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Primed to feel, not to flare: Early life adversity and psychological sensitivity to interleukin-6 in a randomized trial among middle-aged female breast cancer survivors

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ABSTRACT

Background: There have been recent calls to investigate potential moderators of inflammation's psychological effects in humans. In a small observational study, Kuhlman et al. (2020b) found that individuals with higher early life adversity (ELA) showed heightened psychological sensitivity (i.e., more depressed mood and poorer cognition but not decreased social connection) in response to influenza vaccine-induced increases in interleukin-6 (IL-6). In a larger cohort with a placebo-controlled experimental design, we examined ELA's moderating effects on (1) vaccine-induced IL-6 reactivity, (2) increases in IL-6 reactivity and psychological outcomes, and (3) the effect of injection type on psychological outcomes.

Method: Female breast cancer survivors (N = 172) received the typhoid vaccine and saline placebo injection in a randomized sequence at two separate visits. At screening, early life adversity was indexed using two measures: the Childhood Trauma Questionnaire-Short Form and the Kessler Childhood Adversity Index. During each visit, IL-6 was measured six times over 7.5 h, and psychological outcomes (sadness, focus difficulty, memory difficulty, social connection) were repeatedly assessed across 8.5 h.

Abbreviations: ELA, early life adversity; MDD, major depressive disorder; IL-6, interleukin-6; IL-1Ra, interleukin-1 receptor antagonist; typhoid ViCPS, typhoid Vi polysaccharide; CTRA, Conserved Transcriptional Response to Adversity; CTQ-SF, Childhood Trauma Questionnaire Short Form; BBB, blood–brain barrier; HP, hippocampus; PFC, prefrontal cortex.

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Results: Neither ELA index moderated vaccine-induced IL-6 reactivity (*ps* > 0.17) nor moderated the effect of injection type on psychological outcomes (*ps* > 0.25). Instead, those with more ELA had greater psychological sensitivity to inflammatory increases. Among individuals with higher ELA exposure (≥2 adverse events), increases in IL-6 were associated with greater sadness ($p = 0.030$) and focus difficulty ($p = 0.048$), marginally greater memory difficulty ($p = 0.067$), but were unrelated to feelings of social connection (*ps* > 0.81). These associations were nonsignificant among individuals who reported zero or one adverse event.
Conclusion: Our findings suggest that among individuals with greater exposure to early life adversity, those with heightened inflammatory reactivity may be particularly vulnerable to IL-6′s psychological effects, highlighting a potential target for identifying and supporting individuals at risk for inflammation-associated depression.

1. Introduction

Early life adversity (ELA), highly stressful or traumatic events occurring before age 18 (e.g., abuse, neglect, parental death), is prevalent among individuals with major depressive disorder (MDD) in the United States. Up to 83% of those who are depressed report at least one adverse experience (Ahn et al., 2024; LeMoult et al., 2020; Merrick, 2019; Zisook et al., 2022). Early life adversity is widely recognized as a transdiagnostic risk factor, exerting broad and lasting pleiotropic effects across psychiatric, health, economic, behavioral, and social outcomes (Bhushan et al., 2020; Herzog and Schmahl, 2018; McGinnis et al., 2022; Waehrer et al., 2020). These widespread effects are particularly relevant for depression, where early life adversity has been linked to immune dysregulation that may increase vulnerability to inflammation-associated depression (Iob et al., 2020; Kuhlman et al., 2020a, 2020b; Müller et al., 2019). Notably, one-third of individuals with MDD have clinically elevated inflammation despite the absence of medical illness (Krishnadas and Cavanagh, 2012; Pitharouli et al., 2021). This subgroup experiences greater treatment resistance, poorer prognosis, and reduced health-related quality of life (Hassamal, 2023; Strawbridge et al., 2019; Suneson et al., 2021), contributing to growing calls to define an inflammatory subtype of depression in the DSM-6 (Jha et al., 2025). Yet, heightened inflammation alone does not uniformly lead to depression (Raison and Miller, 2013). Approximately 17% of individuals with clinically elevated inflammation do not develop depression (Pitharouli et al., 2021). Therefore, it is critical to examine potential moderators of inflammation's psychological effect (Lasselin, 2021), such as early life adversity.

Two theoretical frameworks provide mechanistic insight into how early life adversity may shape vulnerability to inflammation-associated depression: the Neuroimmune Network Hypothesis and the Conserved Transcriptional Response to Adversity (CTRA). The Neuroimmune Network Hypothesis posits that early life adversity sensitizes cortico-amygdala circuits involved in threat processing and concurrently activates peripheral immune cells, resulting in chronic low-grade systemic inflammation (Nusslock and Miller, 2016). This inflammation engages in bidirectional crosstalk with neural circuits governing threat, reward, and executive control, forming a feedforward loop that exacerbates neuroimmune dysregulation (Nusslock and Miller, 2016). As a result, individuals exposed to ELA may have greater inflammatory reactivity, leading to stronger psychological and behavioral impacts. The CTRA complements this framework by describing a chronic adversity-induced conserved transcriptional profile in immune cells characterized by upregulation of proinflammatory genes and downregulation of antiviral response genes (Cole, 2019). Specifically, CTRA outlines a signal transduction pathway in which sympathetic nervous system-mediated β-adrenergic signaling alters transcriptional activity in leukocytes, producing a consistent pattern of increased inflammatory gene expression across species and stress contexts (Cole, 2019). Although not yet tested, this model assumes that greater CTRA gene expression relates to increased inflammatory reactivity to acute immune stimuli like stress, vaccination, or endotoxin.

The CTRA framework conceptualizes early life adversity within a mediation pathway, proposing that early adversity fosters inflammatory sensitization that subsequently increases risk for depression and related health sequelae. However, the mediation pathway alone cannot explain the substantial heterogeneity among individuals exposed to ELA, many of whom never develop chronic low-grade inflammation and/or depressive symptoms (Iob et al., 2020; Krishnadas and Cavanagh, 2012; Pitharouli et al., 2021). Rather, the Neuroimmune Network Hypothesis offers a broader perspective because it conceptualizes early life adversity as a potential moderator of inflammation's psychological effects; that is, early life adversity may confer heightened psychological sensitivity to inflammation. This moderation model accounts for variability in ELA-related mental and physical health outcomes.

Animal models provide the only causal evidence of early life adversity's effects, showing that ELA's immune effects are not deterministic but context dependent. Across rodent paradigms, early life adversity is typically modeled by separating pups from their mothers or by creating poor nesting conditions. ELA-exposed rodents show transient increases in peripheral proinflammatory markers shortly after an immune challenge (Dutcher et al., 2020; Hohmann et al., 2017), although these elevations typically dissipate by adulthood unless stressors persist or reoccur across development. These dynamics align with "two-hit" models in which early life adversity, as the first hit, primes physiological systems such that a second hit (i.e., later life stress) elicits exaggerated inflammatory responses and increases vulnerability to depression-relevant symptoms (Cheng et al., 2024; Deng et al., 2023; Dutcher et al., 2020; Peña et al., 2017).

Systematic reviews in rodents further reveal tissue-specific inflammatory patterns. Early life adversity does not produce long-term peripheral cytokine elevations (Dutcher et al., 2020) yet leads to persistent interleukin-6 (IL-6) increases in the brain (Lumertz et al., 2022). This suggests that early life adversity may prime microglia to mount heightened neuroinflammatory responses even when peripheral cytokines remain unchanged. Sex and developmental stages also shape these effects (Park et al., 2021; Solarz et al., 2023; Speranza et al., 2024), underscoring the need to consider contextual moderators when translating findings to humans. Behaviorally, ELA-exposed rodents display enhanced depressive-like responses to immune activation including anhedonia, reduced locomotion, social withdrawal, reduced saccharin and sucrose preference, increased immobility in forced swim and tail suspension tests, and suppressed sexual behavior, with some studies noting that these depressive-like behaviors persist even after acute sickness symptoms subside (Bay-Richter et al., 2011; Biesmans et al., 2013; Biswas et al., 2024; Frenois et al., 2007; Hashimoto et al., 2020; Kim et al., 2021; Yirmiya, 1996). These data suggest that early life adversity heightens behavioral sensitivity to inflammation, but translating these findings to humans requires models that explicitly test moderation processes to capture psychological and subjective sensitivity to an immune stimuli's effect (Lasselin, 2021).

To date, human literature is more mixed. Some studies have reported positive associations between ELA and inflammatory reactivity following acute social stress challenges such as the Trier Social Stress Test (Carpenter et al., 2010), endotoxin-induced inflammation via LPS administration (De Koning et al., 2022), and basal inflammatory levels (Dennison et al., 2012). In contrast, a subset of well-controlled studies using exogenous immune stimuli, including vaccination paradigms,

have observed null effects (Bedwell et al., 2025; Kuhlman et al., 2020a, 2020b), as have studies employing the Trier Social Stress Test (Hantsoo et al., 2019; Schreier et al., 2020; Shalev et al., 2020). Manigault et al. (2021) found that early life adversity did not moderate the association between CRP and depressive symptoms, though concurrent stress sensitized female breast cancer survivors to depressive symptoms when basal inflammation was elevated. Irwin et al. (2019) likewise found no evidence that early life adversity moderated mood responses to endotoxin.

Key methodological differences may help explain these null findings. Manigault et al. (2021) examined natural fluctuations in basal inflammation in female breast cancer survivors without using external inflammatory stimuli. In contrast, Irwin et al. (2019) administered an experimental endotoxin model to induce inflammation in healthy adults but did not assess whether ELA moderated inflammatory reactivity's effect on depressed mood—an important point because people can have vastly different inflammatory responses to endotoxin (Lasselin et al., 2020). Of note, this study included both males and females, which may have obscured effects given that the associations between ELA and inflammation (Lasselin et al., 2018; Logue & Nemeroff, 2025) and between inflammation and depression (Bekhbat & Neigh, 2018; Jarkas et al., 2024; Slavich & Sacher, 2019) are stronger among females.

Kuhlman et al. (2020b) provides important context for interpreting these null findings. This small observational influenza vaccine study showed that individuals with higher ELA had greater increases in depressed mood and subjective cognitive difficulties—but not reduced feelings of social connection—only when early life adversity was modeled as a moderator of inflammatory reactivity rather than of the immune stimuli itself. Also, those with ELA did not have heightened inflammatory reactivity to the influenza vaccine. Extending this framework to acute psychosocial stress (i.e, Trier Social Stress Test), Kuhlman et al. (2023) similarly found that ELA moderated the association between stress-induced IL-6 increases and reward and risk processing in adolescents, without altering the magnitude of the IL-6 response itself. Together, a growing body of work suggests that early life adversity may not uniformly intensify the immune responses to stimuli but rather shape psychological and cognitive responses to inflammation (Bedwell et al., 2025; Kuhlman et al., 2020b). Collectively, these findings challenge the generalizability of the direct ELA-to-inflammation model of depression risk and instead highlight notable heterogeneity in inflammatory responses to ELA—heterogeneity that may reflect resilience pathways and adaptive immune calibration despite early adversity (Gouin et al., 2017).

To our knowledge, Kuhlman et al. (2020b) remains the only known study to test these competing hypotheses derived from preclinical observations in a human sample using an exogenous immune stimulus. The present study seeks to replicate and extend Kuhlman et al.'s (2020b) work in several novel ways. First, we examine a larger sample from a clinical population—middle-aged female breast cancer survivors who are at increased risk to develop depression and cognitive impairment (Carreira et al., 2018; Janelsins et al., 2017)—compared to Kuhlman et al.'s (2020b) smaller sample of younger mostly female undergraduate students (N = 41, F = 73.2%; M_{age} = 18.49). Second, we use the typhoid vaccine as the exogenous immune stimulus, which is advantageous because all participants were naive to it. In contrast, Kuhlman et al. (2020b) used the flu vaccine, for which prior exposure and yearly formula carryover may introduce variability in immune responses. Third, we implement a double-blind within-subject, randomized-to-sequence, placebo-controlled design, wherein each participant received both a saline placebo injection and the typhoid vaccine, allowing us to control for non-specific effects and assess outcomes across multiple time points. Guided by Kuhlman et al.'s (2020b) competing hypotheses, we tested (1) whether early life adversity moderates post-vaccination (placebo vs. vaccine) inflammatory response or (2) whether early life adversity instead moderates greater psychological sensitivity to inflammatory responses. Consistent with prior findings, we predicted that only the latter hypothesis would be supported. As a secondary aim, we tested whether early life adversity moderated the effect of injection type on psychological outcomes, and we did not expect to find evidence of this, given findings from Irwin et al. (2019).

2. Methods

2.1. Participants

Participants were postmenopausal female breast cancer survivors (N = 172; M_{age} = 56.6) recruited from the James Cancer Hospital breast cancer clinics or the Army of Women website for the parent study (Table 1, Fig. 1) (Kiecolt-Glaser et al., 2022). Eligible individuals had completed all primary treatments for stage I-IIIA breast cancer 1–9 years prior to enrollment, though ongoing hormonal therapies were permitted (Kiecolt-Glaser et al., 2022). Individuals were excluded if they had a history of any cancer other than non-melanoma skin cancer (i.e., basal or squamous cell carcinoma), or if they had experienced conditions such as stroke, diabetes, anemia, liver disease, autoimmune and/or inflammatory diseases, current heart disease, or unmanaged hypertension. Additional exclusion criteria included prior typhoid vaccination, alcohol/drug abuse, smoking, medical conditions that would limit participation (i.e., cognitive dysfunction), or use of any medication with anti-inflammatory properties (i.e., steroids, statins). The Ohio State University Institutional Review Board approved the study, and all participants provided informed consent. The parent study was registered at Clinicaltrials.gov (NCT02415387). We reported this trial in accordance with the CONSORT guidelines (Schulz et al., 2010).

As shown in Fig. 1, a large number of individuals were screened but did not meet inclusion criteria for several reasons. First, inclusion criteria required post-menopausal status and completion of breast cancer treatment within the prior 10 years, narrowing the eligible pool. The protocol also included a VO2 max test, which excluded participants with significant back or knee limitations. Second, because this is the first study of its kind in breast cancer survivors, a relatively healthy sample was needed; yet, comorbidities and chronic medication use are common among breast cancer survivors, with 30–70% having pre-existing chronic conditions and over half taking long-term non-cancer medications (Dumas et al., 2024). Several medication classes within immunomodulatory properties were part of the exclusion criteria, including statins, autoimmune medications, long-term steroids, and anticoagulants. Statin use was a particularly common reason for exclusion: global statin use rose 25% between 2015 and 2020, with higher rates in North

Table 1
Sample demographics at visit 1.

	N	Mean (SD) or N (%)	Range
Age	172	56.64 (8.40)	36–78
Race	172		
White		159 (92.44%)	
Black		10 (5.81%)	
Asian		1 (0.58%)	
Multiracial		2 (1.16%)	
Trunk fat, kg (DXA)	172	15.68 (6.70)	3.14–34.26
Chemotherapy treatment	172	116 (67.44%)	
Radiation treatment	172	105 (61.05%)	
Cancer stage	172		
Stage I		81 (47.09%)	
Stage II		82 (47.67%)	
Stage III		9 (5.23%)	
CTQ-SF Walker Sum Cutoff [+]	159	0.93 (1.41)	0–5
Kessler Childhood Adversity Index[+]	159	1.36 (1.58)	0–7
Baseline focus difficulty	164	1.20 (1.37)	0–8
Baseline memory difficulty	164	1.23 (1.46)	0–9
Baseline sadness	172	2.65 (1.40)	1–8
Baseline social connection	172	5.08 (0.94)	1.25–6
Fasting IL-6, pg/mL	171	2.84 (6.14)	0.42–78.37

[+] Assessed at screening visit.

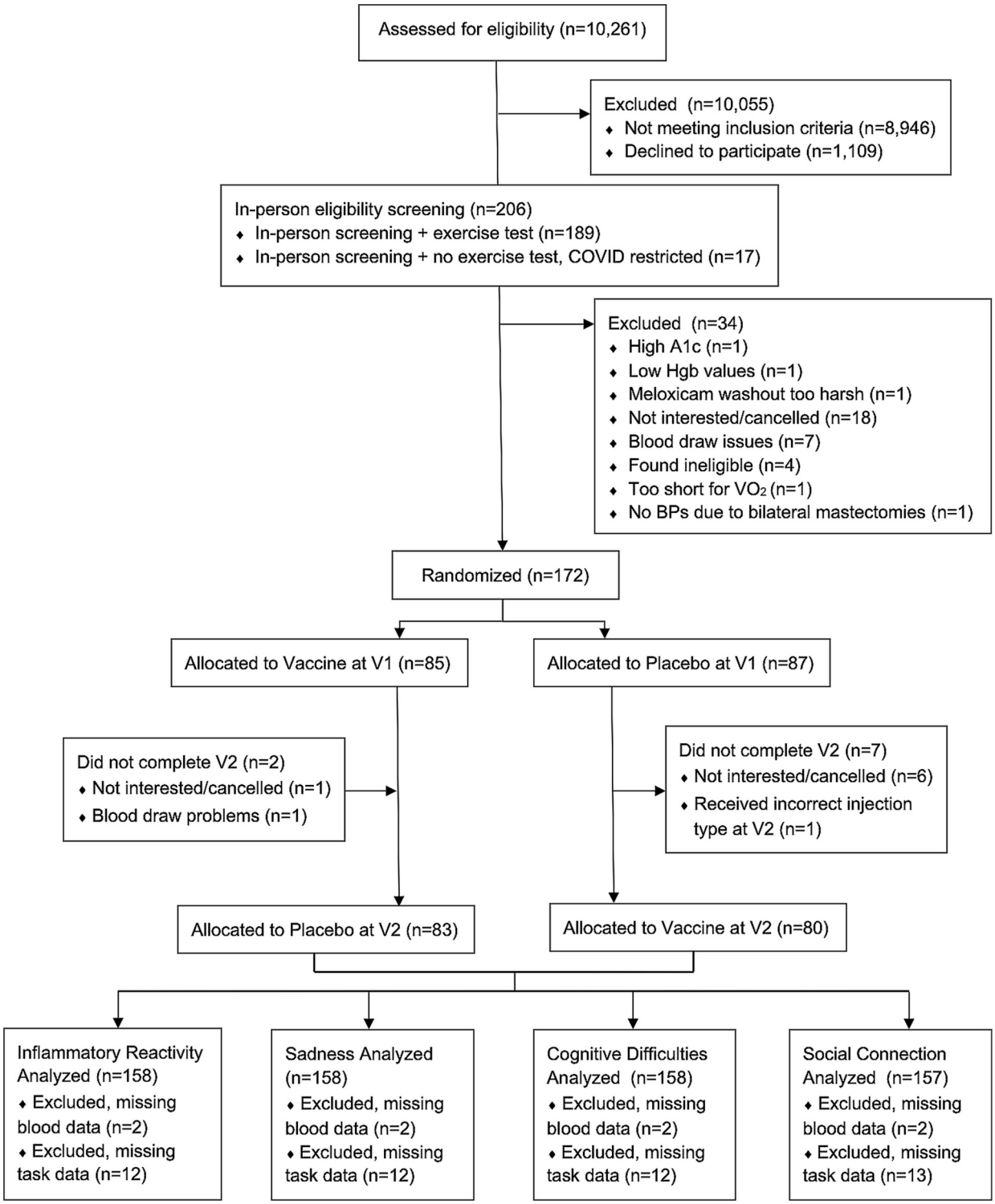

Fig. 1. Flow of Participants through the Study.

America (Guadamuz et al., 2022), and Murto et al. (2023) reported that among 40.7% of female breast cancer survivors used statins since diagnosis. Recruiting relatively healthy breast cancer survivors was therefore difficult. Third, the time-intensive study, which included three in-person visits (a 2-hour screening visit and two 9.5-hour experimental visits) and a typhoid vaccine inflammatory challenge, led otherwise eligible individuals to decline participation. Together, these factors account for the large number of individuals screened who did not meet criteria or elected not to enroll.

2.2. Procedure

The study used a double-blind, randomized crossover design (Fig. 2). At the first of two full-day laboratory visits, participants were randomly assigned to receive either the vaccine-placebo or placebo-vaccine sequence. Each of the two laboratory visits lasted approximately 9.5 h, and visits were separated by 26–420 days ($M = 46.87$, $SD = 47.48$), with delays attributed to the COVID-19 pandemic (Kiecolt-Glaser et al., 2022). A data manager who was not involved in study visits oversaw the

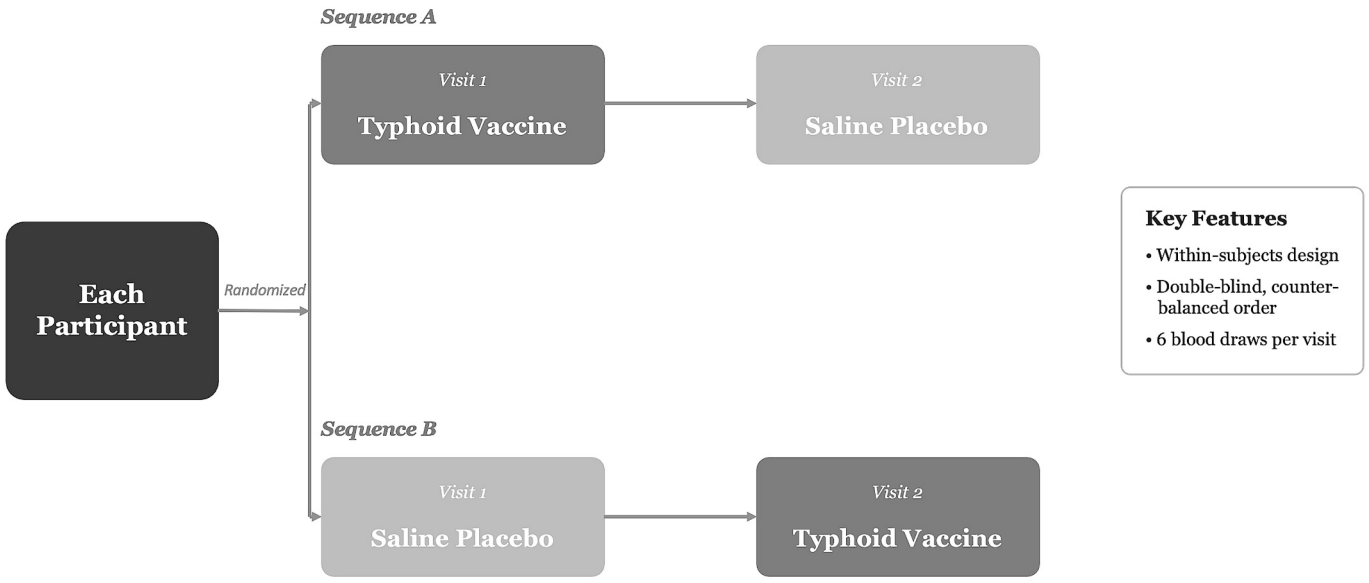

Fig. 2. Randomized crossover design.

randomization sequence. Research assistants were blinded to condition, and the nurse administering the injection differed from the nurse conducting blood draws throughout the visit. Blinding efficacy was evaluated using the Bang et al. blinding index (Bang et al., 2004). As expected, given differential arm discomfort between vaccine and placebo injections, participants demonstrated partial unblinding, whereas blinding remained highly effective among study staff (see Kiecolt-Glaser et al., 2022).

Participants were instructed to consume their final meal by 7:30 PM the evening before each visit. They were also asked to abstain from alcohol and vigorous physical activity for 48 h prior to each visit. Use of aspirin and other nonsteroidal anti-inflammatory drugs was discontinued for seven days prior to each visit. To minimize confounding from acute illness or recent vaccination, participants were instructed before the study visits to contact the study team and reschedule if they experienced illness with fever or flu-like symptoms, began antibiotics within two weeks of a visit, or received any vaccination within four weeks of a visit. Participants were also advised to schedule their two study visits during a time period when they were not planning to get a vaccine. On the day of each visit, temperature was measured, and participants with a temperature above 99.7 °F or sickness symptoms were rescheduled.

Upon arrival, an intravenous catheter was inserted, followed by a 20–30 min acclimation period before baseline blood collection. At around 8:30 AM after the baseline blood draw, a nurse injected either the saline placebo or the typhoid vaccine into the non-dominant deltoid muscle. Within five minutes before the injection, participants completed the baseline self-report questionnaires including the Self-Assessment Manikin scale and self-reported measures of focus and memory difficulty. The Social Connection Scale was completed within five minutes after the injection, prior to any vaccine-induced inflammatory response (Paine et al., 2013; see details below). They then consumed a standardized breakfast. Subsequent blood samples were collected at 90-minute intervals over a 7.5-hour period. At each visit, IL-6 was measured at six time points (baseline, 1.5, 3, 5, 6.5, 8 h post-injection) and assessments of Self-Assessment Manikin scale and self-reported measures of focus and memory difficulty were completed with each blood draw (Supplemental Fig. 1). The Social Connection Scale was completed a second time approximately 8.5 h after the injection aligning with the peak inflammatory response to the typhoid vaccine which typically occurs 6–8 h post-injection (Paine et al., 2013; Supplemental Fig. 1).

2.3. Questionnaires

2.3.1. Early life adversity

ELA was assessed at a single timepoint during the initial screening visit using two measures: the Childhood Trauma Questionnaire Short Form (CTQ-SF; Bernstein et al., 2003) and the Kessler Childhood Adversity Index (Kessler and Magee, 1993). Consistent with recommendations in the literature, we used multiple measures to capture the multidimensional nature of ELA and examined each index separately in analyses (Evans et al., 2013).

The CTQ-SF is a 28-item questionnaire that retrospectively assesses participants' exposure to five types of childhood maltreatment: emotional abuse, physical abuse, emotional neglect, physical neglect, and sexual abuse (Cronbach's $\alpha = 0.93$). The CTQ-SF assesses subjective perceptions of maltreatment severity and frequency (e.g., *"I felt loved", "I believe that I was emotionally abused", "I thought my parents wished I had never been born"*). Participants rated each item on a 5-point Likert scale, ranging from 1 (never true) to 5 (very often true). Following established scoring procedures (Walker et al., 1999), clinically significant cutoff scores were: emotional abuse $\geq$10, physical abuse $\geq$8, emotional neglect $\geq$15, physical neglect $\geq$8, and sexual abuse $\geq$8. The total CTQ-SF Walker sum score thus ranged from 0 to 5, reflecting the number of maltreatment types meeting the clinical threshold.

The Kessler Childhood Adversity Index assesses nine types of ELA using a dichotomous yes/no response format. It captures objective, discrete major life events occurring before age 17 within the immediate family. In the present study, we included only seven items (i.e., immediate family drinking problem, immediate family mental illness, serious parental marital problems, death of mother, death of father, parental separation, and maternal exposure to abuse or violence) based on a landmark study demonstrating that these seven items are the most predictive of depression (Kessler & Magee, 1993).

2.3.2. Sadness

Sadness was assessed six times per visit using the Self-Assessment Manikin (SAM) scale. Specifically, the sadness-to-happiness pictorial continuum, a 9-point visual analog scale, was used to capture intensity of sadness (Bradley and Lang, 1994).

2.3.3. Cognitive difficulties

Cognitive difficulties were assessed six times per visit through participants' subjective reports of focus and memory difficulty. Participants rated the intensity of their focus and memory difficulties on a 10-point Likert scale following each blood draw, with higher scores indicating greater cognitive difficulty (Kiecolt-Glaser et al., 2022).

2.3.4. Social connection

Social connection was assessed twice at each visit using an eight-item Social Connection Scale. Participants rated their current feelings of social connection on a seven-point Likert scale, ranging from 0 (strongly disagree) to 6 (strongly agree). Each item began with the prompt, "Right now I feel" followed by statement such as "disconnected from other people", "lonely", "loved by other people", or "cared for by other people" (αs = 0.83——0.87 across administrations) (Jaremka et al., 2017).

2.4. Inflammation

Multiple typhoid vaccine studies have shown that the typhoid vaccine reliably induces significant increases in IL-6 reactivity (Brydon et al., 2009; Chia et al., 2003; Paine et al., 2013). Previous systematic reviews and *meta*-analyses illustrate associations between ELA and IL-6 (Baumeister et al., 2016; Kuhlman et al., 2020a), and between depression and IL-6 (Dowlati et al., 2010), with more recent work demonstrating that IL-6 shows robust effects at the intersection of ELA, depression, and broader psychiatric disorders (Gill et al., 2020; Zagaria et al., 2024; Den Noortgate et al., 2025). Also, Kuhlman et al. (2020b)—the study that we seek to replicate and extend—focused on IL-6; therefore, we chose to do so as well. However, in a sensitivity analysis, we tested whether results held for interleukin-1 receptor antagonist (IL-1Ra), which was measured at three time points (baseline, 6.5, 8 h post-injection), consistent with its slower response timescale relative to IL-6 (Table S2).

To minimize assay variability, all serum samples for each participant were assayed in a single run using the same reference standards across time points. Serum IL-6 was assayed with the Quantikine HS ELISA kit (R & D Systems, Minneapolis, MN), and serum IL-1Ra was assayed using an electrochemilluminescence method with Meso Scale Discovery kits. The IL-6 assay had a sensitivity of 0.03 pg/mL, and the corresponding value was 6.3 pg/mL for IL-1Ra. The inter-assay coefficients of variation for IL-6 and IL-1Ra were 6.5% and 8.6%, respectively, and the intra-assay coefficients of variation were both 4.1%.

2.4.1. Analytic method

We computed a zero-order correlation among key study variables at Visit 1, included in the regression analyses (Table 2). Prior to hypothesis testing, changes in IL-6, sadness, memory difficulty, and focus difficulty were quantified using AUCi, such that higher scores reflected greater increases from pre- to post-vaccine. For social connection, the second timepoint was analyzed while controlling for the first timepoint.

All primary analyses were conducted using linear mixed-effects models to account for repeated measures within participants, and each predictor/outcome combination was examined in separate models. These models maximize the use of all available data by including participants with incomplete data. Random intercepts were specified for each participant to account for within-subject correlations both within and between visits. Covariates included type of visit, trunk fat mass, chemotherapy treatment, radiation treatment, age, and baseline levels of the relevant predictor and outcome variables (e.g., basal IL-6, focus, memory, sadness, or social connection) for all models. Statistical significance was determined using two-tailed $\alpha = 0.05$. All analyses were conducted in R version 4.5.1.

The first set of models examined the interaction between each ELA index (CTQ-SF Walker sum score or Kessler Childhood Adversity Index) and injection type to predict IL-6 AUCi. The second set of models examined whether early life adversity moderated the association between IL-6 AUCi and psychological outcomes. Separate models were conducted for each outcome variable: subjective sadness, focus difficulty, memory difficulty, and social connection. For significant ELA × IL-6 AUCi interactions, simple slopes were probed at ELA = 0, 1, and 2, as most participants fell within this range (CTQ-SF Walker sum cutoff score: 82.4%; Kessler Childhood Adversity Index: 48.8%). All semi-partial effects were obtained using partR2 package in R, which estimates the unique variance explained by a specified predictor in a mixed model (Nakagawa and Schielzeth, 2013). The third set of models tested whether early life adversity moderated the effect of injection type on the same psychological outcomes.

The analytic sample size varied slightly across models due to intermittently missing data (see Fig. 1). Excluded participants did not differ significantly from included participants on any key demographic variable, with the exception of chemotherapy treatment. All 15 excluded participants had received chemotherapy, compared to a lower proportion among included participants (Fisher's exact test, $p = 0.003$).

As sensitivity analyses, all primary models were re-run under three alternative specifications. First, models were adjusted for time from cancer treatment to baseline visit and the number of days between visits, which reduced the analytic sample by 6–8 participants due to missing covariate data. Second, models were re-run using the CTQ-SF total sum score in place of the CTQ Walker sum cutoff, which reduced the sample by 11 participants (5 had missing items within the CTQ-SF, and the remainder did not complete the CTQ-SF). Third, models were re-run using an additional inflammatory marker, IL-1Ra.

Table 2
Zero order correlations for all key study variables at Visit 1.

	Correlations										
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. Age	1.00										
2. Trunk fat, kg (DXA)	−0.02	1.00									
3. Chemotherapy treatment	−0.21**	0.06	1.00								
4. Radiation treatment	0.13	0.04	−0.07	1.00							
5. CTQ-SF Walker Sum Cutoff +	−0.03	0.09	0.09	0.04	1.00						
6. Kessler Childhood Adversity Index+	−0.24**	0.08	0.08	0.01	0.57***	1.00					
7. Baseline focus difficulty	−0.04	−0.03	0.13	0.05	0.17*	0.18*	1.00				
8. Baseline memory difficulty	−0.02	−0.05	0.03	0.13	0.15	0.12	0.78***	1.00			
9. Baseline sadness	−0.18*	0.11	0.03	0.07	0.16*	0.20*	0.18*	0.22**	1.00		
10. Baseline social connection	0.29***	−0.05	−0.02	−0.15*	−0.16*	−0.20*	−0.23**	−0.26**	−0.57***	1.00	
11. Fasting IL-6, pg/mL	0.07	0.17*	0.09	0.09	0.01	−0.05	−0.01	−0.02	0.03	0.01	1.00

+ Assessed at screening visit.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

3. Results

3.1. Preliminary results

Table 2 provides the descriptive statistics and zero-order correlations for all key variables at Visit 1. As expected, the CTQ-SF Walker sum score and the Kessler Childhood Adversity Index were moderately correlated ($r = 0.56$, $p < 0.001$), reflecting shared variance. However, given conceptual differences in the types of adversity assessed by each measure, they were analyzed in separate models in subsequent analyses. Notably, greater CTQ-SF Walker sum score and Kessler Childhood Adversity Index were significantly associated with higher baseline sadness and lower social connection scores ($ps < 0.05$), but not with basal IL-6 ($ps > 0.55$).

Participants' scores on the five CTQ-SF Walker sum cutoff (Walker et al., 1999) subscales (i.e., emotional abuse, physical abuse, emotional neglect, physical neglect, and sexual abuse) showed that 59.5% did not meet the clinical cutoff for any abuse or neglect subscale, 17.7% met criteria on one subscale, 5.1% on two, 9.5% on three, 5.1% on four, and 3.2% on all five subscales ($M = 0.93$, $SD = 1.41$), indicating that a notable proportion of participants experienced moderate to severe maltreatment in one or more domains. For emotional abuse, 24.1% of participants met the cutoff score, followed by 22.3% for physical neglect, 16.7% for emotional neglect, 15.2% for sexual abuse, and 14.6% for physical abuse. A total of 8.3% of participants met clinically significant cutoffs across four or more maltreatment domains. Given that the CTQ-SF Walker sum cutoff represents the breadth of clinically significant exposure across distinct maltreatment subtypes, this percentage may represent a particularly high-risk subgroup, as endorsing clinical thresholds across four or more domains aligns closely with the polyvictimization threshold (Finkelhor et al., 2007). For the Kessler Childhood Adversity Index, participants endorsed between 0 and 7 (maximum) counts of adverse events, with a mean score of 1.36 ($SD = 1.58$). The distribution was as follows: 41.8% of participants reported no adverse event, while 22.2% endorsed 1 adverse event, 12.7% endorsed 2 or 3 adverse events, and smaller percentages (5.7%, 3.2%, 1.3%, and 0.6%) endorsed 4, 5, 6, or 7 adverse events, respectively. A total of 10.8% of participants endorsed four or more adverse events, consistent with the threshold identified in the epidemiological literature as conferring greatest risk (Bhushan et al., 2020).

3.2. Inflammatory reactivity

As previously reported, participants in the typhoid vaccine condition showed significantly higher IL-6 reactivity compared to the placebo at all postbaseline measurement timepoints ($F(4, 1247) = 82.38$, $p < 0.0001$; Madison et al., 2023; Table S1). Neither the CTQ-SF Walker sum score ($p = 0.53$) nor the Kessler Childhood Adversity List ($p = 0.17$) moderated the effect of injection type on the inflammatory response. The two ELA indices also did not moderate vital sign responses (heart rate, systolic and diastolic blood pressure, temperature) to typhoid vaccine versus saline placebo (Table S3).

3.3. Sadness

CTQ-SF Walker sum scores did not moderate the effect of IL-6 reactivity on sadness ($p = 0.84$), whereas the Kessler Childhood Adversity Index did ($b = 0.02$, $SE = 0.01$, $t(138) = 2.19$, $p = 0.030$, $R^2_{sp} = 0.01$). For 0 and 1 adverse event, IL-6 reactivity was not significantly associated with change in sadness ($ps > 0.09$). However, the association became significant among individuals reporting two or more adverse events (Fig. 3). For example, at ELA = 2, greater IL-6 reactivity predicted larger increases in sadness AUCi ($b = 0.03$, $SE = 0.01$, 95% CI [0.01, 0.06], $p = 0.015$, $R^2_{sp} = 0.02$), and similar patterns emerged for >2 adverse events. Neither CTQ-SF Walker sum cutoff score ($p = 0.63$) nor Kessler Childhood Adversity Index ($p = 0.29$) significantly moderated the effect of injection type on sadness AUCi.

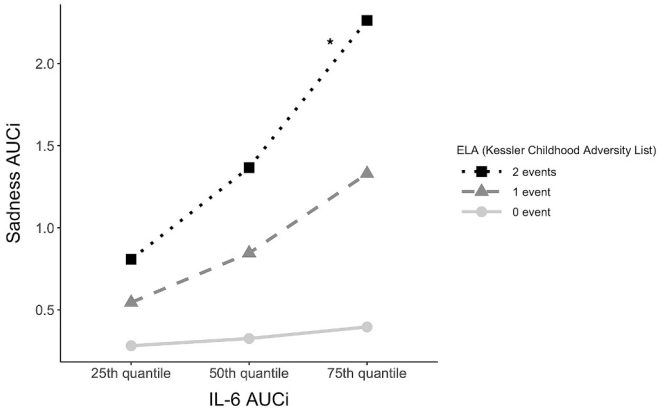

Fig. 3. Early life adversity (indexed by Kessler Childhood Adversity Index) moderated the association between IL-6 reactivity and change in sadness, such that among individuals with ≥2 adverse events, greater IL-6 reactivity was associated with increases in sadness AUCi but not among individuals endorsing zero or one adverse event. *indicates a significant slope.

3.4. Cognitive difficulties

The CTQ-SF Walker sum scores trended toward moderating the relationship between IL-6 reactivity and change in memory difficulty ($b = 0.01$, $SE = 0.01$, $t(137) = 1.84$, $p = 0.067$, $R^2_{sp} = 0.01$). Simple slopes analysis revealed that among individuals with higher CTQ-SF Walker sum scores, those with greater IL-6 reactivity had marginally increased memory difficulties. For a CTQ-SF Walker sum score of 0, IL-6 reactivity was not associated with memory difficulty ($p = 0.36$), whereas at the maximum CTQ-SF Walker sum score of 5, IL-6 reactivity showed a positive, trending association ($b = 0.06$, $SE = 0.04$, 95% CI [-0.01, 0.13], $p = 0.094$). This effect was not observed with the Kessler Childhood Adversity Index ($p = 0.99$).

The CTQ-SF Walker sum scores significantly moderated the relationship between IL-6 reactivity and change in focus difficulty ($b = 0.02$, $SE = 0.01$, $t(137) = 1.99$, $p = 0.048$, $R^2_{sp} = 0.01$). However, simple slopes analysis showed that the association was not statistically significant at any observed CTQ-SF Walker sum value, despite the effect trending in the same direction as the overall interaction. For a CTQ-SF Walker sum score of 0, IL-6 reactivity was not associated with focus difficulty ($p = 0.23$), whereas at the maximum CTQ-SF Walker sum score of 5, IL-6 reactivity showed a positive, trending association with focus difficulty ($b = 0.07$, $SE = 0.04$, 95% CI [-0.01, 0.14], $p = 0.084$) (Fig. 4). This interaction was not significant when using the Kessler Childhood Adversity Index ($p = 0.70$).

Neither CTQ-SF Walker sum score nor the Kessler Childhood Adversity Index significantly moderated the effects of injection type on focus difficulty ($p = 0.30$, $p = 0.80$) or memory difficulty ($p = 0.25$, $p = 0.63$), respectively.

3.5. Social connection

The CTQ-SF Walker sum score ($p = 0.83$) and the Kessler Childhood Adversity Index ($p = 0.81$) did not moderate the relationship between IL-6 reactivity and feelings of social connection. Likewise, there was no evidence that early life adversity moderated the effect of injection type on social connection, as neither CTQ-SF Walker sum score ($p = 0.46$) nor Kessler Childhood Adversity Index ($p = 0.84$) yielded significant interaction effects.

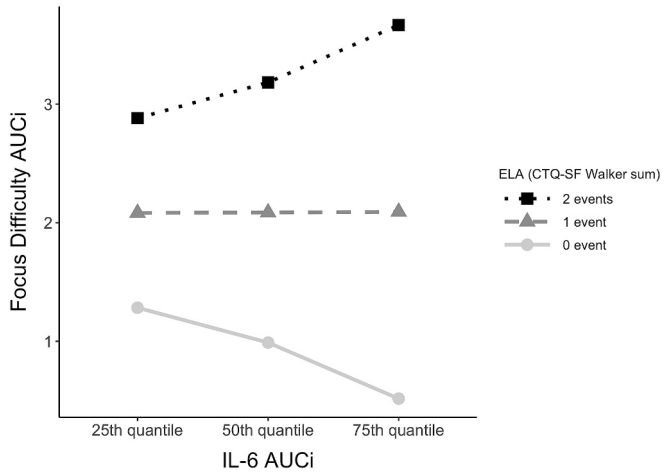

Fig. 4. Early life adversity (indexed by CTQ-SF Walker sum) significantly moderated the association between IL-6 reactivity and change in focus difficulty. Although simple slopes analysis was not statistically significant at any CTQ-SF Walker sum value represented in the sample, the effects consistently trended in the hypothesized direction.

3.6. Sensitivity analyses

First, when the models were adjusted for time from cancer treatment to baseline visit and the number of days between visits, the patterns were largely unchanged. The one exception was that the CTQ-SF Walker sum cutoff shifted from significant to trending in the relationship between IL-6 reactivity and focus difficulty ($p = 0.059$; see Table S4 for full sensitivity analysis results). Second, when the models were re-run with the CTQ-SF total sum score, the results were consistent, except interaction effects for focus difficulty became trending ($p = 0.082$) and memory difficulty became nonsignificant ($p = 0.186$; see Table S4 for full sensitivity analysis results). Third, when the models were re-run with IL-1Ra, all results were nonsignificant ($ps > 0.124$; see Table S5 for full sensitivity analysis results).

4. Discussion

This study leveraged a robust immune stimulus experimental model to examine whether early life adversity confers heightened psychological sensitivity to IL-6. Using the typhoid vaccine, we replicated and extended Kuhlman et al. (2020b) in a larger and more rigorously controlled study design. Consistent with prior findings, early life adversity was not associated with greater vaccine-induced inflammatory or psychological reactivity. Rather, individuals with higher ELA were more psychologically and cognitively—but not socially—sensitive to IL-6 increases. Effect sizes were small, which is consistent with prior work showing that the typhoid vaccine is related to mild inflammatory responses (Kiecolt-Glaser et al., 2022; Sharpley et al., 2016) and sickness symptoms (Strike et al., 2004; Brydon et al., 2009), as well as with *meta*-analytic evidence that ELA-inflammation associations in adulthood are small in magnitude (Baumeister et al., 2016). However, over time, similar effects occurring in the context of chronic systemic inflammation may become clinically meaningful—perhaps portending risk for inflammation-associated depression.

The current study and Kuhlman et al.'s (2020b) study showed that among individuals exposed to ELA, mild immune stimuli such as the influenza or the typhoid vaccine does not universally lead to heightened inflammatory reactivity. Although some studies have reported positive associations between ELA and inflammatory reactivity (Carpenter et al., 2010; De Koning et al., 2022; Dennison et al., 2012; Kuhlman et al., 2023), other studies using exogenous immune stimuli have similarly observed null effects (Bedwell et al., 2025; Kuhlman et al., 2020a, 2020b), as have studies using social stress paradigms such as the Trier Social Stress Test (Hantsoo et al., 2019; Schreier et al., 2020; Shalev et al., 2020). Other literature has also shown that ELA may not universally lead to heightened basal inflammation; resilience may moderate this relationship (Gouin et al., 2017). Together, these findings complicate a direct ELA-to-inflammation pathway to depression and instead suggest that immune responses to early adversity are heterogenous.

For inflammatory reactivity, the typhoid vaccine condition reliably showed significantly higher IL-6 reactivity than the placebo condition. The placebo group increase in IL-6 concentration (from 2.76 to 8.90 pg/mL, approximately three-fold) may be toward the higher end of typical diurnal fluctuation, for several reasons. First, even in healthy individuals, IL-6 shows marked circadian variation, with most pronounced changes occurring across the morning hours (Nilsonne et al., 2016). Moreover, the lab visits involved an intensive 9.5-hour laboratory day with repeated blood draws, and the sample consisted of breast cancer survivors, a clinical population with known immune dysregulation that may amplify cytokine fluctuations. Importantly, the vaccine condition produced a peak IL-6 response nearly double that of placebo, indicating a clear vaccine-specific effect independent of this diurnal drift and supporting the validity of the observed placebo-group difference.

Notably, only the Kessler Childhood Adversity Index, not the CTQ-SF Walker sum score, moderated IL-6 induced sadness. This finding supports our rationale to use the seven items from the Kessler Childhood Adversity Index that are most predicative of depression as reported by Kessler and Magee (1993). These results further support the Kessler Childhood Adversity Index as a measure capturing early life adversity linked to affective sensitivity, whereas this pattern was not evident when using the CTQ-SF Walker sum score. One possibility for this unique effect is that the Kessler Childhood Adversity Index primarily captures objective, discrete major life events that either occurred or not, often reflecting intense social threats within the immediate family context (e.g., parental separation, serious illness, death of parents). Such events may "tune" the neural systems that integrate social threat and immune signaling including the amygdala, anterior insula, and anterior cingulate cortex and thereby sensitize individuals to perceive inflammatory reactivity as an affective threat signal. This interpretation aligns with the Social Safety Theory of Depression (Slavich, 2020), whereby early exposure to uncontrollable social stressors may lead to increased inflammatory sensitivity and thus greater risk for depressive-like symptoms including increased sadness during inflammatory activation.

By contrast, the CTQ-SF Walker sum score moderated IL-6 induced cognitive difficulties. This sum score assesses more subjective perceptions of maltreatment and victimization over time (i.e., "I felt loved", "I felt that someone in my family hated me", "I believe that I was emotionally abused.") that may extend beyond the immediate family and emphasize more subjective retrospective interpretations of adversity—with the possibility for recall bias. Accordingly, CTQ-SF Walker sum score may be more strongly linked to cognitive difficulties following immune activation, consistent with prior evidence linking CTQ-SF to impairments in cognitive difficulties (King et al., 2023, 2021; Zhang et al., 2025). These findings undergird the benefits of employing a dual-measure approach to capture the complex nature of early life adversity (Evans et al., 2013; Shonkoff et al., 2012).

Finally, our results suggest that social connectedness may not significantly change following milder forms of immune challenge such as the typhoid or influenza vaccine, aligning with Kuhlman et al.'s (2020b) results. Madison et al. (2023) discusses that the strength of the inflammatory stimulus is a key determinant of whether perceived social connection or disconnection is impacted, depending on the magnitude of peak IL-6 reactivity. From a clinical perspective, mild inflammatory challenges, such as the typhoid or influenza vaccine, may serve as a more ecologically valid proxy for the inflammatory subtype of depression, as they do not elicit the exaggerated acute sickness behaviors typically observed in endotoxin paradigms (Lindsay, 2022).

Results were largely consistent across the first two sets of sensitivity

analyses. Adjusting for time from cancer treatment to baseline visit and days between visits did not significantly alter the pattern of findings, with the interaction predicting focus difficulty shifting from significant to trending, likely reflecting the primary model's proximity to the alpha threshold and modest data loss from missing covariate data. When models were re-run using the CTQ-SF total sum score, which similarly involved modest participant loss, the interaction predicting focus difficulty again became trending and the interaction predicting memory difficulty shifted from trending to nonsignificant. This shift may be due to data loss, or it could suggest that the breadth of clinically significant exposure, rather than overall severity, may be the more biologically meaningful dimension linking early life adversity to inflammation-related cognitive outcomes. For the third set of sensitivity analyses, models re-run using IL-1Ra were all nonsignificant. This contrast with IL-6 may reflect differences in how directly each marker captures its underlying signaling pathway. IL-1β exerts proinflammatory effects at low circulating concentrations, and immunoassays often lack the sensitivity to reliably detect (Cavalli and Dinarello, 2018). Thus, IL-1Ra, an endogenous antagonist produced in response to IL-1 signaling, has been used in prior research as an indirect index of IL-1 pathway activity, though it remains an indirect readout of IL-1 signaling. IL-6, by contrast, was measured directly and is known to cross the blood–brain barrier (BBB), reliably linking peripheral inflammation to both early life adversity and psychological symptoms. The null findings for IL-1Ra may therefore reflect the limitations of an indirect measurement rather than the absence of a true underlying association.

Although we did not test early life adversity's mechanisms directly, as it cannot be manipulated in humans, preclinical studies offer clues about the biological pathways that may underlie these effects. First, early life adversity may induce lasting alterations in microglial function that heighten the brain's sensitivity to peripheral inflammatory signals. Preclinical animal studies show that early life adversity is associated with persistent changes in microglial density, morphology, and inflammatory responses within the central nervous system (Ahmed et al., 2024b; Bilbo and Schwarz, 2012; Calcia et al., 2016), and early life stress has been linked to elevated inflammatory cytokines, including IL-6, within the brain itself (Lumertz et al. 2022). Both animal and human research link microglial activation to depression phenotypes (Holmes et al., 2018; Lehmann et al., 2016; Schnieder et al., 2014; Steiner et al., 2008; Wang et al., 2018). These microglial alterations can disrupt emotion- and cognition-related circuitry in regions such as the amygdala, hippocampus (HP), and prefrontal cortex (PFC) (Ahmed et al., 2024a; Bolton et al., 2022; Dayananda et al., 2023), thereby amplifying psychological responses to even moderate levels of peripheral inflammatory reactivity. Complementing this, emerging evidence suggests that peripheral myeloid lineage cells may also play a role, with non-classical monocytes implicated as drivers of immune dysregulation in ELA-exposed individuals, suggesting that early adversity may reprogram immune function at the cellular and molecular level in ways that extend beyond the CNS (Kuhlman et al., 2024).

Second, early life adversity may compromise BBB integrity. Stress- and inflammation-related changes following early life adversity can increase BBB permeability, allowing peripheral cytokines or immune cells to infiltrate the CNS and potentiate neuroinflammatory responses (Danese and Lewis, 2017; Solarz et al., 2023). Supporting this pathway, chronic social stress increased BBB permeability in the nuclear accumbens in mice, facilitating IL-6 infiltration and promoting depression-like behaviors (Menard et al., 2017). Peripheral cytokines may also stimulate astrocytes or endothelial cells at the BBB to produce central cytokines, propagating inflammatory signals without direct immune-cell infiltration (Danese and Lewis, 2017).

Thirdly, the lens of predictive processing theory offers a complementary psychological mechanism (Kaye and Krystal, 2020; Kube et al., 2020; Ramamurthy and Chen, 2025). Individuals with ELA may develop perseverative cognitive patterns and negative expectations about their bodily and emotional states (Krugers et al., 2017). When an immune challenge elicits fewer symptoms than expected, this mismatch known as prediction error, may buffer against negative mood such as sadness. However, individuals exposed to ELA may have negative cognitive schemas that are resistant to updating, leading them to interpret bodily symptoms negatively and thereby amplify the psychological effects of IL-6. Interventions that target maladaptive expectations or facilitate more adaptive interpretations of interoceptive prediction errors may be a promising avenue for improving psychological outcomes among individuals exposed to ELA.

Our findings suggest that early life adversity functions as a context-dependent moderator, such that among individuals exposed to ELA, those with greater inflammatory reactivity of IL-6 show the most pronounced psychological responses following immune stimulus. Clinically, this highlights the importance of identifying individuals with a history of early life adversity who also display heightened physiological reactivity to stress (e.g., elevated blood pressure, heart rate, or autonomic arousal during routine medical visits). This may be particularly relevant for ELA-exposed middle-aged female breast cancer survivors, a population at elevated risk for both depressive symptoms and inflammation-related health outcomes. For these individuals, heightened physiological sensitivity to stress may warrant closer monitoring during medical visits not only for physical health concerns, but also for inflammation-associated depressive symptoms. Such physiological sensitivity may serve as an accessible indicator of vulnerability, given established links between sympathetic nervous system activation and inflammatory reactivity (Griton and Konsman, 2018; Körner et al., 2019; Kox et al., 2014). These results underscore the value of assessing both stress history and stress-reactivity profiles when evaluating risk for depression, as this combination may help pinpoint individuals who are most susceptible to inflammation-related mood disturbances.

A key strength of this study is the use of the typhoid vaccine as an immune challenge, offering an ethically viable and ecologically valid model of low-grade inflammation without the confounding sickness behaviors induced by endotoxin administration. A second strength is the focus on a high-risk population of middle-aged female breast cancer survivors, allowing examination of ELA-related inflammation–depression pathways in a group particularly vulnerable to immune dysregulation. We also used a dual-measurement approach to index ELA, which allowed us to differentiate the multidimensional nature of the construct. Lastly, the within-subjects design with a saline placebo and larger sample improves statistical power, controls for individual differences, and enables more precise characterization of immune and psychological responses across time.

Despite these strengths, several limitations should be acknowledged. Future studies with a broader distribution of early life adversity are warranted. The current sample was not specifically recruited for high early life adversity, and likely due to limited variability, simple slopes were non-significant when probing interactions for the cognitive outcomes. Second, while an acute immune challenge provides a valuable experimental model of inflammation-related mood and cognitive changes, its relevance to chronic, low-grade inflammation remains uncertain. Third, while the within-subjects design controlled for individual variability and increased statistical power, this design also led to partial unblinding of the participants, which may affect the outcomes of interest as they were self-reported rather than clinician-rated. Finally, the sample was racially homogeneous and consisted exclusively of female breast cancer survivors, limiting generalizability. The sample was also relatively healthy, as individuals taking anti-inflammatory medications or with a range of comorbid medical conditions were excluded. We therefore cannot determine whether these effects extend to individuals of other racial backgrounds, to males, to those without a history of breast cancer, or to individuals with the medical and medication-related conditions excluded here. Nonetheless, observing significant effects within such a homogeneous sample highlights the importance of replicating these findings in more diverse and clinically varied populations.

Future studies could extend this work by (1) using stronger immune

stimuli, such as replicating Irwin et al.'s (2019) endotoxin paradigm in female-only samples, given the stronger ELA-inflammation and inflammation-depression associations in females, (2) examining whether individuals with ELA and heightened inflammatory reactivity are likely to develop more persistent depressive symptoms following other real-world inflammatory events (e.g., infection, surgery, chemotherapy), and (3) tracking inflammatory and symptom trajectories over longer periods. Replication in more diverse samples, including males, non–cancer populations, and individuals from varied racial and socioeconomic backgrounds, will also be important for testing the generalizability of these conditional effects. Moreover, experimentally manipulating expectations about bodily symptoms or side effects in immune-challenge paradigms could help determine whether ELA-related differences in predictive processing further shape how inflammation translates into mood and cognitive disturbance. Lastly, because it is often assumed that heightened inflammatory responses translate to elevated basal inflammation, future work should empirically evaluate this assumption as well as determine whether CTRA gene expression profiles predict increased inflammatory reactivity to immune challenges, both untested but critical premises of current theoretical frameworks.

To our knowledge, this study represents the largest investigation to date examining the moderating role of early life adversity on typhoid vaccine-induced inflammatory responses and downstream effects on psychological sensitivity. Our findings suggest that among individuals with ELA, those with heightened inflammatory reactivity may be particularly vulnerable to IL-6′s psychological effects, highlighting a potential target for identifying and supporting individuals at risk for inflammation-associated depression.

CRediT authorship contribution statement

Lauren Y. Kim: . **Megan E. Renna:** Writing – review & editing. **M. Rosie Shrout:** Writing – review & editing. **John F. Sheridan:** Writing – review & editing, Resources. **Robert Wesolowski:** Writing – review & editing, Resources. **Anne M. Noonan:** Writing – review & editing, Resources. **Raquel E. Reinbolt:** Writing – review & editing, Resources. **William B. Malarkey:** Writing – review & editing, Resources. **Janice K. Kiecolt-Glaser:** Supervision, Resources, Methodology, Funding acquisition. **Annelise A. Madison:** Writing – review & editing, Validation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2026.106925.

Data availability

Data will be made available on request.

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