Inflammation following childhood maltreatment is associated with executive functioning decline in older adults

Undergraduate Research Thesis

Presented in partial fulfillment of the requirements for graduation *with honors research distinction* in the undergraduate colleges of The Ohio State University.

by

Dalia Einstein

The Ohio State University

April 2024

Project Advisor: Associate Professor Jasmeet Hayes, Department of Psychology

Acknowledgements

I would first like to thank Dr. Jasmeet Hayes for her continual support and guidance throughout my time in the MINDSET Lab. Her mentorship has allowed me to develop and execute numerous independent research projects that I have since presented on the national level. I also want to express my appreciation to Dr. Bennet Givens and Dr. Marc Tassé for serving as enthusiastic members of my committee and providing their valuable knowledge to this project. I would like to acknowledge all members of the MINDSET Lab – specifically Erica Howard and Savana Jurgens – who have been invaluable mentors to me during this project, as well as additional work that has helped prepare me for a future in research. I would not have been able to execute the studies I have without their devoted help.

Finally, I would like to acknowledge funding and professional support. I have been supported through The Ohio State University Undergraduate Research Scholarship (URS) and the Undergraduate Research Apprenticeship Program (URAP). The MINDSET Lab is supported by the National Institute on Aging (NIA) of the National Institutes of Health (NIH; R01AG058822; Jasmeet P. Hayes) and The Ohio State University Discovery Themes Chronic Brain Injury Initiative (Jasmeet P. Hayes).

Abstract

Background: Childhood maltreatment has been linked to cognitive decline in adulthood, specifically within the domains of episodic memory and executive functioning; however, the intermediate pathways underlying this relationship are not well understood. Prior work suggests that systemic inflammation may be one route through which childhood maltreatment leads to later cognitive decline. The current study tested this hypothesis by investigating inflammation as an intermediate pathway by which childhood maltreatment affects episodic memory and executive functioning in adulthood.

Methods: We selected 589 participants (Mean age = 60.8 years) from the Midlife in the United States (MIDUS) Study based on available data for measures of childhood maltreatment (Childhood Trauma Questionnaire (CTQ)), pro-inflammatory biomarkers [C-reactive protein (CRP), interleukin-6 (IL-6), E-selectin, fibrinogen, intracellular adhesion molecule-1 (ICAM-1)], and episodic memory and executive functioning composite scores (Brief Test of Adult Cognition via Telephone (BTACT)). All analyses were conducted using R statistical software; specifically, Spearman's rank correlations tested associations between CTQ scores, cognition, and biomarker data across the entire cohort. These results informed follow-up mediation models that tested indirect effects of inflammation on relationships between childhood maltreatment and cognitive impairments using model 4 of the PROCESS macro.

Results: Correlations demonstrated significant associations between inflammation and overall childhood maltreatment (total CTQ composite score) as well as specific domains of childhood maltreatment (physical abuse, sexual abuse, emotional abuse, physical neglect CTQ scores; all $p < 0.05$). Inflammation was also negatively associated with executive functioning ($p = 0.004$) but not episodic memory performance ($p > 0.05$). Follow-up mediation analyses revealed significant indirect pathways linking both overall (total CTQ composite; ß = -0.0005, 95% CI [-0.0012, -0.0000]) and specific domains of childhood maltreatment (physical abuse: ß = -0.0023, 95% CI [-0.0056, -0.001]), sexual abuse: ß = -0.0018, 95% CI [-0.004, -0.001]), physical neglect: ß = -0.0023, 95% CI [-0.0056, -0.0000])) to executive functioning through inflammation.

Conclusions: Results suggests that pro-inflammatory biomarkers may help explain the link between exposure to childhood maltreatment and later executive functioning deficits in adulthood. Specific domains of childhood maltreatment may present increased risk for later executive functioning decline through inflammation.

Keywords: Childhood maltreatment, executive functioning, episodic memory, inflammation

Introduction

Childhood maltreatment has repeatedly been associated with increased risk for a wide range of negative health outcomes (McKay et al., 2020, Weleff & Potter, 2023), including cognitive decline (Matte-Landry et al., 2022). Importantly, various forms of abuse and neglect experienced in childhood can have lasting cognitive effects into adulthood, as exposure to childhood maltreatment may be a risk factor for development of later-life Alzheimer's disease and other dementias (Huang et al., 2023). As of 2020, an estimated 64% of adults reported experiencing at least one instance of maltreatment before 18 years of age (Swedo et al., 2023). Moreover, the U.S. population is aging rapidly, with the number of adults aged 65 years or older projected to nearly double by 2050 (U.S. Census Bureau, 2023). This high prevalence of childhood maltreatment exposure coupled with an aging population highlights a crucial need to understand how early life adversity may lead to later-life cognitive decline.

Inflammation may be one pathway through which childhood maltreatment leads to cognitive decline. Elevated levels of pro-inflammatory biomarkers, including interleukin-6 (IL-6) and C-reactive protein (CRP) – two common indexes of systemic inflammation – have been widely documented among adult populations exposed to childhood maltreatment (Baumeister et al., 2015). Similarly, aging is associated with increased inflammatory burden (Franceschi et al., 2000) and prior work in older adult populations has demonstrated that heightened levels of pro-inflammatory cytokines are associated with poorer cross-sectional performance and steeper decline across a range of cognitive domains (Tangestani-Fard et al., 2022; Heringa, 2014; Tegeler et al., 2016), as well as increased risk for neurodegenerative disease, including dementia (Kuo et al., 2005; Darweesh et al., 2018). Together, these suggest that chronic inflammation may be a promising mechanism linking early-life stress to adverse cognitive outcomes in late-life.

To date, few studies have investigated the effects of childhood maltreatment on cognition and aging, with extant work primarily studying global cognition. However, many of these studies examining effects of maltreatment on adult global cognition have produced null or contradictory results (Ritchie et al., 2010; Feeney et al., 2023). Few studies have investigated the effects of childhood maltreatment on specific cognitive domains classically linked to aging, such as executive functioning (EF) and episodic memory (EM) (Verhaeghen, 2011; Nyberg et al., 2012). It is well established that performance on these cognitive domains declines in adulthood, and may reflect risk for neurodegenerative disease (Silva et al., 2022; Kirova et al., 2015). Notably, EM and EF deficits have likewise been associated with inflammation. Human studies have revealed a specific, negative relationship between EM and inflammation, as only memory scores showed significant associations with heightened levels of pro-inflammatory biomarkers, even when tested amongst other domains of cognition (Krabbe et al., 2005; Reichenberg et al., 2001). Additional studies have also established an association between increased levels of pro-inflammatory cytokines and EF impairments (Tegeler et al., 2016; Heringa, 2014). Given these connections of EM and EF with both aging and inflammation, coupled with the inconclusive effects of childhood maltreatment on global cognitive aging, this study sought to investigate the impact of childhood maltreatment on specific cognitive domains (EM and EF) through an inflammatory pathway within the context of aging.

Furthermore, prior work suggests that the effects of childhood maltreatment on both inflammatory processes and cognitive functioning may vary according to the domain of maltreatment experienced (Brown et al., 2021; Matte-Landry et al., 2022). Indeed, neuroimaging studies have found domain-specific effects of maltreatment on aspects of neural integrity and function (Wang et al., 2016; Teicher & Samson, 2016; Choi et al., 2009), and certain forms of childhood abuse, but not neglect, have been differentially associated with elevated CRP levels (Fanning et al., 2015; Mitchell et al., 2018). Some studies have also used the Childhood Trauma Questionnaire (CTQ) to retroactively assesses exposure to childhood maltreatment across five domains: physical abuse, emotional abuse, sexual abuse, emotional neglect, and physical neglect (Bernstein et al., 1994). Scores from the CTQ can be operationalized as total scores, representing cumulative exposure to childhood maltreatment, or as domain-specific scores, representing exposure to specific forms of abuse and neglect. Studies have yielded differing results when measuring total CTQ scores compared to domain-specific effects on adult cognition. While Grainger and colleagues (2019) found no associations between overall CTQ scores and global cognition in adulthood, when assessing each domain independently, physical neglect was negatively correlated with cognitive outcomes. Moreover, Geoffroy and colleagues (2016) only showed associations between cognitive deficits and neglect, independent of different domains of abuse, whereas Xie et al., (2023) found an increased risk of late-life dementia with exposure to physical, emotional, and sexual abuse. Overall, these studies suggest that the CTQ may provide a feasible measure of domain-specific effects of childhood maltreatment, and the investigation of these effects on inflammation and cognition is likely to provide a more nuanced understanding of early-life risk factors that predispose for adverse cognitive outcomes in late-life.

To the best of our knowledge, only two existing studies have explored these links between childhood maltreatment, inflammatory pathways, and cognition. One study conducted by Davis and colleagues (2018) demonstrated that IL-6 levels partially accounted for the association between greater exposure to childhood maltreatment and worsened global cognition in a community sample of mid-life adults. More recently, D'Amico and colleagues (2022) examined cross-sectional relationships between childhood maltreatment severity, allostatic load, and cognition in a sample of adults aged 25-84. Allostatic load was operationalized via a binarized 20-point index which included pro-inflammatory biomarkers in addition to markers of cardiovascular, neuroendocrine, and metabolic function. Results revealed that greater severity of childhood maltreatment was associated with higher allostatic load, which in turn was associated with impaired performance on measures of global cognition and EF. While these studies provide support for the notion that systemic inflammation may be a viable pathway linking childhood maltreatment to cognitive health in adulthood, the sample demographics of both studies may limit generalizability of these findings to older adults, who are most likely to experience cognitive changes and develop neurodegenerative disease. Moreover, both studies looked only at total CTQ composite scores, without investigating the potential for domain-specific effects of these pathways. Therefore, the current study aimed to expand upon extant literature by examining inflammation as an indirect pathway linking childhood maltreatment to adverse cognitive outcomes in a large sample of older adults (>50 years). Furthermore, this study aimed to examine whether specific domains of maltreatment differentially impact these relationships. We hypothesized that increased exposure to various domains of childhood maltreatment would lead to heightened levels of inflammatory cytokines, and in turn, lead to worse performance on EM and EF tasks.

Materials and methods

Participants

Data used in this study were obtained from the Survey of Midlife in the United States (MIDUS) project. MIDUS began in 1995 as a longitudinal study aimed at examining various biopsychosocial factors that might impact health and well-being in aging adults. Additional information can be found at https://midus.wisc.edu/scopeofstudy.php. CTQ and biomarker data were obtained from the MIDUS II dataset (N = 4889), a longitudinal follow-up of the original MIDUS sample that includes additional cognitive variables and biomarker data (Cognitive and Biomarkers subprojects), collected between the years 2004 and 2006 (Ryff et al., 2021). Cognitive data were gathered from the MIDUS III dataset (N = 3294), a separate follow-up study of the original MIDUS sample collected from 2013-2014 which repeated baseline assessments to measure longitudinal cognitive outcomes (Ryff et al., 2019). Cognitive data were assessed 10 years post blood tests for pro-inflammatory biomarkers.

Procedures

Figure 1 outlines inclusion criteria used to generate our sample of 943 older adults from the MIDUS II cohort. Inclusion criteria were completion of the Childhood Trauma Questionnaire (CTQ), a blood draw, and the Brief Test of Adult Cognition via Telephone (BTACT). Participants less than 50 years of age were excluded (N = 354). Data collection was approved by the Institutional Review Board at MIDUS testing sites (University of California – Los Angeles, University of Wisconsin – Madison, George Town University) and informed consent was obtained from all participants.

Measures

Childhood Trauma Questionnaire (CTQ)

To assess for exposure to childhood maltreatment, participants completed the Childhood Trauma Questionnaire (CTQ), a 70-item self-report measure indexing the severity of five different categories of childhood maltreatment: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect (Bernstein et al., 1994). Items are scored on a 5-point Likert scale (1 = "Never true" to 5 = "Very often true"). Example items include the following: "People in my family called me things like ''stupid,' 'lazy,' or 'ugly'" (Emotional abuse); "People in my family hit me so hard that it left me with bruises or marks" (Physical abuse); "Someone tried to touch me in a sexual way, or tried to make me touch them" (Sexual abuse); "My family was a source of strength and support" (Emotional neglect); and "I knew that there was someone to take care of me and protect me" (Physical neglect). An overall maltreatment score was calculated by summing all 70 items. Domain-specific subscale scores were also obtained ranging from 5-25, representing different severity classifications (see *Table 1*). Overall, the CTQ has moderately strong internal reliability, both for the entire test ($\alpha = 0.852$; Peng et al., 2023) as well as for each of the five subscales ($\alpha = 0.491 – 0.857$; Peng et al., 2023).

<u>Brief Test of Adult Cognition via Telephone (BTACT) interview</u>

Participants were administered the Brief Test of Adult Cognition via Telephone (BTACT), a remote means of measuring cognitive performance in healthy adults (Tun & Lachman, 2006). The BTACT is comprised of five subtests measuring episodic verbal memory, working memory span, verbal fluency, inductive reasoning, processing speed, and reaction time. The BTACT has demonstrated good concurrent validity with other cognitive assessments (Lachman et al., 2013).

Factor analysis in the MIDUS dataset found evidence supporting a two-factor model of the BTACT, with underlying factors representing EF and EM domains (Lachman et al., 2021). Composite measures of EF and EM are available through MIDUS and were obtained by averaging the z-scores of included subtests. EM composite was comprised of summed scores from the Word List Immediate and Word List Delayed tasks, and EF composite was comprised of summed scores from the Digits Backward, Category Fluency, Number Series, and Backward Counting tasks. These composites have demonstrated good internal consistency (α = 0.712; Lachman et al., 2021). For additional information regarding the subtests and composite calculations, see https://midus-study.github.io/public-documentation/M2P3/Documentation/M2_P3_BTACT_DataFile_Notes_20211122.pdf.

Inflammatory Biomarkers

Consistent with prior work (Hostinar et al., 2015; Knight et al., 2021), systemic inflammation was indexed by five blood pro-inflammatory markers: CRP, IL-6, E-selectin, fibrinogen, and intracellular adhesion molecule-1 (ICAM-1). IL-6 is a pro-inflammatory cytokine that is released in response to tissue damage and infection (Tanaka et al., 2014), and CRP is an acute-phase reactant protein released in response to increased levels of IL-6 (Nehring et al., 2023). E-selectin is a molecule expressed on endothelial cells that is upregulated by other proinflammatory molecules (Timmerman et al., 2016), and fibrinogen is a glycoprotein involved in blood clotting (Kaur & Jain, 2023). ICAM-1 is another glycoprotein expressed on endothelial cells that aids in leukocyte recruitment during inflammation (Bui et al., 2020).

Serum IL-6, E-selectin, and ICAM-1 concentrations were measured via enzyme-linked immunosorbent assay (ELISA) kits, and CRP was assayed via a particle enhanced immunonephelometric assay. Immunochemical reactions determined fibrinogen levels. Specific information regarding collection and processing protocols for each biomarker can be found at https://midus-study.github.io/public-documentation/M2P4/Documentation/M2_Blood_Urine_Saliva_Data_FINAL_20220531.pdf.

Systemic inflammation was measured as a composite score of the levels of these five pro-inflammatory biomarkers. Scores of each biomarker were log-transformed to correct for nonnormality, and the composite score was generated by averaging the z-score values of CRP, IL-6, E-selectin, Fibrinogen, and ICAM-1.

Data Analysis

All analyses were conducted using R statistical software (version 4.2.3; Dalthorp, 2021) and a two-tailed test with $\alpha = 0.05$. Shapiro-Wilk tests indicated that biomarker data was normally distributed, but CTQ and BTACT scores were not ($p > 0.05$).

Analyses were conducted in a two-step process. First, Spearman's rank correlations tested associations between CTQ scores, cognitive variables, and biomarker data across the entire cohort (*Table 2*). These initial analyses informed follow-up mediation models testing the indirect effects of inflammation on relationships between childhood maltreatment and cognition. Mediations were assessed using model 4 of the PROCESS macro with bootstrapping (N = 10,000) and standardization (Hayes, 2017). For each iteration of the mediation analyses, the dependent variable represented a cognitive domain while the independent variable was a domain of maltreatment as outlined in the CTQ. The mediator for each iteration was the inflammation composite score, computed as described above.

Multiple external factors are known to influence the pathways investigated in this study, and thus were included as covariates in our mediation models. Older age is associated with both immune dysfunction (Müller et al., 2019) and cognitive deficits (Murman, 2015). Additionally, sex differences have been noted in immune function (Klein & Flanagan, 2016). Socioeconomic status (SES) is associated with childhood maltreatment, such that children from higher SES backgrounds are less likely to experience maltreatment (Assari, 2020). Moreover, SES is also negatively associated with levels of systemic inflammation (Muscatell et al., 2020). Given these extant relationships, analyses were statistically adjusted for self-reported age, sex, and SES. SES was measured using the socioeconomic index (Elliot & Chapman, 2016), which operationalizes the construct as a composite score of the participant's occupation, highest degree of education (grade school to doctoral degree), and the participant's household income.

Moreover, studies have demonstrated that individuals with a smoking history exhibit elevated levels of pro-inflammatory biomarkers (Arnson et al., 2010) and those suffering from diabetes display heightened levels of inflammation (Tsalamandris et al., 2019). Thus, these health variables were also included as covariates in the mediation analyses.

Results

Demographics and Sample Characteristics

Figure 1 provides demographic characteristics and descriptive statistics of inflammatory markers for our sample (N = 589). Correlation values between observed variables are reported in Table 2. Participants were mid-to-late life adults (*M* = 60.8 years; *SD* = 7.59; *range* = 50 – 82 years), and there was a relatively equal proportion of males and females (43% males, 57% female). SES was in the average range (*M* = 0.05; *SD* = 0.604). In regard to health variables, 12.6% of the sample reported having diabetes and 37.5% of the sample reported a history of smoking.

Correlations

Correlation values between observed variables are reported in Table 2. Positive correlations were found between the inflammation composite score and CTQ composite scores, sexual assault scores, physical abuse scores, emotional abuse scores, and physical neglect scores (all $p < 0.05$). The inflammation composite score was significantly correlated with EF (p = 0.004), but not EM performance (p = 0.233). EF scores were negatively associated with CTQ scores in sexual assault (p = 0.043) and physical neglect (p = 0.007) domains, but EF was not associated with any other domains of childhood maltreatment ($p > 0.05$). EM scores were not associated with any of the childhood maltreatment variables (all $p > 0.05$). These correlation results informed subsequent mediation analyses testing the indirect effects of composite inflammation on the relationships between the CTQ composite, sexual assault, physical abuse, emotional abuse, and physical neglect scores and EF performance.

Mediation Analyses

<u>CTQ Composite Score</u>

The path coefficients for this mediation model are presented in Figure 2. There was a significant indirect effect of total CTQ scores on EF through inflammation (ß = -0.0005, *SE* = 0.0003, 95% CI [-0.0012, -0.0000]). Higher levels of maltreatment were associated with elevated inflammatory biomarkers (A path: ß = 0.0039, *SE* = 0.0014, 95% CI [0.0012, 0.0066]), which in turn predicted worse EF performance (B path: ß = -0.1248, *SE* = 0.0584, 95% CI [-0.2394, -0.0101]). In total, the indirect effect explained 11.9% of the total variance in the relationship between total CTQ scores and EF. The direct effect of total CTQ score on EF was not significant (95% CI [-0.0075, 0.0001]).

<u>Physical Abuse</u>

The path coefficients for this mediation model are presented in Figure 3. There was a significant indirect effect of physical abuse scores on EF through inflammation (ß = -0.0023, *SE* = 0.0014, 95% CI [-0.0056, -0.001]). Higher levels of physical abuse were associated with elevated inflammatory biomarkers (A path: ß = 0.0185, *SE* = 0.0068, 95% CI [0.0051, 0.0319]), which in turn predicted worse EF performance (B path: ß = -0.1251, *SE* = 0.0583, 95% CI [-0.2396, -0.0107]). In total, the indirect effect explained 10.6% of the total variance in the relationship between physical abuse scores and EF. The direct effect of physical abuse scores on EF was also significant (95% CI [-0.1859, -0.0209]).

Sexual Abuse

The path coefficients for this mediation model are presented in Figure 4. There was a significant indirect effect of sexual assault scores on EF through inflammation (ß = -0.0018, *SE* = 0.001, 95% CI [-0.004, -0.001]). Higher levels of sexual abuse were associated with elevated inflammatory biomarkers (A path: ß = 0.0138, *SE* = 0.005, 95% CI [0.0039, 0.0236]), which in turn predicted worse EF performance (B path: ß = -0.1271, *SE* = 0.0584, 95% CI [-0.2481, -0.0124]). In total, the indirect effect explained 13.6% of the total variance in the relationship between sexual abuse scores and EF. The direct effect of sexual assault scores on EF was not significant (95% CI [-0.0254, 0.0026]).

Emotional Abuse

The path coefficients for this mediation model are presented in Figure 5. There was an insignificant indirect effect of emotional abuse scores on EF through inflammation (ß = -0.0011, *SE* = 0.0009, 95% CI [-0.003, 0.0003]). Higher levels of sexual abuse were not significantly associated with elevated inflammatory biomarkers (A path: ß = 0.0077, *SE* = 0.0048, 95% CI [-0.0017, 0.0172]), but elevated levels of inflammation did predict worse EF performance (B path: ß = -0.1363, *SE* = 0.0583, 95% CI [-0.2507, -0.0219]). In total, the indirect effect explained 31.4% of the total variance in the relationship between sexual abuse scores and EF. The direct effect of emotional abuse scores on EF was also insignificant (95% CI [-0.0158, 0.0109]).

Physical Neglect

The path coefficients for this mediation model are presented in Figure 6. There was a significant indirect effect of physical neglect scores on EF through inflammation (ß = -0.0023, *SE* = 0.0015, 95% CI [-0.0056, -0.0000]). Higher levels of physical neglect were associated with elevated inflammatory biomarkers (A path: ß = 0.0195, *SE* = 0.0069, 95% CI [0.0058, 0.0331]), which in turn predicted worse EF performance (B path: ß = -0.1159, *SE* = 0.058, 95% CI [-0.2299, -0.002]). In total, the indirect effect explained 6.8% of the total variance in the relationship between physical neglect scores and EF. The direct effect of physical neglect scores on EF was also significant (95% CI [-0.0509, -0.0125]).

Discussion

This study examined inflammation as an indirect pathway linking childhood maltreatment to later EF and EM performance in a large sample of healthy, older adults. In addition, we investigated whether specific domains of maltreatment differentially affected cognitive outcomes in late-life through inflammatory pathways. Consistent with prior research (D'Amico et al., 2022; Davis et al., 2018), we confirmed a significant, negative association between childhood maltreatment and later-life EF performance. Mediation analyses revealed a significant indirect effect of inflammation on the relationship between total CTQ scores and EF performance 10 years post-measurement of an elevated inflammatory state. These overall associations with total CTQ composite appeared to be specifically driven by sexual abuse, physical abuse, emotional abuse, and physical neglect forms of maltreatment, as these domain-specific effects on EF remained robust when disaggregating CTQ scores by type of childhood maltreatment. Despite these findings linking childhood maltreatment to EF, childhood maltreatment did not significantly affect later-life EM performance in the present study. Taken together, our findings suggest that higher levels of both general and domain-specific childhood maltreatment may lead elevated concentrations of inflammatory biomarkers, and in turn, predict worse EF skills in later adulthood.

In the present study, CTQ scores were significantly associated with inflammation. These results confirm previous research investigating the link between childhood maltreatment and pro-inflammatory biomarkers, as numerous studies have indicated a significant relationship between the two variables (Brown et al., 2021; Kerr et al., 2021). Still, other studies have shown positive associations between childhood maltreatment and levels of CRP, but only amongst patients experiencing various forms of psychopathology (Chamberlain et al., 2019; Quide et al., 2019). When assessing inflammation compositely, however, studies have shown positive predictive relationships between maltreatment experienced in childhood and inflammation in adulthood (Hostinar et al., 2015; Petrov et al., 2016). Therefore, the present study utilized a composite approach to measure pro-inflammatory biomarkers, given its superiority to individual biomarker assessment.

Our mediation results support the hypothesis that systemic inflammation may underlie the negative relationship between childhood maltreatment exposure and EF performance in late-life. Exposure to maltreatment early in life has been shown to have detrimental effects on the development of various neural pathways (Dye, 2018). Given the increased plasticity of the brain in childhood (Kolb et al., 2017), alterations to these neural pathways early in life can create permanent damage to areas involved in information processing (Briere & Scott, 2006), as well as induce systemic inflammation in adulthood (Danese & Baldwin, 2017). Maltreatment experienced in childhood may disrupt the homeostatic control of immune responses in the brain, leading to inflammation of the peripheral and central nervous systems (Nettis et al., 2019). Specifically, childhood maltreatment can lead to changes in the hypothalamic-pituitary-adrenal (HPA) axis – the main brain circuit responsible for regulating stress (Nemeroff, 2004). Indeed, children who have experienced maltreatment have been shown to have elevated daily cortisol levels, which can have sustained, negative effects on brain development (Danese & McEwen, 2012). Disrupted cortisol can create a pro-inflammatory state, and sustained levels of systemic inflammation throughout the life course may predispose those exposed to maltreatment early in life to worse cognitive outcomes at later time points. Thus, our findings suggest that these inflammatory consequences of childhood maltreatment may be the driving factor contributing to the cognitive deficits previously established in adulthood (Murman, 2015).

Based on findings from domain-specific mediation analyses, physical abuse, sexual abuse, and physical neglect scores all emerged as strong predictors of later EF through inflammation. The only maltreatment subtype that we did not find to be directly associated with inflammation was emotional neglect, which is consistent with a previous meta-analysis investigating levels of IL-6, CRP, and TNF–α on the five domains of maltreatment outlined in the CTQ (Brown et al., 2021).

When analyzing domain-specific effects of maltreatment on inflammation, our findings align with prior work from Kraynak and colleagues (2019) who found that total CTQ scores, physical abuse scores, and physical neglect scores all correlated with levels of IL-6, while emotional abuse did not. Additionally, levels of CRP and IL-6 have been shown to be positively associated with sexual abuse during adolescence (Bertone-Johnson et al., 2012). Given the strong correlations found between inflammation and physical abuse, sexual abuse, and physical neglect, it can be inferred as to why the indirect effect of these domains of maltreatment on EF through inflammation occurred. Though our results indicate a significant direct association between emotional abuse and the inflammation composite score, the finding barely reached significance ($p = 0.04$), suggesting why this domain of maltreatment did not indirectly affect post-follow-up EF scores through inflammation.

While the relationship between childhood maltreatment and EF in mid-to-late adults has been previously established (D'Amico et al., 2022), inconsistent findings remain in the literature. Prior work has revealed a link between childhood maltreatment and cognitive decline in adulthood (Ritchie et al., 2010; Feeney et al., 2023). However, an incredibly low percentage of the overall sample in these studies were exposed to abuse (6% from Feeney et al., 2023 and 26 people from Ritchie et al., 2010), and the researchers did not account for other forms of maltreatment or specific domains of cognition, weakening the overall power and significance of their findings**.** Moreover, few extant studies have investigated domain-specific effects of maltreatment on EF. Nikulina & Widom (2013) studied physical abuse, sexual abuse, and physical neglect compositely, revealing a negative association with EF in adulthood; however, when assessing each domain of maltreatment independently, only physical neglect showed associations with EF deficits. In another study comparing children exposed to physical abuse and neglect to those solely neglected found that both physical abuse and neglect yielded worse performance on tests of EF compared to just neglect (Nolin & Ethier, 2007); however, this study only investigated cognitive outcomes in children. The present study expands upon this existing research to help solidify the association between childhood maltreatment and later cognitive decline in *adulthood* while providing novel findings that physical/sexual abuse and physical neglect may specifically drive this relationship.

In contrast to our original hypothesis, EM demonstrated null associations with both childhood maltreatment and inflammation. There are many reasons as to why this result may have been observed, as prior studies investigating inflammation levels and memory outcomes have yielded mixed results. Arnold and colleagues (2002) found that individuals who were administered IL-6 performed as well on tests of EM as controls. In fact, individuals who received IL-6 treatment actually demonstrated *improved* memory performance over time as compared to controls. Other studies have also found few strong associations between inflammatory biomarkers and EM, and these relationships became null after adjusting for age and sex (Stenfors et al., 2017). Previous work examining the effects of childhood maltreatment on EM and EF have also shown significant effects of maltreatment on EF, but not EM, in similar samples to the current study (Lynch & Lachman, 2020; D'Amico et al., 2022). Therefore, our results support previous findings that neither inflammation nor exposure to maltreatment during childhood are significantly associated with episodic memory deficits. One plausible justification for these null EM, but significant EF, results is the frontal lobe hypothesis of aging which postulates that the prefrontal cortex (PFC) shows signs of decline earlier and of greater intensity than other brain regions (Moscovitch & Winocur, 1995). The PFC is a key brain area known to be involved in the performance of EF (Stuss & Benson, 1984; Yuan & Raz, 2014), and numerous behavioral and neuroimaging studies have revealed that the PFC, but not non-frontal regions, demonstrate greater age-related cognitive and structural declines (West, 2000). Thus, hippocampal-dependent tasks (i.e., EM) may not show as profound declines with aging as PFC-dependent (i.e., EF) tasks, supporting findings from the current study that age-related cognitive deficits were found for EF, but not EM.

There are several limitations that should be considered when interpreting the results of the present study. Firstly, though numerous covariates were accounted for, there are several other factors that may confound relationships examined here that were not considered in the current study, namely psychopathology. Danese and colleagues (2009) found an increased risk for the development of depression in those exposed to adverse childhood experiences. These individuals also displayed elevated levels of CRP at age 32 compared to adults without childhood maltreatment, suggesting a link between maltreatment, depression, and inflammation. Furthermore, Korten et al (2014) demonstrated that childhood maltreatment only impacts older adults' processing speed through depression .Other psychiatric disorders such as posttraumatic stress disorder (PTSD), anxiety disorder, and substance use disorder have also been shown to be associated with exposure to childhood maltreatment (McLaughlin et al., 2012). Given the extensive research relating psychopathology to elevated levels of pro-inflammatory biomarkers (Su, 2012) and cognitive impairments (Abramovitch et al., 2021), future studies should take these additional factors into account in order to provide more robust conclusions pertaining to the indirect effect of childhood maltreatment on cognition through inflammation. In addition to psychopathology confounds, there were study design flaws that may have influenced results. The only measure of EF provided by MIDUS was from the BTACT, which is a brief telephone cognitive screener that may not provide the most robust assessment of cognitive functioning. Future studies should focus on conducting more in-depth, comprehensive neuropsychological assessments to further evaluate effects of childhood maltreatment on later adult cognition.

Overall, our findings suggest that experiences of maltreatment during childhood – specifically physical abuse, sexual abuse, and physical neglect – may lead to elevated levels of systemic inflammation, in turn leading to reduced executive functioning in older age. These results shed light on how early adversity may predispose for later negative cognitive outcomes. In addition, these results suggest that cognitive health consequences of exposure to maltreatment may be better understood when considering domains of maltreatment.

References

Abramovitch, A., Short, T., & Schweiger, A. (2021). The C factor: Cognitive dysfunction as a transdiagnostic dimension in psychopathology. *Clinical Psychology Review*, *86*, 102007. https://doi.org/10.1016/j.cpr.2021.102007

Arnold, M. C., Papanicolaou, D. A., O'Grady, J. A., Lotsikas, A., Dale, J. K., Straus, S. E., & Grafman, J. (2002). Using an interleukin-6 challenge to evaluate neuropsychological performance in chronic fatigue syndrome. *Psychological Medicine*, *32*(6), 1075–1089. https://doi.org/10.1017/s0033291702006086

Arnson, Y., Shoenfeld, Y., & Amital, H. (2010). Effects of tobacco smoke on immunity, inflammation and autoimmunity. *Journal of Autoimmunity*, *34*(3). https://doi.org/10.1016/j.jaut.2009.12.003

Assari, S. (2020). Family socioeconomic status and exposure to childhood trauma: Racial differences. *Children*, *7*(6), 57. https://doi.org/10.3390/children7060057

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2015). 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

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry*, *151*(8), 1132–1136. https://doi.org/10.1176/ajp.151.8.1132

Bertone-Johnson, E. R., Whitcomb, B. W., Missmer, S. A., Karlson, E. W., & Rich-Edwards, J. W. (2012). Inflammation and early-life abuse in women. *American Journal of Preventive Medicine*, *43*(6), 611–620. https://doi.org/10.1016/j.amepre.2012.08.014

Briere, J., & Scott, C. (2006). Biology and psychopharmacology of trauma. *Principles of trauma therapy: A guide to symptoms, evaluation, and treatment*, 185-229.

Brown, M., Worrell, C., & Pariante, C. M. (2021). Inflammation and early life stress: An updated review of childhood trauma and inflammatory markers in adulthood. *Pharmacology Biochemistry and Behavior*, *211*, 173291. https://doi.org/10.1016/j.pbb.2021.173291

Bui, T. M., Wiesolek, H. L., & Sumagin, R. (2020). ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. *Journal of Leukocyte Biology*, *108*(3), 787–799. https://doi.org/10.1002/jlb.2mr0220-549r

Chamberlain, S. R., Cavanagh, J., de Boer, P., Mondelli, V., Jones, D. N. C., Drevets, W. C., Cowen, P. J., Harrison, N. A., Pointon, L., Pariante, C. M., & Bullmore, E. T. (2018). Treatment-resistant depression and peripheral C-reactive protein. *British Journal of Psychiatry*, *214*(1), 11–19. https://doi.org/10.1192/bjp.2018.66

Choi, J., Jeong, B., Rohan, M. L., Polcari, A. M., & Teicher, M. H. (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biological Psychiatry*, *65*(3), 227–234. https://doi.org/10.1016/j.biopsych.2008.06.022

D'Amico, D., Amestoy, M. E., & Fiocco, A. J. (2022). The mediating role of allostatic load in the relationship between early life adversity and cognitive function across the adult lifespan. *Psychoneuroendocrinology*, *141*, 105761. https://doi.org/10.1016/j.psyneuen.2022.105761

Dalthorp, D. (2021). *GenEst--R Installation*. Generalized Mortality Estimator. https://cran.r-project.org/web/packages/GenEst/readme/README.html

Danese, A., & Baldwin, J. R. (2017). Hidden wounds? Inflammatory links between childhood trauma and psychopathology. *Annual Review of Psychology*, *68*(1), 517–544. https://doi.org/10.1146/annurev-psych-010416-044208

Danese, A., & McEwen, B. S. (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & Behavior*, *106*(1), 29–39. https://doi.org/10.1016/j.physbeh.2011.08.019

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. *Archives of Pediatrics & Adolescent Medicine, 163*(12), 1135–1143. https://doi.org/10.1001/archpediatrics.2009.214

Darweesh, S. K. L., Wolters, F. J., Ikram, M. A., de Wolf, F., Bos, D., & Hofman, A. (2018). Inflammatory markers and the risk of dementia and Alzheimer's disease: A meta-analysis. *Alzheimer's & Dementia*, *14*(11), 1450–1459. https://doi.org/10.1016/j.jalz.2018.02.014

Davis, M. C., Lemery-Chalfant, K., Yeung, E. W., Luecken, L. J., Zautra, A. J., & Irwin, M. R. (2018). Interleukin-6 and depressive mood symptoms: Mediators of the association between childhood abuse and cognitive performance in middle-aged adults. *Annals of Behavioral Medicine*, *53*(1), 29–38. https://doi.org/10.1093/abm/kay014

Dye, H. (2018). The impact and long-term effects of childhood trauma. *Journal of Human Behavior in the Social Environment*, *28*(3), 381–392. https://doi.org/10.1080/10911359.2018.1435328

Elliot, A. J., & Chapman, B. P. (2016). Socioeconomic status, psychological resources, and inflammatory markers: Results from the MIDUS study. *Health Psychology*, *35*(11), 1205–1213. https://doi.org/10.1037/hea0000392

Fanning, J. R., Lee, R., Gozal, D., Coussons-Read, M., & Coccaro, E. F. (2015). Childhood trauma and parental style: Relationship with markers of inflammation, oxidative stress, and aggression in healthy and personality disordered subjects. *Biological Psychology*, *112*, 56–65. https://doi.org/10.1016/j.biopsycho.2015.09.003

Feeney, J., Kamiya, Y., Robertson, I. H., & Kenny, R. A. (2013). Cognitive function is preserved in older adults with a reported history of childhood sexual abuse. *Journal of Traumatic Stress*, *26*(6), 735–743. https://doi.org/10.1002/jts.21861

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., & De Benedictis, G. (2000). Inflamm-aging: An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences*, *908*(1), 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x

Geoffroy, M.-C., Pinto Pereira, S., Li, L., & Power, C. (2016). Child neglect and maltreatment and childhood-to-adulthood cognition and mental health in a prospective birth cohort. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(1). https://doi.org/10.1016/j.jaac.2015.10.012

Grainger, S. A., Crawford, J. D., Kochan, N. A., Mather, K. A., Chander, R. J., Draper, B., Brodaty, H., Sachdev, P. S., & Henry, J. D. (2019). An investigation into early-life stress and cognitive function in older age. *International Psychogeriatrics*, *32*(11), 1325–1329. https://doi.org/10.1017/s1041610219001583

Hayes, A. F. (2017). Partial, conditional, and moderated moderated mediation: Quantification, inference, and interpretation. *Communication Monographs*, *85*(1), 4–40. https://doi.org/10.1080/03637751.2017.1352100

Heringa, S. M., van den Berg, E., Reijmer, Y. D., Nijpels, G., Stehouwer, C. D. A., Schalkwijk, C. G., Teerlink, T., Scheffer, P. G., van den Hurk, K., Kappelle, L. J., Dekker, J. M., & Biessels, G. J. (2014). Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population – The Hoorn Study. *Psychoneuroendocrinology*, *40*, 108–118. https://doi.org/10.1016/j.psyneuen.2013.11.011

Hostinar, C. E., Lachman, M. E., Mroczek, D. K., Seeman, T. E., & Miller, G. E. (2015). Additive contributions of childhood adversity and recent stressors to inflammation at midlife: Findings from the MIDUS study. *Developmental Psychology, 51*(11), 1630–1644. https://doi.org/10.1037/dev0000049

Huang, Z., Jordan, J. D., & Zhang, Q. (2023). Early life adversity as a risk factor for cognitive impairment and Alzheimer's disease. *Translational Neurodegeneration*, *12*(1). https://doi.org/10.1186/s40035-023-00355-z

Kaur, J., & Jain, A. (2023, May 8). *Fibrinogen*. StatPearls [Internet]. https://pubmed.ncbi.nlm.nih.gov/30725869

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). https://doi.org/10.1371/journal.pone.0243685

Kirova, A.-M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed Research International*, *2015*, 1–9. https://doi.org/10.1155/2015/748212

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

Kolb, B., Harker, A., & Gibb, R. (2017). Principles of plasticity in the developing brain. *Developmental Medicine & Child Neurology*, *59*(12), 1218–1223. https://doi.org/10.1111/dmcn.13546

Korten, N. C., Penninx, B. W., Pot, A. M., Deeg, D. J., & Comijs, H. C. (2014). Adverse childhood and recent negative life events. *Journal of Geriatric Psychiatry and Neurology*, *27*(2), 128–138. https://doi.org/10.1177/0891988714522696

Krabbe, K. S., Reichenberg, A., Yirmiya, R., Smed, A., Pedersen, B. K., & Bruunsgaard, H. (2005). Low-dose endotoxemia and human neuropsychological functions. *Brain, Behavior, and Immunity*, *19*(5), 453–460. https://doi.org/10.1016/j.bbi.2005.04.010

Kraynak, T. E., Marsland, A. L., Hanson, J. L., & Gianaros, P. J. (2019). Retrospectively reported childhood physical abuse, systemic inflammation, and resting corticolimbic connectivity in midlife adults. *Brain, Behavior, and Immunity*, *82*, 203–213. https://doi.org/10.1016/j.bbi.2019.08.186

Kuo, H.-K., Yen, C.-J., Chang, C.-H., Kuo, C.-K., Chen, J.-H., & Sorond, F. (2005). Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: Systematic review and meta-analysis. *The Lancet Neurology*, *4*(6), 371–380. https://doi.org/10.1016/s1474-4422(05)70099-5

Lachman, M. E., Tun, P. A., & Murphy, C. L. (2021, December). *MIDUS 2, Project 3: Data File Notes -- Cognitive Test Battery*. Midlife in the United States (MIDUS). X:\Administrative Database\DBS\MIDUS 2\Project 3\Public Release\Updates\Dec2021\Documentation\M2_P3_BTACT_DataFile_Notes_20211122.docx

Lynch, K. S., & Lachman, M. E. (2020). The effects of lifetime trauma exposure on cognitive functioning in midlife. *Journal of Traumatic Stress*, *33*(5), 773–782. https://doi.org/10.1002/jts.22522

Matte-Landry, A., Grisé Bolduc, M.-È., Tanguay-Garneau, L., Collin-Vézina, D., & Ouellet-Morin, I. (2022). Cognitive outcomes of children with complex trauma: A systematic review and meta-analyses of longitudinal studies. *Trauma, Violence, & Abuse*, *24*(4), 2743–2757. https://doi.org/10.1177/15248380221111484

McKay, M. T., Cannon, M., Chambers, D., Conroy, R. M., Coughlan, H., Dodd, P., Healy, C., O'Donnell, L., & Clarke, M. C. (2021). Childhood trauma and adult mental disorder: A systematic review and meta-analysis of Longitudinal Cohort Studies. *Acta Psychiatrica Scandinavica*, *143*(3), 189–205. https://doi.org/10.1111/acps.13268

McLaughlin, K. A., Greif Green, J., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2012). Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. *Archives of General Psychiatry*, *69*(11), 1151–1160. https://doi.org/10.1001/archgenpsychiatry.2011.2277

Mitchell, A. M., Porter, K., & Christian, L. M. (2018). Examination of the role of obesity in the association between childhood trauma and inflammation during pregnancy. *Health Psychology*, *37*(2), 114–124. https://doi.org/10.1037/hea0000559

Moscovitch, M., & Winocur, G. (1995). Frontal lobes, memory, and aging. *Annals-New York Academy of Sciences*, *769*, 119-150.

Müller, L., Di Benedetto, S., & Pawelec, G. (2019). The immune system and its dysregulation with aging. *Subcellular Biochemistry*, 21–43. https://doi.org/10.1007/978-981-13-3681-2_2

Murman, D. (2015). The impact of age on cognition. *Seminars in Hearing*, *36*(03), 111–121. https://doi.org/10.1055/s-0035-1555115

Muscatell, K. A., Brosso, S. N., & Humphreys, K. L. (2018). Socioeconomic status and inflammation: A meta-analysis. *Molecular Psychiatry*, *25*(9), 2189–2199. https://doi.org/10.1038/s41380-018-0259-2

Nehring, S. M., Patel, B. C., & Goyal, A. (2023, July 10). *C reactive protein*. StatPearls [Internet]. https://pubmed.ncbi.nlm.nih.gov/28722873/

Nemeroff, C. B. (2004). Neurobiological consequences of childhood trauma. *The Journal of Clinical Psychiatry*, *65*(1), 18–28.

Nettis, M. A., Pariante, C. M., & Mondelli, V. (2019). Early-life adversity, systemic inflammation and comorbid physical and psychiatric illnesses of adult life. *Neuroinflammation and Schizophrenia*, *44*, 207–225. https://doi.org/10.1007/7854_2019_89

Nikulina, V., & Widom, C. S. (2013). Child maltreatment and executive functioning in middle adulthood: A prospective examination. *Neuropsychology*, *27*(4), 417–427. https://doi.org/10.1037/a0032811

Nolin, P., & Ethier, L. (2007). Using neuropsychological profiles to classify neglected children with or without physical abuse. *Child Abuse & Neglect*, *31*(6), 631–643. https://doi.org/10.1016/j.chiabu.2006.12.009

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences*, *16*(5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005

Peng, C., Cheng, J., Rong, F., Wang, Y., & Yu, Y. (2023). Psychometric Properties and normative data of the Childhood Trauma Questionnaire-Short Form in Chinese adolescents. *Frontiers in Psychology, 14*. https://doi.org/10.3389/fpsyg.2023.1130683

Petrov, M. E., Davis, M. C., Belyea, M. J., & Zautra, A. J. (2016). Linking childhood abuse and hypertension: Sleep disturbance and inflammation as mediators. *Journal of Behavioral Medicine*, *39*(4), 716–726. https://doi.org/10.1007/s10865-016-9742-x

Quidé, Y., Bortolasci, C. C., Spolding, B., Kidnapillai, S., Watkeys, O. J., Cohen-Woods, S., Berk, M., Carr, V. J., Walder, K., & Green, M. J. (2018). Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and bipolar-I disorder. *Psychological Medicine*, *49*(16), 2736–2744. https://doi.org/10.1017/s0033291718003690

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., & Pollmächer, T. (2001). Cytokine-associated emotional and cognitive disturbances in humans. *Archives of General Psychiatry*, *58*(5), 445. https://doi.org/10.1001/archpsyc.58.5.445

Ritchie, K., Jaussent, I., Stewart, R., Dupuy, A.-M., Courtet, P., Malafosse, A., & Ancelin, M.-L. (2010). Adverse childhood environment and late-life cognitive functioning. *International Journal of Geriatric Psychiatry*, *26*(5), 503–510. https://doi.org/10.1002/gps.2553

Ryff, C. D., Almeida, D. M., Ayanian, J. Z., Carr, D. S., Cleary, P. D., Coe, C., Davidson, R. J., Krueger, R. F., Lachman, M. E., Marks, N. F., Mroczek, D. K., Seeman, T. E., Seltzer, M. M., Singer, B. H., Sloan, R. P., Tun, P. A., Weinstein, M., & Williams, D. R. (2021). *Midlife in the United States (MIDUS 2), 2004-2006* [dataset]. Inter-university Consortium for Political and Social Research [distributor]. https://doi.org/10.3886/ICPSR04652.v8

Ryff, C., Almeida, D., Ayanian, J., Binkley, N., Carr, D. S., Coe, C., Davidson, R., Grzywacz, J., Karlamangla, A., Krueger, R., Lachman, M., Love, G., Mailick, M., Mroczek, D., Radler, B., Seeman, T., Sloan, R., Thomas, D., Weinstein, M., & Williams, D. (2019). *Midlife in the United States (MIDUS 3), 2013-2014* [dataset]. Inter-university Consortium for Political and Social Research [distributor]. https://doi.org/10.3886/ICPSR36346.v7

Silva, P. C., de Oliveira, L. L., Teixeira, R. L., Brito, M. L., & Filippe, A. R. (2022). Executive functions in Alzheimer's disease: A systematic review. *Journal of Alzheimer's Disease Reports*, *6*(1), 81–99. https://doi.org/10.3233/adr-210059

Stenfors, C. U. D., Jonsdottir, I. H., Magnusson Hanson, L. L., & Theorell, T. (2017). Associations between systemic pro-inflammatory markers, cognitive function and cognitive complaints in a population-based sample of working adults. *Journal of Psychosomatic Research*, *96*, 49–59. https://doi.org/10.1016/j.jpsychores.2017.03.010

Stuss, D. T., & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychological bulletin*, *95*(1), 3–28.

Su, K.-P. (2012). Inflammation in psychopathology of depression: Clinical, biological, and therapeutic implications. *BioMedicine*, *2*(2), 68–74. https://doi.org/10.1016/j.biomed.2012.03.002

Swedo, E. A., Aslam, M. V., Dahlberg, L. L., Niolon, P. H., Guinn, A. S., Simon, T. R., & Mercy, J. A. (2023, June 29). *Prevalence of adverse childhood experiences among U.S. adults - behavioral risk factor surveillance system, 2011–2020*. Centers for Disease Control and Prevention. https://www.cdc.gov/mmwr/volumes/72/wr/mm7226a2.htm

Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. *Cold Spring Harbor Perspectives in Biology*, *6*(10). https://doi.org/10.1101/cshperspect.a016295

Tangestani-Fard, M., Savage, K. M., & Stough, C. K. (2022). Peripheral inflammation marker relationships to cognition in Healthy Older Adults – A systematic review. *Psychoneuroendocrinology*, *144*, 105870. https://doi.org/10.1016/j.psyneuen.2022.105870

Tegeler, C., O'Sullivan, J. L., Bucholtz, N., Goldeck, D., Pawelec, G., Steinhagen-Thiessen, E., & Demuth, I. (2016). The inflammatory markers CRP, IL-6, and Il-10 are associated with cognitive function—Data from the Berlin Aging Study II. *Neurobiology of Aging*, *38*, 112–117. https://doi.org/10.1016/j.neurobiolaging.2015.10.039

Teicher, M. H., & Samson, J. A. (2016). Annual research review: Enduring neurobiological effects of childhood abuse and neglect. *Journal of Child Psychology and Psychiatry*, *57*(3), 241–266. https://doi.org/10.1111/jcpp.12507

Timmerman, I., Daniel, A. E., Kroon, J., & van Buul, J. D. (2016). Leukocytes crossing the endothelium: A matter of communication. *International Review of Cell and Molecular Biology*, *322*, 281–329. https://doi.org/10.1016/bs.ircmb.2015.10.005

Tsalamandris, S., Antonopoulos, A. S., Oikonomou, E., Papamikroulis, G.-A., Vogiatzi, G., Papaioannou, S., Deftereos, S., & Tousoulis, D. (2019). The role of inflammation in diabetes: Current concepts and future perspectives. *European Cardiology Review*, *14*(1), 50–59. https://doi.org/10.15420/ecr.2018.33.1

Tun, P. A., & Lachman, M. E. (2006). Telephone assessment of cognitive function in adulthood: The Brief Test of Adult Cognition by Telephone. *Age and Ageing*, *35*(6), 629–632. https://doi.org/10.1093/ageing/afl095

US Census Bureau. (2023, October 31). *2023 National Population Projections Tables: Main Series*. United States Census Bureau. https://www.census.gov/data/tables/2023/demo/popproj/2023-summary-tables.html

Verhaeghen, P. (2011). Aging and executive control: Reports of a demise greatly exaggerated. *Current Directions in Psychological Science*, *20*(3), 174–180. https://doi.org/10.1177/0963721411408772

Wang, L., Yang, L., Yu, L., Song, M., Zhao, X., Gao, Y., Han, K., An, C., Xu, S., & Wang, X. (2016). Childhood physical neglect promotes development of mild cognitive impairment in old age – a case-control study. *Psychiatry Research*, *242*, 13–18. https://doi.org/10.1016/j.psychres.2016.04.090

Weleff, J., & Potter, D. (2023). Key updates to understanding roles of childhood trauma in overall health. *AMA Journal of Ethics*, *25*(2), E116-122. https://doi.org/10.1001/amajethics.2023.116

West, R. (2000). In defense of the frontal lobe hypothesis of cognitive aging. *Journal of the International Neuropsychological Society*, *6*(6), 727–729. https://doi.org/10.1017/s1355617700666109

Xie, Z., Li, M., Sun, H., Zhou, C., Fu, C., Wang, Q., Dong, C., Hao, W., Zhen, X., & Zhu, D. (2023). Childhood, adulthood, and cumulative traumatic events experienced from childhood to adulthood and dementia risk: A population-based cohort study. *Journal of Public Health*. https://doi.org/10.1007/s10389-023-02140-8

Yuan, P., & Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *42*, 180–192. https://doi.org/10.1016/j.neubiorev.2014.02.0

Appendix

Table 1. Childhood Trauma Severity Classifications.

	None to minimal	Slight to moderate	Moderate to severe	Severe to extreme
Emotional abuse	5–8	9–12	13–15	16–25
Physical abuse	5–7	8–9	10–12	13–25
Sexual abuse	5	6–7	8–12	13–25
Emotional neglect	5–9	10–14	15–17	18–25
Physical neglect	5–7	8–9	10–12	13–25

Table 1

Severity classifications for the five domains of childhood maltreatment as outlined by Bernstein et al., 1994.

Note: All domains were included in the CTQ composite score, but Emotional Neglect did not reach significance with inflammation and episodic memory scores independently, so this domain of maltreatment was excluded from consequent mediation analyses.

Table 2. Pearson correlations table

	EF	**EM**	**CTQ Composite Score**	**Sexual Assault**	**Physical Abuse**	**Emotional Abuse**	**Emotional Neglect**	**Physical Neglect**	**Inflammation Composite Score**	**Age**	**Sex**	**SES**
EF	1	-	-	-	-	-	-	-	-	-	-	-
EM	**0.3351***	1	-	-	-	-	-	-	-	-	-	-
CTQ Composite Score	-0.0461	-0.0139	1	-	-	-	-	-	-	-	-	-
Sexual Assault	**-0.0828***	-0.0057	**0.6482***	1	-	-	-	-	-	-	-	-
Physical Abuse	-0.0287	-0.0210	**0.7420***	**0.3683***	1	-	-	-	-	-	-	-
Emotional Abuse	0.0143	0.0346	**0.8657***	**0.4276***	**0.6229***	1	-	-	-	-	-	-
Emotional Neglect	-0.0020	-0.0270	**0.8451***	**0.3289***	**0.5031***	**0.7014***	1	-	-	-	-	-
Physical Neglect	**-0.1100***	-0.0479	**0.7599***	**0.3665***	**0.5021***	**0.5427***	**0.6352***	1	-	-	-	-
Inflammation Composite Score	**-0.1454***	-0.0492	**0.1285***	**0.1405***	**0.0986***	**0.0836***	0.0700	**0.1212***	1	-	-	-
Age	**-0.3338***	-0.2642	**-0.1931***	-0.0693	**-0.1803***	**-0.2100***	**-0.1675***	**-0.1160***	0.0510	1	-	-
Sex	**-0.1212***	0.3300	**0.1455***	**0.1974***	-0.0053	**0.1620***	**0.0891***	**0.0857***	**0.1460***	-0.0078	1	-
SES	0.0103	-0.0329	-0.0627	-0.0443	-0.0425	-0.0771	-0.0463	-0.0240	-0.0495	**0.2162***	-0.003	1

Table 2. Pearson correlations among all childhood maltreatment variables for inflammation, episodic memory, and executive functioning, including covariates.

Note: Bolded and asterisked associations were significant at $p < 0.05$. Correlations in red were included in mediation analyses.

Figure 1. Demographics and Sample Characteristics.

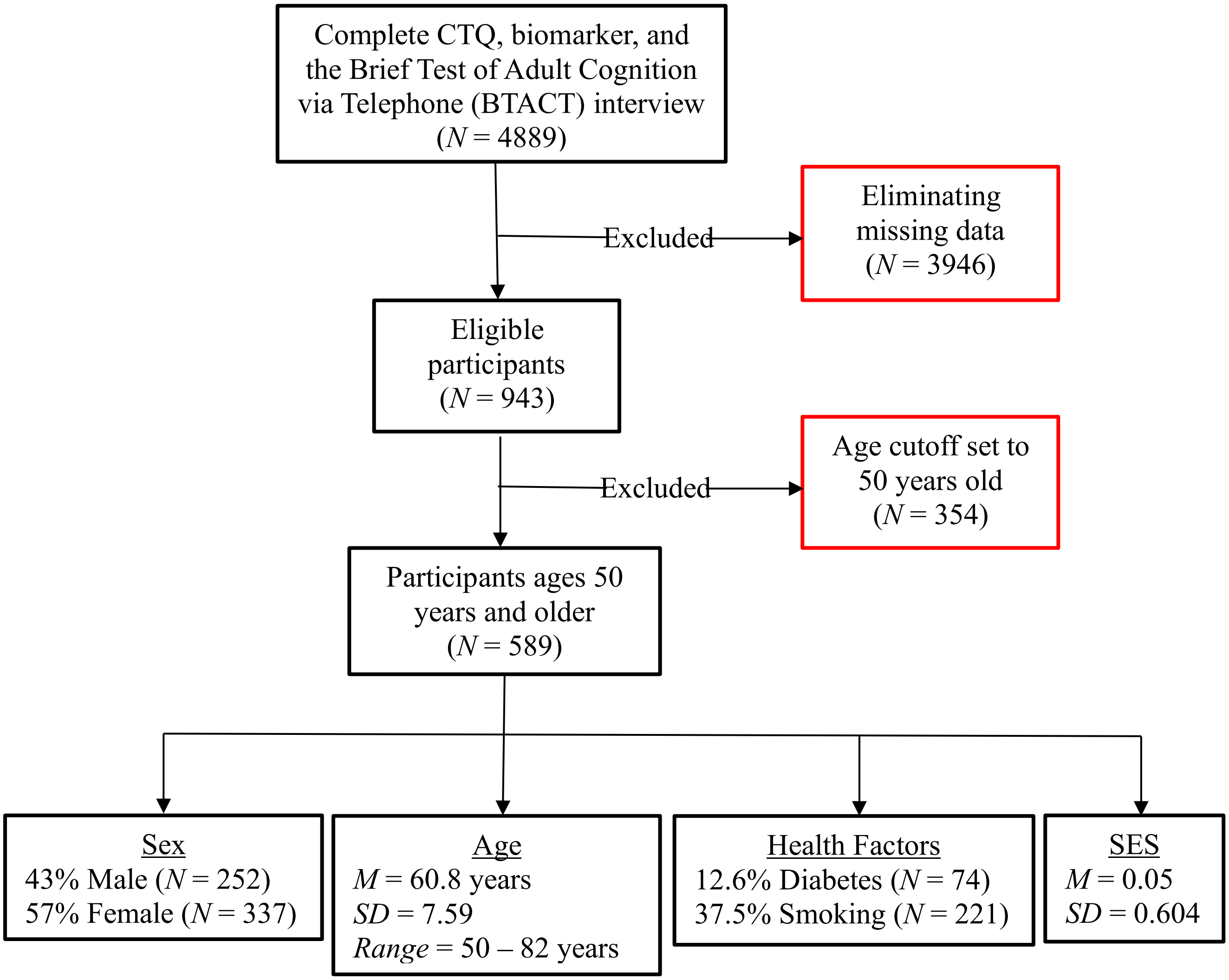

Figure 1.

Inclusion and exclusion criteria utilized to gather the total number of participants in the study. Breakdowns of sample characteristics for each covariate were included.

Note: N = number. *M* = mean. *SD* = standard deviation.

Figure 2. CTQ composite intermediate pathways.

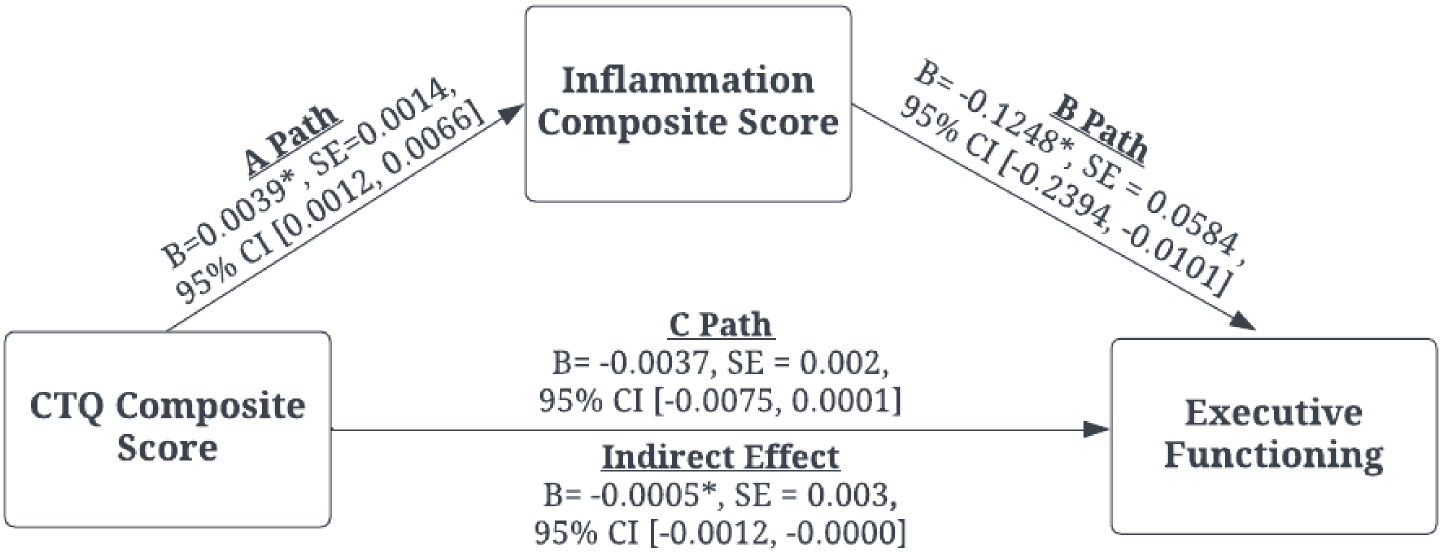

Figure 2

Pathways of an indirect effect of CTQ composite score on executive functioning through inflammation composite score with age, sex, SES, diabetes, and smoking status covaried.

Note. CTQ composite score = summed scores of all five CTQ domains (Emotional abuse, Physical abuse, Sexual abuse, Emotional neglect, Physical neglect). Inflammation composite score = log-transformed values of the measured biomarkers (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). Executive functioning = standardized scores on the Brief Test of Adult Cognition via Telephone (BTACT) interview. **p* < 0.05.

Figure 3. Physical abuse intermediate pathways.

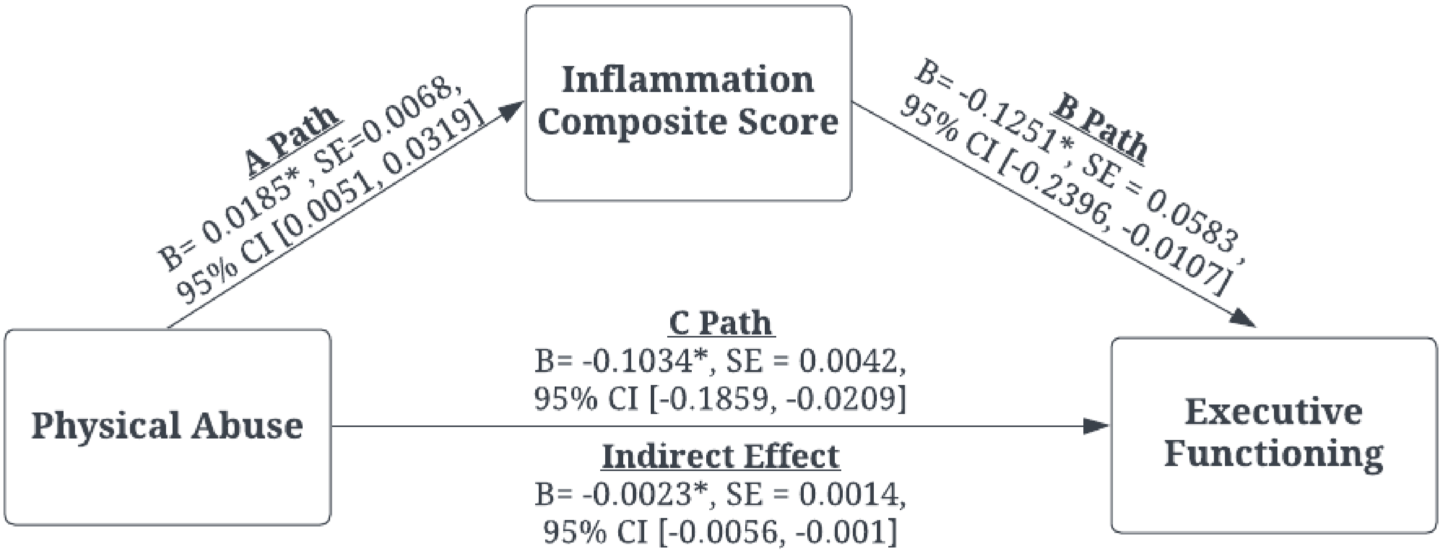

Figure 3

Pathways of an indirect effect of physical abuse on executive functioning through inflammation composite score with age, sex, SES, diabetes, and smoking status covaried.

Note. Inflammation composite score = log-transformed values of the measured biomarkers (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). Executive functioning = standardized scores on the Brief Test of Adult Cognition via Telephone (BTACT) interview. *$p < 0.05$.

Figure 4. Sexual assault intermediate pathways.

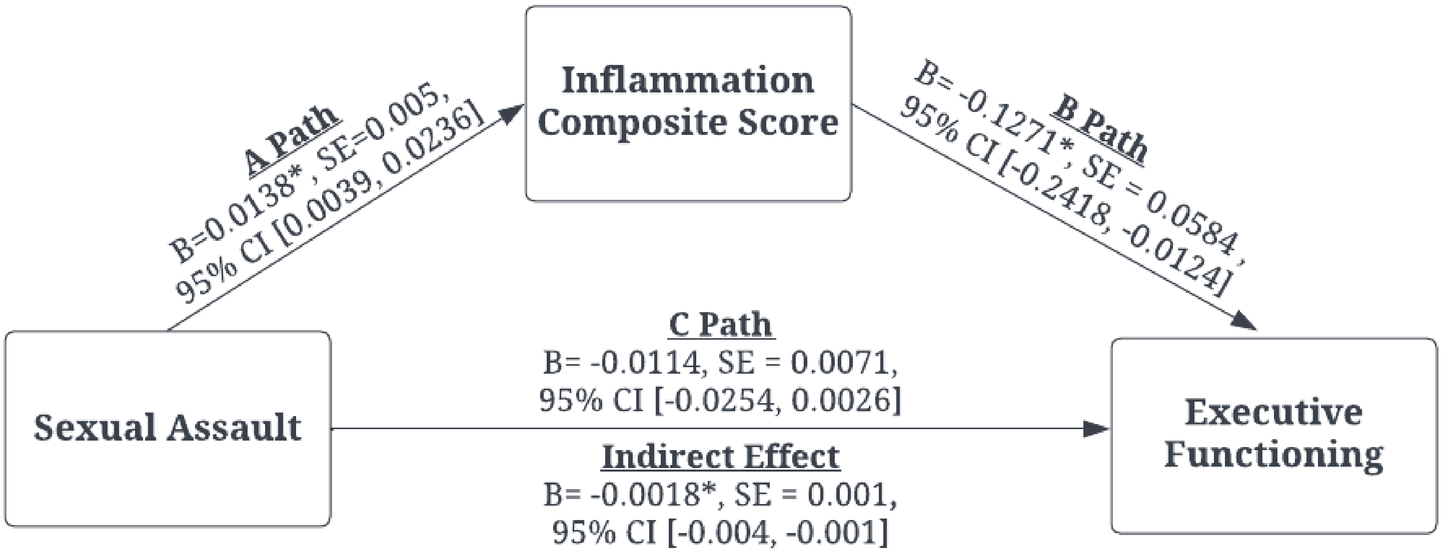

Figure 4

Pathways of an indirect effect of sexual assault on executive functioning through inflammation composite score with age, sex, SES, diabetes, and smoking status covaried.

Note. Inflammation composite score = log-transformed values of the measured biomarkers (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). Executive functioning = standardized scores on the Brief Test of Adult Cognition via Telephone (BTACT) interview. *$p < 0.05$.

Figure 5. Emotional abuse intermediate pathways.

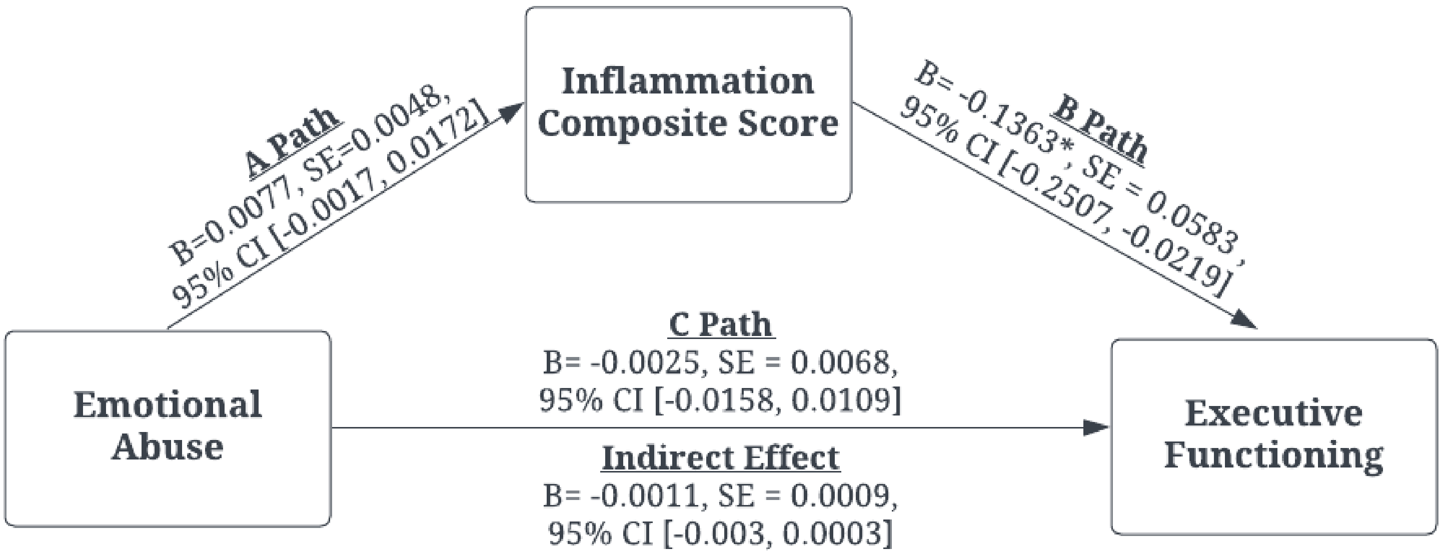

Figure 5

Pathways of an indirect effect of emotional abuse on executive functioning through inflammation composite score with age, sex, SES, diabetes, and smoking status covaried.

Note. Inflammation composite score = log-transformed values of the measured biomarkers (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). Executive functioning = standardized scores on the Brief Test of Adult Cognition via Telephone (BTACT) interview. **p* < 0.05.

Figure 6. Physical neglect intermediate pathways.

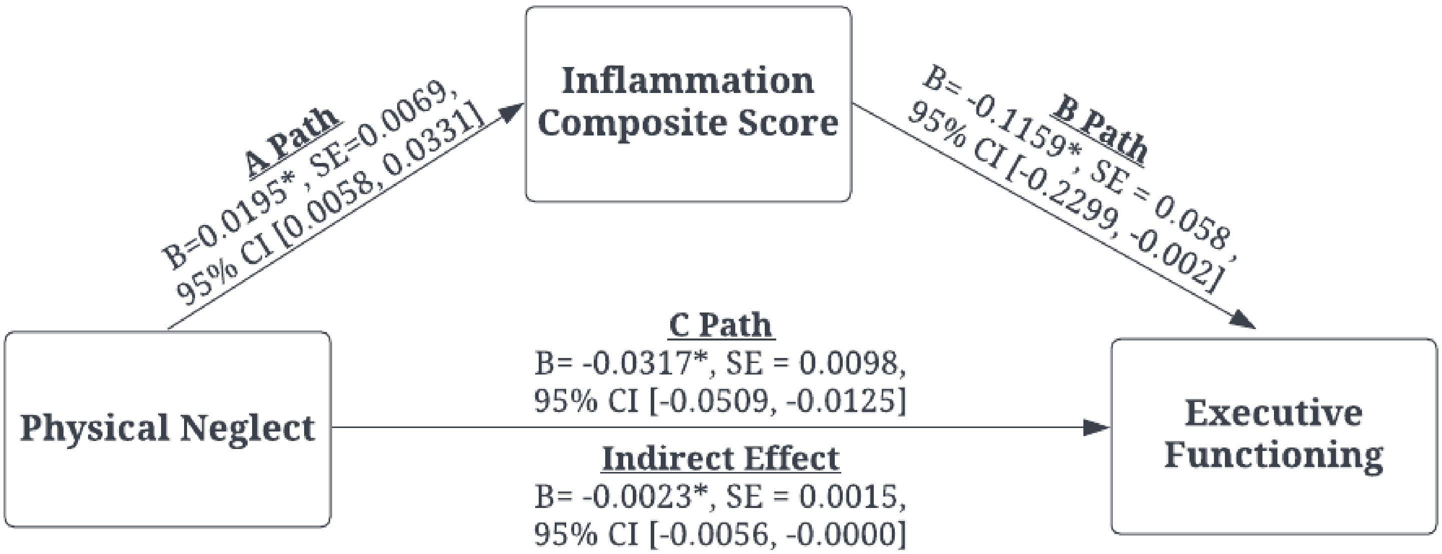

Figure 6

Pathways of an indirect effect of physical neglect on executive functioning through inflammation composite score with age, sex, SES, diabetes, and smoking status covaried.

Note. Inflammation composite score = log-transformed values of the measured biomarkers (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). Executive functioning = standardized scores on the Brief Test of Adult Cognition via Telephone (BTACT) interview. **p* < 0.05.