin, 2014). Notably, the associations between increased inflammation and MDD are thought to be bi-sustaining, with inflammatory signaling increasing depressive symptoms and depressive symptoms leading to cognitive patterns and health behaviors associated with increased inflammation (Messay et al., 2012).

The focus of SST on how social situations affect downstream inflammatory signaling that helps explain the association between childhood maltreatment and MDD also yields insights into gendered differences in MDD. For decades, females have reported around twice the incidence of MDD as males, starting at the onset of puberty (Nolen-Hoeksema, 1987; Nolen-Hoeksema & Girgus, 1994). Given onset timing, one potential mechanism for this gendered difference in incidence may be the role of sex-hormones. Immune cells which release inflammatory molecules associated with the stress response have sex hormone receptors and the effects of those hormones can have complex effects on inflammatory signaling. For instance, Progestin may increase IL-6 levels, a key pro-inflammatory cytokine implicated in depressive symptoms, although progestin and androgen may be associated with lower tumor-necrosis factor signaling, which is a key mediator of the blood brain barrier that allows IL-6 to target the brain (Klein & Flanagan, 2016). Further, males and females tend to report differences in their experiences of childhood maltreatment and different types of childhood maltreatment have different effects on MDD, suggesting differences in inflammatory impact. Emotional abuse specifically is the most common form of childhood maltreatment and is associated with earlier onset of MDD in both

males and females (Dong et al., 2024). However, women may be more likely to experience multiple types of abuse, and common measures of childhood maltreatment such as the Childhood Trauma Questionnaire have shown a linear relationship between multiple types of abuse and depressive symptoms (Humphreys et al., 2020). When considering that different types of childhood maltreatment increase inflammatory markers differently, poly-victimization associated with childhood maltreatment may result in consequently different health outcomes between males and females (Baumeister et al., 2016). Further, when faced with mental health problems related to childhood maltreatment, adolescent girls have may be more likely to seek care from a friend group while adolescent boys may be more likely to seek care from health professionals. However, an important caveat from this work is that adolescent boys tend to seek out care from health professionals only when faced with more severe mental health problems such as suicidal ideations. Thus, several biological and psychosocial factors may coalesce to affect inflammation and depressive symptoms in adulthood within the context of a history childhood maltreatment.

The Present Study

Social Safety Theory proposes that experiences of social threats early in life calibrate the body's stress response, influencing downstream physiological systems such as the immune systems and inflammatory response that help explain an increased association with MDD. The early diagnosis of MDD could provide important inroads for establishing social safety, potentially reducing the longitudinal impact on inflammatory signaling. Additionally, the effective early treatment of MDD could reduce the effects of depressive symptoms on inflammatory health via a reduction in cognitive symptoms and behaviors that drive increases in inflammatory signaling. Unfortunately, no known studies have investigated how the early identification of MDD could be related to changes in the associations between early childhood

maltreatment, inflammation, and depressive symptoms. Thus, the objective of the present study was to understand how diagnosis timing is related to associations between early childhood maltreatment, inflammation, and depressive symptoms and whether any gendered differences exist among these associations.

Method

Data Source and Sample

The present study utilized data from the National Survey of Adolescent to Adult Health (Add Health). The Add Health survey is a panel study which originally sampled 90,118 U.S. adolescents in a school-based survey and followed up with 20,745 of those students for an expanded in-home survey. Since the initial survey, four subsequent waves of data have been collected from the sample. The present study utilizes data from the Wave 1 in home survey including the Wave 1 parent survey (1994-1995, as well as data from Wave 3 (2001-2002), Wave 4 (2008-2009), and Wave 5 (2016-2018). The present study draws data only from the participants that also participated in the biomarker subproject of Wave 5, leaving a potential data frame of 1,932 participants.

Among these 1,932 participants, 269 participants were removed due to alcohol consumption that could affect CRP levels. Subsequently, an additional 158 participants were removed due to having CRP levels greater than 10 mg/L and reporting at least one symptom of an active infection at the time of venous blood collection. These symptoms included flu symptoms, fever, night sweats, diarrhea, nausea, vomiting, bloody stool, polyuria, or skin rash. This allowed for the retention of participants with CRP levels greater than 10mg/L which may be associated with greater depressive symptoms (Moriarity et al., 2021). The final analytic sample for this study was N = 1,505.

Measures

Early Childhood Maltreatment was assessed via self-report and included as an index of five types of childhood maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Emotional abuse was assessed at Wave 4 by asking "before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?" Participants that reported one or more experience of emotional abuse were then asked, "how old were you the first time this happened?" The occurrence of early sexual abuse was coded as occurring (1) if the participant reported this occurring before 12 years of age. Physical abuse was assessed at Wave 4 by asking "Before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or down the stairs?" Participants that reported one or more experience of physical abuse were then asked, "how old were you the first time this happened?" The occurrence of early physical abuse was coded as occurring (1) if the participant reported this occurring before 12 years of age. Sexual abuse was assessed at Wave 4 by asking "How often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?" Participants that reported one more experience of sexual abuse were then asked, "How old were you the first time this happened?" The occurrence of early sexual abuse was coded as occurring (1) if the participant reported this occurring before 12 years of age. Physical neglect was assessed at Wave 3 by asking "by the time you started the 6th grade, how often had your parents or other adult caregivers not taken care of your basic needs, such as keeping you clean or providing food or clothing?" Participants who affirmed any instance of physical neglect were coded as occurring (1). Emotional neglect was assessed using the parental warmth questions at Wave 1 and

emotional neglect frequency question at Wave 3. Parental warmth was assessed with three prompts: 1) “most of the time, your mother/father is warm and loving toward you;” 2) “you are satisfied with the way your mother/father and you communicate with each other;” 3) “overall, you are satisfied with your relationship with your mother/father.” For each prompt, participants responded via Likert scale ranging from 1= strongly agree to 5=strongly disagree. To prevent bias against single parent households, scores were averaged at the individual item level and then summed, with greater scores indicating lower parental emotional warmth. Consistent with prior iterations of this measure, a sum score of 8 or more indicated low parental warmth (Brumley et al., 2017). Emotional neglect frequency was assessed at Wave 3 by asking, “by the time you started 6th grade, how often had your parents or other adult caregivers left you home alone when an adult should have been with you?” Participants who qualified as low-parental emotional warmth and affirmed at least one instance of emotional neglect were coded as emotional neglect occurring (1). The occurrence of childhood maltreatment events was indexed to create a potential range of 0-5, with greater values indicating experiencing a greater number of early childhood maltreatment type exposure.

Major depression diagnosis was assessed via participant self-report at wave 5. Participants were first asked, “has a doctor, nurse, or other health care provider ever told you that you have or had depression?” Participants that affirmed a health care provider told them they had depression were then asked, “how old were you when you were diagnosed by a doctor, nurse, or other health care provider with depression?” Ages of reported first diagnosis ranged from age 11 to age 41. Ages were collapsed into no history of diagnosis (0), early diagnosis (ages 11-18, 1), and adult diagnosis (ages 19-41, 1).

Body mass index (BMI) was assessed at Wave 5. The typical formulation was for BMI was used: weight in kilograms divided by squared height in meters. Both participant height and weight were obtained during the in-home interview portion of the survey by a trained Add Health Interviewer. Height was measured to the nearest 0.05cm while the participants were standing upright with their head, shoulders, buttocks, and heels flat against the wall. Weight was measured to the nearest 0.1kg by a digital scale with the participant standing unassisted.

C-reactive protein was assessed at Wave 5. Samples were derived from plasma, collected as venous blood via venipuncture by a phlebotomist as the final stage of the in-home visit. Samples were stored in collection tubes and chilled at 4◦ C for up to 2 hours before being processed into serum and plasma via centrifuging. Samples were then shipped overnight to the University of Vermont where serum samples were assayed via CRP-specific particle enhanced immunonephelometric assay via Siemens BNII/BN Prospec System (Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany). Sensitivity for Wave 5 CRP assay methods was dependent on the lower limit of the reference curve related, determined by the concentration of the protein in the N Rheumatology Standard SL (Whitsel et al., 2022).

Depressive symptoms were assessed at Wave 5 using a 5-item version of the Center for Epidemiological Studies-Depression scale. These items mainly consisted of four affective symptoms “could not shake off the blues,” “felt depressed,” “you were happy,” and “felt sad,” as well as one symptom added to the measure by the add health team: “you felt life was not worth living.” For each symptom participants were asked to rate their experience as either 0 “rarely or none of the time (less than 1 day),” 1 “some or a little of the time (1-2 days),” 2 “occasionally or a moderate amount of the time (3-4 days),” or 3 “most or all of the time (5-7 days).” Items were summed to create a potential score range of 0-15, with higher scores indicating a greater

experience of past-week depressive symptoms. Cronbach's alpha calculated based on the analytic sample for the present study was 0.83, indicating good internal consistency.

Sex was included categorically as female (1), or male (0) based on participant self-report.

Control variables included alcohol use, tobacco cigarette smoking status, indicators of a chronic medical condition, current antidepressant use, current anti-inflammatory use, current exogenous sex-hormone use. Alcohol use at Wave 5 was included continuously based on participant self-report of the usual number of alcoholic drinks per day over the course of the past 30 days. Tobacco cigarette smoking status at Wave 5 was included categorically as currently smokes tobacco cigarettes (1) or no current tobacco cigarette smoking (0). The presence of a physical health problem was included categorically as the presence (1) or absence (0) of heart disease, high blood cholesterol, high triglycerides, high lipids, or evidence of current diabetes. Evidence of current diabetes was assessed via HbA1c scores greater than 6.5 %, fasting blood glucose levels greater than or equal to 200mg/dL, or current antidiabetic medication use). Antidepressant use at Wave 5 was included categorically as current use (1) or no current use (0) if the participant reported the recent use of SSRI, tricyclic, phenylpiperazine, tetracyclic, SSNRI, or another miscellaneous antidepressant. Anti-inflammatory use at Wave 5 was included categorically as current use (1) or no current use (0) if the participant reported the recent use of NSAID and salicylates, cox-2 inhibitors, inhaled corticosteroid, corticotropin/ glucocorticoid, antirheumatic/antipsoriatic, or immunosuppressives. Exogenous sex hormone use at Wave 5 was included categorically as current use (1) or no current use (0) if the participant reported recent use of oral contraceptives, androgens and anabolic steroids, estrogens, gonadotropins, progestins, sex hormone combinations, or other miscellaneous sex hormones.

Sociodemographic variables included age, sex, race, ethnicity, family socioeconomic status, and neighborhood socioeconomic disadvantage. All sociodemographic variables were measured at Wave 1. Age was included as a continuous variable with a potential range of 12-21 years. Racial/ethnic identity was included categorically as non-Hispanic White (0), non-Hispanic Black (1), Hispanic only (1), other racial/ethnic identity including multi-racial/ethnic identities (1). Family socioeconomic status was approximated via Social Origins score, pre-calculated by the Add Health Team (Belsky et al., 2018). Social Origins scores were derived via principal components analysis of parental education, parental occupation, household income, and household receipt of public assistance, before then being z-transformed. Neighborhood socioeconomic disadvantage was also precalculated by the Add Health team. Scores were based on the proportion of five items: female-headed households, individuals living below the poverty threshold, individuals receiving public assistance, adults with less than a high school education, and adults who were unemployed within the participant's census tract. Each item was scored and then summed on a scale of 1-10, resulting in a potential range of 5-50 (Belsky et al., 2019).

Analytic Strategy

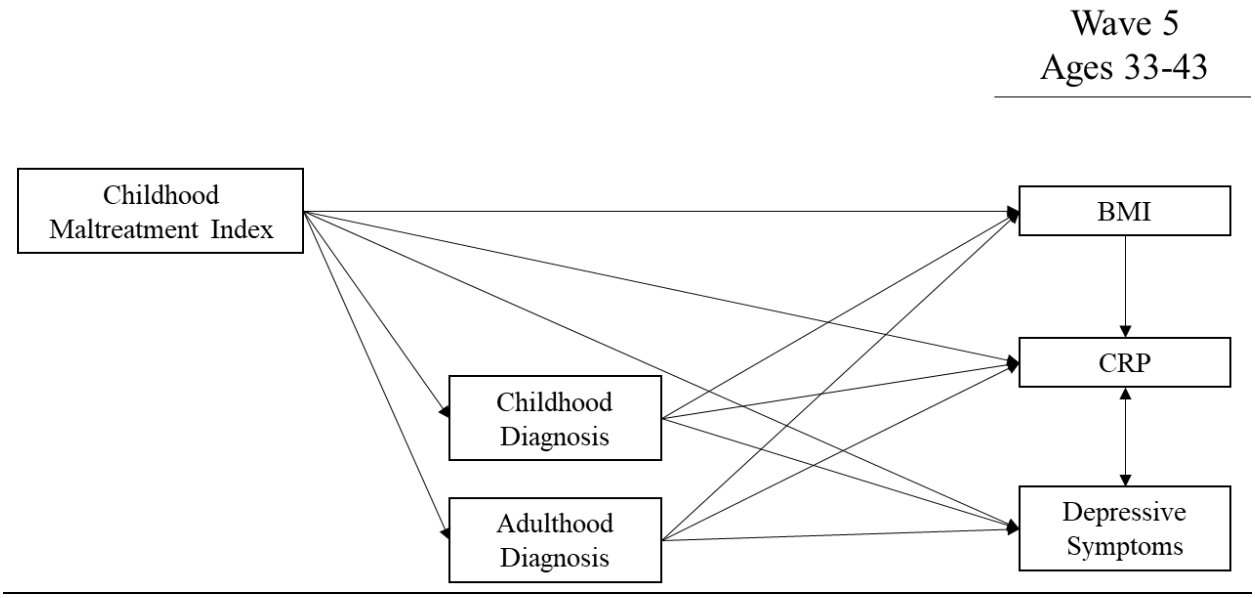
A longitudinal path modeling approach was used to assess the associations between early childhood maltreatment, diagnosis timing of major depression, inflammation, and depressive symptoms. Depressive symptoms at Wave 5 and CRP levels at Wave 5 were both predicted by MDD diagnosis timing and index of early childhood maltreatment. MDD diagnosis was predicted by the index of early childhood maltreatment. Based on theoretical support that CRP and depressive symptoms co-vary, their association was included as a covariance. Additionally, based on evidence that BMI may be a pathway that drives increasing inflammatory levels but weakens the association between CRP and depressive symptoms when included as a covariate,

BMI at Wave 5 was included only as predicting CRP levels at Wave 5 (Moriarity et al., 2023). To assess how indexed early childhood maltreatment events and MDD diagnosis timing may affect this pathway, each of these variables was modeled as predicting BMI at Wave 5. All control variables were modeled as predicting BMI, CRP, and depressive symptoms at Wave 5. All sociodemographic variables were modeled as predicting BMI at Wave 5, CRP at Wave 5, depressive symptoms at Wave 5, MDD diagnosis timing, and early childhood maltreatment. Figure 4.1 provides a visual depiction of the tested model.

Of the 1,505 participants, 78.93% had complete data for all relevant study variables. A missing values analysis showed that the missing data was not missing at random and therefore, multiple imputation via chained equations was utilized to reduce potential bias in the model. All main study variables were included in the imputation model, as well as depressive symptoms at Wave 4, CRP levels at Wave 4, BMI at Wave 4, Self-rated health at Waves 4 and 5, and waist circumference at Wave 4 as auxiliary variables. Per the recommendations of He (2022), the complex sampling design units were included in the imputation model, with the region and primary sampling units being included as factors.

All analyses were conducted in R version 4.4.0 (R Core Team, 2021). Multiple imputation via chained equations was conducted using the MICE package (van Buuren & Groothuis-Oudshoorn, 2011). Complex survey design elements were incorporated via the survey package recommended by Lumley et al. (2004) and passed to the lavaan package for path modeling (Roseel, 2012) via mi.tools package (Lumley, 2006). The lavaan.survey (Oberski, 2014) was used to account for the complex survey design elements based on the recommendations of the Add Health team (Chen & Harris, 2020).

Figure 4.1: Tested Model



Covariates omitted for visual clarity

Results

Sample Description

The sample was primarily non-Hispanic White (74.38%) and female (71.76%). The overall sample had relatively low depressive symptoms (*M*=2.42, *SE*=0.11), with a maximum potential score of 15. C-reactive protein levels had a mean 3.73 (*SE*=0.40), which is above the typical 3m/dL cutoff used as an indicator of increased risk for heart disease. However, median CRP levels were 2.04, indicating a significant positive skew in CRP levels. The mean reported early childhood maltreatment index was 0.91 (*SE*=0.04), indicating that a little over half of the participants did not experience any early childhood maltreatment. Although, 31.44% of the sample reported at least one early experience of childhood maltreatment and 25.53% experienced two or more early experiences of childhood maltreatment. A complete report of sample descriptive statistics can be reviewed in Table 4.1.

Table 4.1: Sample Descriptive Statistics

	M(*SE*) or %
Substantive Variables	
Depressive Symptoms	2.42 (0.11)
C-reactive protein	3.73 (0.18)
BMI	30.62 (0.40)
Depression Diagnosis: None	62.36%
Depression Diagnosis: Early	9.20%
Depression Diagnosis: Adulthood	27.36%
Childhood Maltreatment Index	0.91 (0.04)
Controls	
Antidepressant use	17.86%
Anti-inflammatory use	36.22%
Exogenous sex hormone use	10.98%
Recent Alcohol use	1.20 (0.03)
Current tobacco cigarette smoking	16.34%
Ongoing health problem	26.89%
Sociodemographics	
Non-Hispanic White	74.38%
Non-Hispanic Black	10.83%
Hispanic only	6.28%
Other racial/ethnic identity	8.50%
Female	71.76%
Age	15.87 (0.12)
Family Socioeconomic	0.26 (0.07)
Neighborhood	23.68 (0.95)

All statistics reported based on the application of survey design, but not imputation

Multivariate analysis

Model fit indices for the multivariate model based on the total sample indicated mixed results. The standardized root mean square residual identified excellent fit (0.02) and the root mean square error of approximation began to approach acceptable fit (0.8, 95% CI:[0.07-0.09]). However, the Comparative fit indices (0.83), Tucker Lewis Index (0.16), and model chi-square (245.77, df=19, p<0.001) did not indicate ideal fit. The ratio of the tested model chi-square

divided by degrees of freedom (12.93) relative to the baseline model (15.35) did indicate superior relative fit for the tested model.

Results from the total sample model identified that early childhood maltreatment was positively associated with an early diagnosis of MDD (β=0.11, *SE*=0.01, $p<0.001$), an adulthood diagnosis of MDD (β=0.14, *SE*=0.01, $p<0.001$), depressive symptoms at Wave 5 (β=0.12, *SE*=0.21, $p<0.001$), and BMI at Wave 5 (β=0.05, *SE*=0.21, $p<0.05$). An early diagnosis of MDD (β=0.29, *SE*=0.21, $p<0.001$) and an adulthood diagnosis of MDD (β=0.29, *SE*=0.13, $p<0.001$) were both positively associated with depressive symptoms at Wave 5. Wave 5 BMI was positively associated with CRP at Wave5 (β=0.32, *SE*=0.01, $p<0.001$). No positive covariance was identified between CRP at Wave 5 and depressive symptoms at Wave 5 ($p=0.96$). A full report of model coefficients can be reviewed in Table 4.2.

Table 4.2: Total Sample Multivariate Model

	Depressive Symptoms	CRP	BMI	Diagnosed Early	Diagnosed Adulthood	Childhood Maltreatment Index
Depressive symptoms	-	-	-	-	-	-
CRP	-	-	-	-	-	-
BMI	-	0.32 (0.01)***	-	-	-	-
Diagnosed Early	0.29 (0.21)***	-0.03 (0.47)	0.01 (0.74)	-	-	-
Diagnosed Adulthood	0.29 (0.13)***	0.04 (0.31)	0.04 (0.48)	-	-	-
Childhood Maltreatment Index	0.12 (0.06)***	-0.01 (0.13)	0.05 (0.21)	0.14 (0.01)***	0.11 (0.01)***	-
Antidepressant use	0.05 (0.15)*	-0.01 (0.35)	0.04 (0.54)	-	-	-
Anti-inflammatory use	0.08 (0.12)***	0.01 (0.28)	0.02 (0.43)	-	-	-
Exogenous sex hormone use	-0.03 (0.19)	0.12 (0.43)	0.01 (0.67)	-	-	-
Recent Alcohol use	-0.02 (0.05)	-0.01 (0.12)	-0.06 (0.19)**	-	-	-
Current tobacco cigarette smoking	0.05 (0.16)*	0.02 (0.37)	-0.10 (0.57)***	-	-	-
Ongoing health problem	0.01 (0.13)	-0.01 (0.31)	0.14 (0.48)***	-	-	-
Non-Hispanic Black	-0.01 (0.22)	-0.01 (0.49)	0.02 (0.77)	-0.10 (0.02)***	-0.12 (0.04)***	-0.01 (0.09)
Hispanic only	0.09 (0.25)***	0.03 (0.57)	0.01 (0.89)	-0.07 (0.03)**	-0.04 (0.04)	0.03 (0.10)
Other racial/ethnic identity	0.04 (0.21)*	-0.03 (0.48)	0.01 (0.75)	-0.04 (0.02)	-0.01 (0.04)	-0.01 (0.09)
Female	-0.04 (0.13)	0.11 (0.30)***	-0.03 (0.47)	0.04 (0.01)	0.01 (0.02)	0.02 (0.01)
Age	0.02 (0.03)	0.01 (0.07)	-0.03 (0.11)	-0.04 (0.01)	0.03 (0.01)	0.04 (0.01)
Family Socioeconomic	-0.04 (0.05)	0.01 (0.11)	-0.17 (0.18)***	-0.01 (0.01)	0.07 (0.01)**	-0.13 (0.02)***
Neighborhood	0.05 (0.01)*	0.03 (0.01)	0.08 (0.02)**	0.04 (0.01)	0.15 (0.01)***	0.03 (0.01)

Coefficients reported as standardized betas (standard errors)
*p<0.05, **p<0.01, ***p<0.001

Mean and proportion comparisons across men and women

When considering differences across sex-disaggregated samples, self-identified men and women were similar on most measures, including MDD diagnosis timing (p=0.30), depressive symptoms at Wave 5 (p=0.34), and BMI at Wave 5 (p=0.52). Despite this, women (M= 4.19, SE= 0.22) had greater mean CRP levels than men (M= 2.58, SE= 0.21), $t(124)=5.29$, $p<0.001$; while men (11.12%) were more likely to have an ongoing health problem than women (5.54%), $F(1,125)= 7.71$, $p<0.01$. A complete report of sex-disaggregated descriptive statistics and comparisons can be reviewed in Table 4.3.

Table 4.3: Mean and Proportion Comparisons Across Self-Identified Men and Women

	Female Mean (*SE*) or %	Male Mean (*SE*) or %	Test statistic
Substantive Variables			
Depressive Symptoms	2.35 (0.12)	2.60 (0.24)	-0.94
C-reactive protein	4.19 (0.22)	2.58 (0.21)	5.29***
BMI	30.46 (0.45)	31.04 (0.81)	-0.633
Depression Diagnosis: None	44.20%	18.90%	1.20
Depression Diagnosis: Early	7.34%	1.96%	1.20
Depression Diagnosis: Adulthood	20.08%	7.58%	
Childhood Maltreatment Index	0.91 (0.04)	0.88 (0.10)	0.25
Controls			
Antidepressant use	13.68%	4.17%	1.85
Anti-inflammatory use	10.39%	25.82%	0.04
Exogenous sex hormone use	10.59%	0.51	36.44***
Recent Alcohol use	1.20 (0.04)	1.19 (0.08)	0.12
Current tobacco cigarette smoking	10.79%	10.95%	1.53
Ongoing health problem	5.54%	11.12%	7.71**
Sociodemographics			
Non-Hispanic White	21.00%	53.38%	0.77
Non-Hispanic Black	2.42%	8.40%	
Hispanic only	2.31%	3.96%	
Other racial/ethnic identity	2.54%	5.95%	
Age	15.75 (0.13)	16.19 (0.19)	-2.44
Family Socioeconomic	0.25 (0.08)	0.29 (0.11)	-0.38
Neighborhood	23.84 (1.05)	23.26 (1.07)	0.55

Mean comparisons tested via t-test
Proportion comparisons are tested via adjusted Wald F test
*$p<0.05$, **$p<0.01$, ***$p<0.001$

Sex-disaggregated multivariate models

Model fit indices for sex-disaggregated multivariate models indicated similar results in terms of model fit. The standardized root mean square residual continued to indicate excellent fit (0.03), although root mean square error of approximation worsened (0.09, 95% CI: [0.08-0.10]). Comparative Fit Index (0.84), Tucker Lewis Index (0.21), and model chi-square (female: 181.42, *df*=32; male: 69.60, *df*=32) showed slight improvement but did not cross the threshold to indicate strong model fit.

Results from sex-disaggregated models identified several significant differences from the total model. The female model did not identify a significant association between early childhood maltreatment and BMI at Wave 5 (p=0.64); however, this association was still present in the male model (β=0.13, *SE*=0.42, p<0.01). In the female model, childhood maltreatment was positively associated with an early diagnosis of MDD (β=0.12, *SE*=0.01, p<0.01), but an early diagnosis was associated with a decrease in CRP at Wave 5 (β= -0.05, *SE*=0.55, p<0.05). Childhood maltreatment was also associated with an increased risk for an adulthood diagnosis of MDD (β=0.14, *SE*=0.01, p<0.001), and an adulthood diagnosis of MDD was positively associated with BMI at Wave 5 (β=0.11, *SE*=0.53, p<0.001) for the female model. Interestingly, childhood maltreatment was also associated with an increased risk for adulthood diagnosis of MDD (β=0.14, *SE*=0.02, p<0.01) for the male model, but not for an early diagnosis of MDD (p=0.21). However, an early diagnosis of MDD (β= -0.10, *SE*=1.72, p<0.05) and an adulthood diagnosis of MDD (β= -0.11, *SE*=1.01, p<0.05) were both associated with a decrease in BMI at Wave 5 in the male model. In both models, a positive association was still noted between BMI at Wave 5 and CRP at Wave 5 (Female: β=0.36, *SE*=0.02, p<0.001; Male: β=0.23, *SE*=0.02, p<0.001), but no covariance association was noted between CRP at Wave 5 and depressive

symptoms at Wave 5 (Female: p=0.92; Male: p=0.64). A complete report of the female multivariate model results can be reviewed in Table 4.4 and complete report of the male multivariate model results can be reviewed in Table 4.5.

Table 4.4: Female Sample Multivariate Model

	Depressive Symptoms	CRP	BMI	Diagnosed Early	Diagnosed Adulthood	Childhood Maltreatment Index
Depressive symptoms	-			-	-	-
CRP	-	-		-	-	-
BMI	-	0.36 (0.02)***	-	-	-	-
Diagnosed Early	0.33 (0.22)***	-0.05 (0.55)*	0.04 (0.79)	-	-	-
Diagnosed Adulthood	0.27 (0.15)***	0.01 (0.38)	0.11 (0.53)***	-	-	-
Childhood Maltreatment Index	0.12 (0.06)***	-0.04 (0.17)	0.01 (0.24)	0.14 (0.01)***	0.12 (0.01)***	-
Antidepressant use	0.09 (0.16)***	0.01 (0.41)	0.04 (0.59)	-	-	-
Anti-inflammatory use	0.07 (0.13)**	0.01 (0.34)	0.03 (0.48)	-	-	-
Recent Alcohol use	0.02 (0.06)	0.01 (0.15)	-0.04 (0.22)	-	-	-
Current tobacco cigarette smoking	0.01 (0.18)	0.02 (0.47)	-0.10 (0.66)***	-	-	-
Ongoing health problem	-0.03 (0.16)	0.01 (0.40)	0.10 (0.56)***	-	-	-
Non-Hispanic Black	-0.01 (0.23)	-0.01 (0.59)	0.06 (0.84)*	-0.11 (0.03)***	-0.14 (0.04)***	-0.04 (0.09)
Hispanic only	-0.01 (0.29)	0.06 (0.73)*	-0.04 (1.04)	-0.08 (0.03)**	-0.01 (0.05)	0.01 (0.12)
Other racial/ethnic identity	0.02 (0.24)	-0.03 (0.59)	-0.02 (0.85)	-0.03 (0.03)	-0.02 (0.04)	0.02 (0.10)
Age	0.02 (0.03)	-0.01 (0.09)	-0.03 (0.13)	-0.04 (0.01)	-0.03 (0.13)	0.01 (0.01)
Family Socioeconomic	-0.03 (0.05)	0.02 (0.81)	-0.17 (0.20)***	-0.03 (0.01)	0.07 (0.01)*	-0.14 (0.02)***
Neighborhood	0.13 (0.01)***	0.03 (0.95)	0.15 (0.02)***	0.04 (0.01)	0.13 (0.01)***	0.10 (0.01)**

Coefficients reported as standardized betas (standard errors)
*p<0.05, **p<0.01, ***p<0.001

Table 4.5: Male Sample Multivariate Model

	Depressive Symptoms	CRP	BMI	Diagnosed Early	Diagnosed Adulthood	Childhood Maltreatment Index
Depressive symptoms	-	-	-	-	-	-
CRP	-	-		-	-	-
BMI	-	0.23 (0.02)***	-	-	-	-
Diagnosed Early	0.18 (0.49)***	0.01 (0.92)	-0.10 (1.72)*	-	-	-
Diagnosed Adulthood	0.35 (0.29)***	0.08 (0.54)	-0.11 (1.01)*	-	-	-
Childhood Maltreatment Index	0.14 (0.12)**	0.03 (0.22)	0.13 (0.42)**	0.06 (0.01)	0.14 (0.02)**	-
Antidepressant use	-0.05 (0.35)	-0.01 (0.65)	0.07 (1.23)	-	-	-
Anti-inflammatory use	0.11 (0.26)*	-0.01 (0.48)	-0.01 (0.91)	-	-	-
Recent Alcohol use	-0.12 (0.10)**	-0.06 (0.20)	-0.13 (0.37)**	-	-	-
Current tobacco cigarette smoking	0.14 (0.32)**	0.01 (0.59)	-0.07 (1.11)	-	-	-
Ongoing health problem	0.07 (0.26)	-0.02 (0.49)	0.20 (0.91)***	-	-	-
Non-Hispanic Black	-0.02 (0.49)	0.01 (0.91)	-0.09 (1.71)	-0.07 (0.05)	-0.08 (0.09)	0.08 (0.22)
Hispanic only	0.30 (0.48)***	0.01 (0.89)	0.10 (1.67)	-0.02 (0.05)	-0.11 (0.09)	0.06 (0.21)
Other racial/ethnic identity	0.12 (0.44)**	-0.01 (0.81)	0.12 (1.52)*	-0.07 (0.04)	0.05 (0.08)	-0.07 (0.20)
Age	0.04 (0.06)	0.04 (0.12)	-0.01 (0.23)	-0.04 (0.01)	0.10 (0.01)*	0.05 (0.03)
Family Socioeconomic	-0.03 (0.10)	-0.01 (0.19)	-0.12 (0.36)*	0.05 (0.01)	0.07 (0.01)	-0.10 (0.04)
Neighborhood	-0.07 (0.01)	0.02 (0.02)	-0.02 (0.04)	0.01 (0.01)	0.17 (0.01)	-0.13 (0.01)*

Coefficients reported as standardized betas (standard errors)
*p<0.05, **p<0.01, ***p<0.001

Discussion

The present study aimed to better understand how an early diagnosis of MDD may affect the associations between early childhood maltreatment, BMI, CRP, and depressive symptoms. Analyses indicate that an increase in the types of childhood maltreatment experienced prior to the age of 12 is associated with an increased risk for early diagnosis of depression, adulthood diagnosis of depression, and increased depressive symptoms. Early childhood maltreatment was not associated with CRP but was associated with an increase in BMI that may help explain the association. Exploring sex-disaggregated models highlighted several distinctions that were not otherwise observable. For females, the early diagnosis of MDD was associated with a decrease in CRP while an adulthood diagnosis was associated with an increase in BMI. For males, early childhood maltreatment was not associated with an early diagnosis of MDD, although an early diagnosis of MDD was associated with a decrease in BMI. However, early childhood maltreatment was associated with an increased risk for diagnosis of MDD in adulthood which was then associated with a decrease in BMI.

Increasing attention has been drawn to the role of adipose tissue as a central pathway between childhood maltreatment and increased inflammatory signaling. Adipose tissue, frequently proxied by BMI measurement, is composed primarily of adipocytes (fat cells), which can synthesize and release pro-inflammatory cytokines such as IL-6 (Coppack, 2001). In some instances, this logic may indicate the need to focus on interventions that reduce BMI as a method for decreasing down-stream inflammatory signaling. A review of 33 studies identified that decreased weight was associated with a decrease in CRP (Selvin et al., 2007). Further, a study of 162 sedentary men and women found that exercise without weight change did not result in a decrease in CRP, further underscoring the role of adipose tissue in inflammatory signaling

(Church et al., 2010). Although, results from a meta-analysis of 41 studies identified childhood maltreatment as a potentially modifiable risk factor for obesity in adulthood, noting no significant association between childhood maltreatment and childhood onset of obesity (Danese & Tan, 2014). Indeed, meta-analytic results of 15 longitudinal studies identified that MDD and risk for obesity were bi-directional, and thus MDD is a risk factor for the development of future obesity (Luppino et al., 2010). Findings from the present study suggest that, particularly for males, the diagnosis of MDD may be associated lower future BMI. While the early diagnosis of MDD and treatment may not be associated with the absence of depressive symptoms later in life, it may reduce the complexity of an individual's presentation and lead to healthier aging. This is of particular importance given the findings of Prak et al. (2022) who identified that once medical morbidities had been ruled out of a sample of older adults, there was no longer an association between inflammation and depressive symptoms.

The diagnosis timing of MDD for females had substantively different effects on inflammatory signaling. The finding that an early diagnosis of MDD is associated with lower CRP may indicate that treatment by mental health professionals can help prevent associated increases in inflammatory signaling that follow childhood maltreatment, with the caveat that treatment needs to be provided early. One potential explanation is that early identification of MDD may lead to the treatment of maladaptive cognitive schemas, potentially decreasing the activation of inflammatory signaling through lower perceptions of socially threatening situations (Calvete, 2014; Slavich, 2020). Conversely, the identification of early MDD may also be associated with individuals who are already likely to experience socially safe situations, and thus the experience of working with a healthcare provider when a problem such as childhood maltreatment is identified may reinforce socially safe schemas. The divergent finding that

identification of MDD in adulthood is associated with an increase in BMI that is then associated with increases in CRP could yield several interpretations. First, is that BMI tends to increase over time, and therefore a later diagnosis of MDD is more related to the fact that the sample received the diagnosis when they were older; however, this does not explain why men being diagnosed with MDD in adulthood was associated with lower BMI and age at Wave 1 was included as a covariate (Welon et al., 2002).

Another potential factor to consider is how symptom pattern differences may combine with pharmacotherapy side effects. A known side-effect of antidepressants is weight gain, particularly among SSRI's (Fava, 2000). While women and men have been found to have similar adverse drug experiences, women have been found to be more likely to seek help when experiencing a mental or physical health problem (Rushovich et al., 2023). It should be considered that female sex and a history of trauma are both associated with a greater risk for atypical depressive symptoms such as hypersomnia and weight gain (Withers et al., 2013). In the context of the present study, the finding that a diagnosis of MDD in adulthood is associated with increased BMI for women may be related to antidepressant side-effects that compound with an already elevated BMI due to depressive symptom differences.

When considering how results fit with the current literature around childhood maltreatment and depressive symptoms in adulthood, results confirm several prior findings of the field. Namely, childhood maltreatment is associated with increased depressive symptoms in adulthood and is broadly associated with an increased risk for MDD diagnosis (Li et al., 2016; Lippard & Nemeroff, 2020). Importantly, the diagnosis of MDD was not associated with a decrease in depressive symptoms regardless of when MDD was first identified. While several studies have concluded that MDD is frequently recurrent, some have argued that this may be due

to biases in statistical modeling such as issues related to healthy participants being more likely to follow up in longitudinal studies (i.e. Neyman's bias) or only the most severe individuals presenting to receive care (i.e. Berkson's bias ; Eaton et al., 2008; Neyman, 1955; Berkson, 1946). Once accounting for both forms of bias, results from the Baltimore Epidemiologic Catchment Area sample indicated that among those who experience MDD, only 15% had unremitting symptoms and 35% had more than one episode (Eaton et al., 2008). Results from the present study contrast with prior findings, attenuating the potential effects of Berkson's bias by testing the effects of diagnosis timing and identifying that diagnosis at any age was associated with an increase in depressive symptoms at Wave 5. Although this does not necessarily account for Neyman's bias, the results could be expected to be stronger in the context of only healthier participants being retained over time. An argument could be made that depressive symptoms at Wave 5 are not necessarily indicative of recurrent episodes of MDD. However, depressive symptoms in general are associated with an increased risk for a major depressive episode.

When exploring sex differences there was no association between childhood maltreatment and an early diagnosis of MDD in males despite a significant association between adulthood diagnosis and depressive symptoms at Wave 5. Two complimentary explanations may coalesce to explain these findings. First, other more relevant etiological factors may be driving the presentation to mental health professionals that then provide a diagnosis of MDD. For instance, the adverse childhood experiences literature has widely recognized that elements of family dysfunction beyond childhood maltreatment are highly relevant to mental and physical health. For instance, experiences of parental incarceration or familial death by suicide may be more proximal events to a MDD diagnosis. Second, adolescent boys are less likely to seek care when mental health problems occur and thus there may not be diagnosed with related mental

health problems until adulthood (Westwood & Pinzon, 2008). Guidance has been routinely offered for how health practitioners can effectively screen for childhood maltreatment; however, little evidence is available that can identify if there is a gendered difference in childhood maltreatment screenings for adolescents (Hornor, 2013; Teicher et al., 2022). A survey of adults identified gendered disparities in retrospective screenings for childhood maltreatment, with only one in eight women being screened for a history of childhood maltreatment relative to only one in three women. Additional research is needed to confirm if this pattern is reflected in adolescent samples.

Limitations

The present study provides several insights into how early childhood maltreatment, MDD diagnosis timing, and health are related. However, these results should be qualified by several limitations. First, while the present study does provide insights on longitudinal associations, longitudinal studies may also suffer from survivorship bias (Young et al., 2005). For instance, less healthy participants may be less likely to follow up, skewing results towards underestimating the longitudinal effects of early childhood maltreatment. Second, because the present study utilizes diagnosis timing of MDD between waves 1 and 5 the inclusion of covariates that adequately control for within group changes is difficult to assess. Future studies could build on the present study through growth curve modeling and survival analysis approaches that explore how an early diagnosis of MDD after exposure to early childhood maltreatment are associated with depressive symptom change over time. Third, only CRP was used as a marker of inflammation in the present study. While CRP is frequently used as an overall index of inflammation some evidence suggests that specific association may exist between other inflammatory molecules and depressive symptoms, and that these associations may have sex-

differences. Future studies should expand on the present study by exploring the role of other inflammatory molecules such as IL-6. Last, model fit indices for the statistical models presented here indicated poor fit on several measures. While fit indices should not replace a nuanced theoretical approach to model construction, future efforts could bolster results by using alternative modeling strategies that improve fit indices.

Conclusion

Childhood maltreatment is a major risk factor for the development of MDD. An increase in inflammatory signaling, driven partly by increased adipose tissue, has been identified as a potential pathophysiological and bi-sustaining pathway for MDD. The present study shows a diagnosis of MDD, regardless of the timing, is still associated with an increase in depressive symptoms. Although, there are gendered, time specific differences related to MDD diagnosis that could help improve inflammatory related health. Improvements in the early detection of childhood maltreatment and MDD could be a pathway for reducing the medical complexity of individuals who experience MDD and lead to overall healthier aging.

References

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Molecular Psychiatry*, *21*(5), 642-649. https://doi.org/10.1038/mp.2015.67

Berkson, J. (1946). Limitations of the application of fourfold table analysis to hospital data. *Biometrics*, *2*(3), 47-53.

Brumley, L. D., Jaffee, S. R., & Brumley, B. P. (2017). Pathways from childhood adversity to problem behaviors in young adulthood: The mediating role of adolescents' future expectations. *Journal of Youth and Adolescence, 46*(1), 1-14. https://doi.org/10.1007/s10964-016-0597-9

Calvete, E. (2014). Emotional abuse as a predictor of early maladaptive schemas in adolescents: Contributions to the development of depressive and social anxiety symptoms. *Child Abuse & Neglect*, *38*(4), 735-746. https://doi.org/https://doi.org/10.1016/j.chiabu.2013.10.014

Chen, P., & Harris, K. M. (2020). Add Health documentation: Guidelines for analyzing Add Health data. *Carolina Population Center*. https://doi.org/10.17615/C6BW8W

Chen, Y., Shan, Y., Lin, K., Wei, Y., Kim, H., Koenen, K. C., Gelaye, B., & Papatheodorou, S. I. (2023). Association between child abuse and risk of adult coronary heart disease: A systematic review and meta-Analysis. *American Journal of Preventive Medicine*, *65*(1), 143-154. https://doi.org/10.1016/j.amepre.2023.02.028

Church, T. S., Earnest, C. P., Thompson, A. M., Priest, E. L., Rodarte, R. Q., Saunders, T., Ross, R., & Blair, S. N. (2010). Exercise without weight loss does not reduce C-reactive

protein: the INFLAME study. *Medicine & Science in Sports & Exercise*, *42*(4), 708-716. https://doi.org/10.1249/MSS.0b013e3181c03a43

Coppack, S. W. (2001). Pro-inflammatory cytokines and adipose tissue. *Proceedings of the Nutrition Society*, *60*(3), 349-356. https://doi.org/10.1079/pns2001110

Cowell, R. A., Cicchetti, D., Rogosch, F. A., & Toth, S. L. (2015). Childhood maltreatment and its effect on neurocognitive functioning: Timing and chronicity matter. *Development and Psychopathology*, *27*(2), 521-533. https://doi.org/10.1017/s0954579415000139

Danese, A., & Tan, M. (2014). Childhood maltreatment and obesity: Systematic review and meta-analysis. *Molecular Psychiatry*, *19*(5), 544-554. https://doi.org/10.1038/mp.2013.54

Dong, C., Wang, Z., Jia, F., Tian, H., Zhang, Y., Liu, H., Yu, X., Wang, L., & Fu, Y. (2024). Gender differences in the association between childhood maltreatment and the onset of major depressive disorder. *Journal of Affective Disorders*, *351*, 111-119. https://doi.org/https://doi.org/10.1016/j.jad.2024.01.249

Eaton, W. W., Shao, H., Nestadt, G., Lee, B. H., Bienvenu, O. J., & Zandi, P. (2008). Population-based study of first onset and chronicity in major depressive disorder. *Archives of General Psychiatry*, *65*(5), 513-520. https://doi.org/10.1001/archpsyc.65.5.513

Lippard, E. T. C., & Nemeroff, C. B. (2020). The devastating clinical consequences of child abuse and neglect: Increased disease vulnerability and poor treatment response in mood disorders. *American Journal of Psychiatry*, *177*(1), 20-36. https://doi.org/10.1176/appi.ajp.2019.19010020

Fava, M. (2000). Weight gain and antidepressants. *Journal of Clinical Psychiatry, 61 Suppl 11*, 37-41.

Gold, S. M., Köhler-Forsberg, O., Moss-Morris, R., Mehnert, A., Miranda, J. J., Bullinger, M., Steptoe, A., Whooley, M. A., & Otte, C. (2020). Comorbid depression in medical diseases. *Nature Reviews Disease Primers*, *6*(1), 69. https://doi.org/10.1038/s41572-020-0200-2

He, Y. (2022). *Multiple imputation of missing data in practice : basic theory and analysis strategies* [Bibliographies Online Non-fiction Electronic document]. A Chapman & Hall Book, CRC Press. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=cat06564a&AN=uga.9949531239902959&site=eds-live&custid=uga1 https://galileouga.primo.exlibrisgroup.com/openurl/01GALI_UGA/01GALI_UGA:UGA?u.ignore_date_coverage=true&rft.mms_id=9949531239902959

Hornor, G. (2013). Child maltreatment: Screening and anticipatory guidance. *Journal of Pediatric Health Care*, *27*(4), 242-250. https://doi.org/https://doi.org/10.1016/j.pedhc.2013.02.001

Hovdestad, W. E., Shields, M., Shaw, A., & Tonmyr, L. (2020). Childhood maltreatment as a risk factor for cancer: Findings from a population-based survey of Canadian adults. *BMC Cancer*, *20*(1), 70. https://doi.org/10.1186/s12885-019-6481-8

Humphreys, K. L., LeMoult, J., Wear, J. G., Piersiak, H. A., Lee, A., & Gotlib, I. H. (2020). Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, *102*, 104361. https://doi.org/10.1016/j.chiabu.2020.104361

Keller, M. B., Lavori, P. W., Mueller, T. I., Endicott, J., Coryell, W., Hirschfeld, R. M. A., & Shea, T. (1992). Time to recovery, chronicity, and levels of psychopathology in major

depression: A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry, 49*(10), 809-816. https://doi.org/10.1001/archpsyc.1992.01820100053010

Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. *Nature Reviews Immunology*, *16*(10), 626-638. https://doi.org/10.1038/nri.2016.90

Li, M., D'Arcy, C., & Meng, X. (2016). Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: Systematic review, meta-analysis, and proportional attributable fractions. *Psychological Medicine*, *46*(4), 717-730. https://doi.org/10.1017/S0033291715002743

Li, M., Gao, T., Su, Y., Zhang, Y., Yang, G., D'Arcy, C., & Meng, X. (2023). The timing effect of childhood maltreatment in depression: A systematic review and meta-analysis. *Trauma, Violence, & Abuse*, *24*(4), 2560-2580. https://doi.org/10.1177/15248380221102558

Lumley, T. (2004). Analysis of complex survey samples. *Journal of Statistical Software*, *9*(8), 1 - 19. https://doi.org/10.18637/jss.v009.i08

Lumley, T. (2006). mitools: Tools for multiple imputation of missing data. *URL http://CRAN. R-project. org*.

Luning Prak, E. T., Brooks, T., Makhoul, W., Beer, J. C., Zhao, L., Girelli, T., Skarke, C., & Sheline, Y. I. (2022). No increase in inflammation in late-life major depression screened to exclude physical illness. *Translational Psychiatry*, *12*(1), 118. https://doi.org/10.1038/s41398-022-01883-4

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W. J. H., & Zitman, F. G. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry*, *67*(3), 220-229.

https://doi.org/10.1001/archgenpsychiatry.2010.2

Medeiros, G. C., Prueitt, W. L., Minhajuddin, A., Patel, S. S., Czysz, A. H., Furman, J. L., Mason, B. L., Rush, A. J., Jha, M. K., & Trivedi, M. H. (2020). Childhood maltreatment and impact on clinical features of major depression in adults. *Psychiatry Research, 293*, 113412. https://doi.org/https://doi.org/10.1016/j.psychres.2020.113412

Messay, B., Lim, A., & Marsland, A. L. (2012). Current understanding of the bi-directional relationship of major depression with inflammation. *Biology of Mood & Anxiety Disorders, 2*(1), 4. https://doi.org/10.1186/2045-5380-2-4

Moody, G., Cannings-John, R., Hood, K., Kemp, A., & Robling, M. (2018). Establishing the international prevalence of self-reported child maltreatment: A systematic review by maltreatment type and gender. *BMC Public Health*, *18*(1), 1164. https://doi.org/10.1186/s12889-018-6044-y

Moriarity, D. P., Horn, S. R., Kautz, M. M., Haslbeck, J. M. B., & Alloy, L. B. (2021). How handling extreme C-reactive protein (CRP) values and regularization influences CRP and depression criteria associations in network analyses. *Brain, Behavior, and Immunity, 91*, 393-403. https://doi.org/https://doi.org/10.1016/j.bbi.2020.10.020

Moriarity, D. P., Mengelkoch, S., & Slavich, G. M. (2023). Incorporating causal inference perspectives into psychoneuroimmunology: A simulation study highlighting concerns about controlling for adiposity in immunopsychiatry. *Brain, Behavior, and Immunity, 113*, 259-266. https://doi.org/https://doi.org/10.1016/j.bbi.2023.06.022

Neyman, J. (1955). Statistics—Servant of all science. *Science, 122*(3166), 401-406.

Nolen-Hoeksema, S. (1987). Sex differences in unipolar depression: Evidence and theory. *Psychological Bulletin*, *101*(2), 259.

Nolen-Hoeksema, S., & Girgus, J. S. (1994). The emergence of gender differences in depression during adolescence. *Psychological Bulletin, 115*(3), 424-443. https://doi.org/10.1037/0033-2909.115.3.424

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. *PLOS Medicine, 9*(11), e1001349. https://doi.org/10.1371/journal.pmed.1001349

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software, 48*(2), 1 - 36. https://doi.org/10.18637/jss.v048.i02

Rushovich, T., Gompers, A., Lockhart, J. W., Omidiran, I., Worthington, S., Richardson, S. S., & Lee, K. M. N. (2023). Adverse drug events by sex after adjusting for baseline rates of drug use. *JAMA Network Open*, *6*(8), e2329074-e2329074. https://doi.org/10.1001/jamanetworkopen.2023.29074

Russotti, J., Warmingham, J. M., Duprey, E. B., Handley, E. D., Manly, J. T., Rogosch, F. A., & Cicchetti, D. (2021). Child maltreatment and the development of psychopathology: The role of developmental timing and chronicity. *Child Abuse & Neglect, 120*, 105215. https://doi.org/https://doi.org/10.1016/j.chiabu.2021.105215

Selvin, E., Paynter, N. P., & Erlinger, T. P. (2007). The effect of weight loss on C-reactive protein: A systematic review. *Archives of Internal Medicine*, *167*(1), 31-39. https://doi.org/10.1001/archinte.167.1.31

Slavich, G. M. (2020). Social Safety Theory: A biologically based evolutionary perspective on life stress, health, and behavior. *Annual Review of Clinical Psychology, 16*(Volume 16, 2020), 265-295. https://doi.org/https://doi.org/10.1146/annurev-clinpsy-032816-045159

Slavich, G. M., & Cole, S. W. (2013). The emerging field of human social genomics. *Clinical Psychological Science*, *1*(3), 331-348. https://doi.org/10.1177/2167702613478594

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin*, *140*(3), 774-815. https://doi.org/10.1037/a0035302

Team, R. C. (2021). *R: A language and environment for statistical computing*. In R Foundation for Statistical Computing.

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry*, *27*(3), 1331-1338. https://doi.org/10.1038/s41380-021-01367-9

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry*, *169*(2), 141-151. https://doi.org/10.1176/appi.ajp.2011.11020335

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(3), 1 - 67. https://doi.org/10.18637/jss.v045.i03

Welon, Z., Szklarska, A., Bielicki, T., & Malina, R. M. (2002). Sex differences in the pattern of age-dependent increase in the BMI from 20–59 years. *American Journal of Human Biology*, *14*(6), 693-698. https://doi.org/https://doi.org/10.1002/ajhb.10079

Wen, S., Zhu, J., Han, X., Li, Y., Liu, H., Yang, H., Hou, C., Xu, S., Wang, J., Hu, Y., Qu, Y., Liu, D., Aspelund, T., Fang, F., Valdimarsdóttir, U. A., & Song, H. (2024). Childhood maltreatment and risk of endocrine diseases: an exploration of mediating pathways using

sequential mediation analysis. *BMC Medicine, 22*(1), 59. https://doi.org/10.1186/s12916-024-03271-9

Westwood, M., & Pinzon, J. (2008). Adolescent male health. *Pediatrics & Child Health, 13*(1), 31-36. https://doi.org/10.1093/pch/13.1.31

Williams, L. M., Debattista, C., Duchemin, A. M., Schatzberg, A. F., & Nemeroff, C. B. (2016). Childhood trauma predicts antidepressant response in adults with major depression: Data from the randomized international study to predict optimized treatment for depression. *Translational Psychiatry, 6*(5), e799-e799. https://doi.org/10.1038/tp.2016.61

Withers, A. C., Tarasoff, J. M., & Stewart, J. W. (2013). Is depression wtih atypical features associated with trauma history. *The Journal of Clinical Psychiatry, 74*(5), 500-506. https://doi.org/https://doi.org/10.4088/JCP.12m07870

Young, A. F., Powers, J. R., & Bell, S. L. (2006). Attrition in longitudinal studies: Who do you lose? *Australian and New Zealand Journal of Public Health, 30*(4), 353-361. https://doi.org/10.1111/j.1467-842x.2006.tb00849.x

CHAPTER 5

CONCLUSION

Childhood maltreatment is a major risk factor for the development of MDD in adulthood as well as numerous deleterious outcomes including a greater number of depressive symptoms, poorer response to treatment, and greater risk for health morbidities (Gold et al., 2020; Otte et al., 2016; Teicher et al., 2022). Thus, identifying novel treatment and prevention targets may be critical for improving the overall prognosis for a substantive portion of the those affected by MDD. The past few decades have identified that inflammatory signaling may be a key component for understanding how childhood maltreatment and MDD are related (Beurel et al., 2020). This has provided theoretical grounds for biologically plausible modeling of how childhood maltreatment is transduced into depressive symptoms through cell signaling that is mediated by the inflammatory response (Slavich & Irwin, 2014; Slavich et al., 2023). The work presented in this dissertation builds on this framework to identify novel treatment and prevention pathways for adulthood MDD following the experience of childhood maltreatment.

Summary of Findings

Each of the studies presented in this body of work utilized data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative panel study following a cohort of U.S. adolescents into their early 40s. The Add Health data set collected a wide range of psychological, social, and biological measures, allowing for researchers to thoroughly explore the effects of the social environment on health using a longitudinal design.

Study 1

The first study (Chapter 2) focused on building the first statistical model to explore the longitudinal associations between childhood maltreatment, inflammation, and depressive symptoms using a nationally representative data from a U.S. sample with repeated measures. Taking advantage of the wide number of measures available in the Add Health data set, modeling efforts were able to account for how the socioeconomic conditions early in life may be related to different experiences of childhood maltreatment, and how these socioeconomic conditions and childhood maltreatment experiences then affect depressive symptoms and CRP into adulthood.

Findings from the first study provided two important insights into how we understand the associations between childhood maltreatment, inflammation, and depressive symptoms. First, while many studies include measures of socioeconomic status as control variables, the present study highlights that the socioeconomic disadvantage of the family children are born into as well as the neighborhoods they live in have important can affect the risk for experiencing childhood maltreatment and have lasting effects on mental and physical health. Second, depressive symptoms between ages 18-26 and BMI between ages 24-32 and BMI was cross-sectionally associated with CRP at each wave they were measured. Thus, results point towards the potential for early depressive symptom treatment as a method for reducing BMI and improving inflammatory health as individuals age.

Study 2

The second study (Chapter 3) aimed to expand our current understanding of how the early life social environment was associated with inflammation and depressive symptoms by expanding from a solely childhood maltreatment focus to a broader adverse childhood

experiences (ACEs) framework. Using a non-recursive path modeling approach, ten individual ACEs were entered into a model simultaneously, predicting both CRP and depressive symptoms in adulthood. This path modeling approach allowed for the modeling of covariance associations among ACEs, accounting for the interrelatedness that is frequently used as justification for indexing ACEs rather than inclusion as individual predictors. Additionally, the model was then re-run as self-identified sex-disaggregated models, allowing for a comparison of how the associations between ACEs, CRP, and depressive symptoms differ between men and women.

Results from the second study identified notable differences in the effects of different individual ACEs on CRP and depressive symptoms. As has been noted in prior literature emotional abuse seemed to have the strongest effect on depressive symptoms, followed by sexual abuse, emotional neglect, and suicide exposure. However, experiences of physical neglect were associated with lower depressive symptoms in adulthood, pointing towards a potential effect in which physical neglect may be associated with greater early depressive symptoms that decrease over time. Interestingly, ACEs showed similar mixed associations with CRP, with experiences of emotional abuse being associated with lower adulthood CRP and parental incarceration being associated with higher parental incarceration. Interestingly, models differed significantly when disaggregated by sex. While emotional abuse emerged as a significant predictor of depressive symptoms in adulthood for both men and women, exposure to suicide was the strongest predictor of depressive symptoms across all models and was only significant for men. Also of note, experiences of parental incarceration were associated with greater CRP in adulthood for both men and women, while experiences of sexual abuse were associated with greater CRP for men, only.

Study 3

The third study (Chapter 4) aimed to better understand how the diagnosis timing of MDD could affect the associations between early experiences of childhood maltreatment, CRP, and depressive symptoms. Using a path modeling strategy, analyses explored how indexed experiences of childhood maltreatment prior to the age of 12 was related to MDD diagnosis in early age (ages 12-18) vs adulthood (ages 19 and older), and how this timing affected CRP and depressive symptoms in adulthood. After the initial modeling process, the sample, subgroup analyses of self-identified men and women were conducted to understand how these associations may differ by gender.

Analyses presented in the third study identified that early diagnosis of MDD may be a relevant pathway for improving inflammatory health in adulthood. For women, the early diagnosis of MDD was associated with a decrease in CRP in adulthood, indicating that the early identification of MDD cases could be highly relevant for preventing many of the common physical health sequalae of childhood maltreatment that are commonly comorbid with MDD. For men, experiences of childhood maltreatment were not associated with an early diagnosis of MDD. However, childhood maltreatment was associated with an increased likelihood for an adulthood diagnosis of MDD. In both circumstances, a diagnosis of MDD was associated with decreased BMI in adulthood which points towards a similar decrease in inflammation signaling as in women although through a different pathway.

Implications for Social Work

Despite being one of the most common and disabling mental health problems in the U.S., many of the available treatment options for those who experience MDD may be ineffective for a

sizeable portion of those affected (Teicher et al., 2022). Among those who experience MDD, individuals who experience a history of childhood maltreatment have a notably poor prognosis and are less likely to achieve remission through current treatment methods (Teicher et al., 2022). Thus, the primary goal of this dissertation was to identify novel treatment and prevention targets that can attenuate the long-term effects of childhood maltreatment and improve outcomes for those who experience MDD.

Social workers are the most common social services workers in the U.S., with many social workers providing behavioral health treatment to at least 50% of their clients (Mullan Institute, 2021). Thus, despite evidence pointing towards childhood maltreatment and adulthood MDD having a poor prognosis, social workers will most likely be the main work force tasked with providing services for these clients. Optimistically, results from the work presented here indicate that focusing efforts on the early identification of MDD and subsequent treatment could be used to reduce inflammatory signaling. Indeed, results from study 3 identified that the early diagnosis of MDD in both men and women was associated with either a decrease in CRP or a decrease in BMI, which is known to influence CRP. Results from study 3 highlighted that a reduction in depressive symptoms between the ages of 18 and 26 was associated with a later reduction in BMI which was then positively associated CRP. Thus, early MDD treatment may be a method for reducing the risk for many of the overlapping physical health sequalae of childhood maltreatment that are often comorbid with MDD such as coronary artery disease and diabetes mellitus (Furman et al., 2019; Gold et al., 2020). Doing so could reduce the medical complexity of individuals who still need care for MDD as they age into middle and older adulthood, leading to an overall healthier aging process for a group at high risk for physical health morbidities.

One method by which the treatment of MDD may cause a reduction in inflammation may be through changes in cognitive processes. The SST proposes that the experiences of social threats without social safety can lead to the formation of social schemas. These schemas may lead to more frequent activation of the fight or flight response, which in turn increases downstream inflammation through the conserved transcriptional response to adversity (Slavich et al., 2023). Psychosocial treatments such as cognitive behavioral therapy may be either changing these schemas directly through the process of therapy or by providing experiences of social safety through a therapeutic relationship, thereby reducing inflammatory signaling (Shields et al., 2020). A central question then becomes can psychosocial therapies be implemented after the experiences of childhood maltreatment but prior to the development of MDD, reducing the occurrence of both MDD and common health morbidities? This approach could shift towards a preventative approach to MDD, which could make a substantive drop in MDD disability via the reduction of MDD cases that are more likely to be chronic and recurrent (Nanni et al., 2012).

Additionally, results provide support for the use of collaborative care models, particularly for those who have a history of childhood maltreatment. Collaborative care models of healthcare aim to reduce the fractionalization of health care systems by facilitating communication between health care specialists to better meet patient needs, improving health outcomes. Typically, this involves a team of healthcare specialists including mental health providers, primary care providers, and case managers. Current meta-analytic results support the use of collaborative care models in the treatment of MDD, identifying that collaborative care models are associated with increased improvement in depressive symptoms, adherence to prescribed treatment, response to treatment and treatment remission, quality of life, and life satisfaction (Thota, et al., 2012). Despite this, results from Study 1 indicate that waiting for the identification of MDD could result

in a delay to these effective collaborative care programs. For instance, experiences of physical abuse were associated with an increase in CRP, but not depressive symptoms. Thus, individuals with a history of childhood maltreatment could be at risk for the development of heart disease initially which is then associated with an increased risk for MDD (Gold et al., 2020). An alternative approach, supported by the present work, would be to screen individuals for childhood maltreatment history and then to refer them to collaborative care programs at the onset of any common sequalae of childhood maltreatment that have an inflammatory etiological component.

However, another complimentary approach to improving outcomes for those who experience MDD would be to make changes at a policy level. Results from Study 1 indicate that family level socioeconomic conditions influence depressive symptoms and CRP through a network of pathways that include direct pathways, through childhood maltreatment, and through increased in adipose tissue. Further, Study 2 highlights that experiences such as parental incarceration are associated directly with increases in CRP. Policy level changes aimed at reducing socioeconomic inequalities, such as food scarcity and the use of incarceration in the legal system could have wide ranging consequences in improving the overall health of the U.S. population. Future social work research could make strong scientific advancements through showing how policy changes in these areas may be associated with downstream inflammatory signaling.

In conclusion, the work presented through this dissertation makes substantive steps in how we understand the association between childhood maltreatment, inflammation, and MDD. These studies indicate that early identification and treatment of MDD or policy changes that prevent up-stream social environmental risk factors such as parental incarceration and

socioeconomic disadvantages could reduce MDD incidence in the U.S. Further, these approaches could also improve immune and inflammatory related health, reducing the incidence of many common physical health morbidities that often co-occur with MDD.

References

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The Bidirectional Relationship of Depression and Inflammation: Double Trouble. *Neuron*, *107*(2), 234-256. https://doi.org/https://doi.org/10.1016/j.neuron.2020.06.002

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N., & Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine*, *25*(12), 1822-1832. https://doi.org/10.1038/s41591-019-0675-0

Gold, S. M., Köhler-Forsberg, O., Moss-Morris, R., Mehnert, A., Miranda, J. J., Bullinger, M., Steptoe, A., Whooley, M. A., & Otte, C. (2020). Comorbid depression in medical diseases. *Nature Reviews Disease Primers*, *6*(1), 69. https://doi.org/10.1038/s41572-020-0200-2

Institute, M. (2021). *The provision of behavioral health services by recent master of social work (MSW) graduates*. https://www.socialworkers.org/LinkClick.aspx?fileticket=lR_DWY1jimc%3D&portalid=0

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers*, *2*(1), 16065. https://doi.org/10.1038/nrdp.2016.65

Shields, G. S., Spahr, C. M., & Slavich, G. M. (2020). Psychosocial interventions and immune system function: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*, *77*(10), 1031-1043. https://doi.org/10.1001/jamapsychiatry.2020.0431

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin, 140*(3), 774-815. https://doi.org/10.1037/a0035302

Slavich, G. M., Roos, L. G., Mengelkoch, S., Webb, C. A., Shattuck, E. C., Moriarity, D. P., & Alley, J. C. (2023). Social Safety Theory: Conceptual foundation, underlying mechanisms, and future directions. *Health Psychology Review, 17*(1), 5-59. https://doi.org/10.1080/17437199.2023.2171900

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry, 27*(3), 1331-1338. https://doi.org/10.1038/s41380-021-01367-9

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., Chapman, D. P., Abraido-Lanza, A. F., Pearson, J. L., Anderson, C. W., Gelenberg, A. J., Hennessy, K. D., Duffy, F. F., Vernon-Smiley, M. E., Nease Jr., D. E., Williams, S. P., & Community Prevention Services Task Force. (2012). Collaborative care to improve the management of depressive disorders: A community guide systematic review and meta-analysis. *American Journal of Preventative Medicine, 42*(5), 525-538. https://doi.org/10.1016/j.amepre.2012.01.019

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry, 169*(2), 141-151. https://doi.org/10.1176/appi.ajp.2011.11020335