Childhood trauma and LPS-stimulated inflammation in adulthood: results from the Netherlands study of depression and anxiety

Koning, R.M.D.; Kuzminskaite, E.; Vinkers, C.H.; Giltay, E.J.; Penninx, B.W.J.H.

Brain, Behavior, and Immunity 106 (2022) 21–29

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Childhood trauma and LPS-stimulated inflammation in adulthood: Results from the Netherlands Study of Depression and Anxiety

Ricki M. de Koning [a], Erika Kuzminskaite [a], Christiaan H. Vinkers [a,b], Erik J. Giltay [c], Brenda W.J.H. Penninx [a,*]

[a] Amsterdam UMC location Vrije University Amsterdam, Department of Psychiatry, Boelelaan 1117, Amsterdam, The Netherlands, Amsterdam Public Health (Mental Health program) and Amsterdam Neuroscience (Mood, Anxiety, Psychosis, Stress & Sleep program) research institutes, Amsterdam, the Netherlands
[b] GGZ inGeest Mental Health Care, Amsterdam, The Netherlands
[c] Leiden University Medical Center, Department of Psychiatry, Leiden, The Netherlands

ARTICLE INFO

Keywords:
Childhood Trauma
Inflammation
Immune system
LPS
Cytokines

ABSTRACT

Background: Childhood trauma (CT) is robustly associated with psychiatric disorders including major depressive and anxiety disorders across the life span. The innate immune system may play a role in the relation between CT and stress-related psychopathology. However, whether CT influences the innate production capacity of cytokine levels following *ex vivo* stimulation by lipopolysaccharide (LPS), is currently unknown.

Methods: Using data from the Netherlands Study of Depression and Anxiety (NESDA, n=1237), we examined whether CT (emotional neglect, emotional, physical, and sexual abuse before the age of 16), assessed by the Childhood Trauma Interview, was associated with levels in supernatants of interferon (IFN)γ, interleukin-2 (IL-2), IL-4, IL-6, IL-8, IL-10, IL-18, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β, matrix metalloproteinase-2 (MMP-2), TNFα and TNFβ after *ex vivo* stimulation with LPS. Cytokines were analysed individually and cumulatively (overall inflammation index and number of cytokines in high-risk quartile (HRQ)) using linear regression analyses.

Results: After adjustment for demographic, lifestyle, and health-related covariates, total CT severity was associated with the overall inflammation index ($\beta = 0.085$, $P_{FDR} = 0.011$), the number of cytokines in HRQ ($\beta = 0.063$, $P_{FDR} = 0.036$), and individual markers of IL-2 ($\beta = 0.067$, $P_{FDR} = 0.036$), IL-6 ($\beta = 0.091$ $P_{FDR} = 0.011$), IL-8 ($\beta = 0.085$ $P_{FDR} = 0.011$), IL-10 ($\beta = 0.094$ $P_{FDR} = 0.011$), MCP-1 ($\beta = 0.081$ $P_{FDR} = 0.011$), MIP-1α ($\beta = 0.061$ $P_{FDR} = 0.047$), MIP1-β ($\beta = 0.077$ $P_{FDR} = 0.016$), MMP-2 ($\beta = 0.070$ $P_{FDR} = 0.027$), and TNFβ ($\beta = 0.078$ $P_{FDR} = 0.016$). Associations were strongest for individuals with severe CT, reporting multiple types or higher frequencies of trauma. Half of the findings persisted after adjustment for psychiatric status. The findings were consistent across different CT types.

Conclusion: Childhood Trauma is associated with increased LPS-stimulated cytokine levels, with evidence for a dose-response relationship. Our results highlight a dysregulated innate immune system capacity in adults with CT, which could contribute to an increased vulnerability for psychopathology and somatic disorders across the lifespan.

1. Introduction

Childhood trauma (CT), such as the experience of emotional neglect, emotional, physical, or sexual abuse before the age of 16, has been robustly associated with mental and physical illness later in life. Psychiatric disorders like depression or anxiety (Hughes et al., 2017; Kuzminskaite et al., 2021; Norman et al., 2012), and somatic disorders such as cardiovascular disease and type 2 diabetes (Goodwin and Stein, 2004;

Abbreviations: CIDI, Composite International Diagnostic Interview; CRP, C-reactive protein; CT, Childhood Trauma; CTI, Childhood Trauma Interview; CTQ-SF, Childhood Trauma Questionnaire - Short Form; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; LPS, lipopolysaccharide; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; TNF, tumour necrosis factor.

* Corresponding author.
E-mail addresses: rickidekoning@gmail.com (R.M. de Koning), e.kuzminskaite@amsterdamumc.nl (E. Kuzminskaite), c.vinkers@amsterdamumc.nl (C.H. Vinkers), e.j.giltay@lumc.nl (E.J. Giltay), b.penninx@amsterdamumc.nl (B.W.J.H. Penninx).

https://doi.org/10.1016/j.bbi.2022.07.158
Received 9 April 2022; Received in revised form 30 June 2022; Accepted 18 July 2022
Available online 20 July 2022

Jakubowski et al., 2018) are more common in adults with CT. Moreover, CT has been associated with worse psychiatric outcomes, such as recurrent and persistent depressive episodes (Nanni et al., 2012) and more comorbid psychiatric disorders (Cakir et al., 2016). While several underlying mechanisms for the relationship between CT and psychiatric and somatic disorders in adulthood have been proposed, non-resolving over-activation of the innate immune system has been researched with increasing interest in the past decade.

The innate immune system forms the evolutionarily conserved initial line of defence against pathogens and includes the skin as well as proinflammatory cytokines, signalling molecules that mediate the inflammatory response (Alberts, 2015). Importantly, these cytokines act on the brain to induce sickness behaviour, including depressed mood and dysfunctional cognition (Dantzer et al., 2008; van Eeden et al., 2020). Moreover, increased basal inflammatory markers (hereafter referred to as cytokines) have been found in psychiatric disorders such as major depression, schizophrenia and bipolar disorder (Baumeister et al., 2014). Previous systematic reviews and *meta*-analyses revealed CT associations with elevated basal interleukin-6 (IL-6), tumour necrosis factor α (TNFα), and C-reactive protein (CRP) levels in adulthood (Baumeister et al., 2016; Gill et al., 2020), thus possibly mediating the relation between CT and psychiatric disorders. However, a recent review found that most associations between CT and inflammation were non-statistically significant, although several significant results were found for abuse subtypes of CT (rather than neglect), and for CRP and IL-6 (rather than TNFα and IL-1β) (Brown et al., 2021). In line, earlier *meta*-analytic findings also revealed that sexual abuse was only associated with elevated TNFα levels, whereas physical abuse was associated with elevated levels of both TNFα and CRP, suggesting subtle differences between CT types (Baumeister et al., 2016).

Health and lifestyle factors might, at least partly, mediate the association between CT and inflammation. Body mass index (BMI) is the most established factor (Baumeister et al., 2016; Brown et al., 2021), but smoking and chronic diseases were recently found to partly explain the association as well (Kuzminskaite et al., 2020). It is essential to control for a wide array of such factors in the analysis. For example, CT has been associated with heavy drinking, which has pro-inflammatory effects (Campbell et al., 2016; Pilowsky et al., 2009). These and other health and lifestyle factors are less often considered. On the other hand, some evidence revealed that pro-inflammatory effects of CT persisted even after adjustment for health and lifestyle, suggesting potential direct effects of CT on inflammatory status in adulthood (Danese et al., 2007). Another factor of importance might be a dose-response association with more severe CT, characterized by the occurrence of more types and higher frequencies of trauma, being associated with low-grade inflammation (Bock et al., 2020; Danese et al., 2007; Grosse et al., 2016; Kuzminskaite et al., 2020). Taken together, previous research suggests that CT is linked to increased inflammation in adulthood, which might be partly explained by health-related and lifestyle factors, which strengths might differ among CT types and cytokines. Importantly, most previous studies on CT assess inflammation through basal cytokines (Baumeister et al., 2016). Nevertheless, using basal cytokine levels as a measure of immune dysregulation has limitations, as these are generally low, show large intra-individual variability, and may be strongly influenced by disease status and lifestyle factors such as levels of BMI (van der Linden et al., 1998; Vogelzangs et al., 2016). Alternatively, inflammation can be measured after lipopolysaccharide (LPS) stimulation. LPS, also called endotoxin, is part of the membrane of gram-negative bacteria and activates the innate immune system (Zielen et al., 2015) and upregulates cytokines *in vivo* as well as *ex vivo* (Tawfik et al., 2020; van der Linden et al., 1998; van Lier et al., 2019). Notably, both pro- and anti-inflammatory cytokines are strongly upregulated (Vogelzangs et al., 2016). In the *ex vivo* LPS challenge, blood is stimulated with LPS, and cytokine levels are subsequently measured. Therefore, the LPS challenge mimics natural immune challenges (Zielen et al., 2015), and reflects the innate production capacity of cytokines (Vogelzangs et al., 2016). Thus, levels of inflammatory markers measured after an LPS challenge likely provide a more functional account of immune system activity as compared to basal levels of inflammatory markers, which theoretically are expected to be most sensitive to CT. Additionally, since cytokines are produced in many cell types, such as adipocytes, basal levels of inflammatory markers largely reflect properties such as adiposity, whereas cytokines after LPS challenge are more directly produced by immune cells (Coppack, 2001; Ferrante, 2007). Moreover, since the LPS-stimulated cytokine levels are higher than basal levels, their levels are no longer near detection limits, allowing more different cytokine types to be measured. Therefore, levels of LPS-stimulated cytokines may be a more robust and more valid alternative to assess the activity of immune system than basal cytokine levels. Indeed, evidence suggests that LPS stimulated inflammation is more strongly increased than basal inflammation in mental and somatic diseases (van Eeden et al., 2021; van Exel et al., 2009; Vogelzangs et al., 2016).

With regard to CT, LPS-challenged cytokines have been researched only in a few small human and animal studies. CT has been found to correlate weakly but significantly with LPS-stimulated IL-6 in a partly schizophrenic population (King et al., 2021). In a study by Miller and Chen (2010), young women were repeatedly assessed over the course of 1.5 years, and it was found that the harsher the family climate they were raised in was, the more LPS stimulated IL-6 levels increased in these 1.5 years. In another study, low childhood socioeconomic status was associated with higher LPS-stimulated levels of IL-6 in adulthood, but only in the presence of recent adverse life events (John-Henderson et al., 2016). Conversely, it has also been found that early life adversity is not associated with stimulated IL-1β, IL-6, and TNFα levels (Engel et al., 2021), or even with decreased LPS-stimulated IL-6 (Elwenspoek et al., 2017). Additionally, several animal studies have been performed, in which evidence was found for increased LPS-stimulated cytokine levels such as IL-6 or TNFα (Hohmann et al., 2017), but this was not supported by findings from other studies (De Miguel et al., 2018; O'Mahony et al., 2009; Parent et al., 2017). All in all, increasing evidence suggests that LPS-stimulated cytokine levels might be positively associated with CT, but it is largely understudied in large samples, and only a few of the relevant cytokines have been examined.

This study aimed to further elucidate the association between CT and the innate immunity capacity, as measured by various cytokine levels after an LPS-challenge, using data from The Netherlands Study of Depression and Anxiety (NESDA). Considering the high heterogeneity of previous research regarding the effects of CT on specific cytokines, the strong intercorrelations between stimulated cytokine levels (van Eeden et al., 2020, supplementary material), and the need to create a more general measure of innate immune system over-activation, we additionally created two cumulative indices: average inflammation index and a number of cytokines in high-risk quartile (HRQ). Since previous literature is largely heterogenous, we had no specific expectations regarding individual CT types or cytokines and aimed for a more comprehensive understanding of the innate immune activation in relation to CT. It was hypothesized that CT, especially severe CT, would be associated with LPS-stimulated cytokines, and that the strongest associations would be seen with cumulative inflammatory indices.

2. Methods

2.1. Sample

Data used for the current study was retrieved from NESDA (N = 2981), an ongoing longitudinal cohort of Dutch fluent adults (18 - 65 years) with current or past depressive or anxiety disorders (78%), and healthy controls (22%) (Penninx et al., 2008). Those with the following primary clinical diagnoses were excluded: psychotic disorder, obsessive-compulsive disorder, bipolar disorder, and severe addiction disorder. The presence of a depressive disorder (major depressive disorder, dysthymia) and anxiety disorder (social phobia, generalized anxiety

disorder, panic disorder, agoraphobia) was assessed by the Composite International Diagnostic Interview (CIDI WHO, version 2.1) (Wittchen, 1994). At baseline, all participants were assessed for demographics, lifestyle, (mental) health, and biological factors. The ethical review board of each participating centre approved NESDA's protocol. All participants provided written informed consent. For more information on NESDA, see Penninx et al. (2008).

Due to operational reasons, the LPS challenge was only performed with the blood of participants included in the last year of baseline sample collection, and therefore LPS-data was available for a subsample of 1242 participants. Missing CT data led to a total of 1237 participants in the current study. The characteristics of the current sample did not differ from other NESDA participants (n = 1744), except age as they were on average 1.5 years older (42.7 (s.d. = 12.7) vs. 41.3 (s.d. = 13.3), P = 0.002). Remitted depression or anxiety was less common in the included than in the excluded sample (31.5% vs. 36.5%, P = 0.006), and a cold or a fever in the past week was slightly more common (29.8% vs. 26.3%, P = 0.04).

2.2. Childhood trauma

Trained research staff conducted a structured interview that assesses emotional neglect, emotional, physical, and sexual abuse before the age of 16 in a retrospective manner (Hovens et al., 2012). This interview was previously used in Netherlands Mental health Survey and Incidence Study (NEMESIS) (De Graaf et al., 2004). The CT NEMESIS questionnaire is largely similar to the Childhood Trauma Interview (CTI) (Hovens et al., 2012). In this questionnaire, each CT subtype is scored as "never" (0), "once or sometimes" (1), or "regularly, often, or very often" (2). Total CT severity was calculated as the sum of the subtype scores, therefore ranging between 0 - 8. (Hovens et al., 2012). Mild CT was conceptualized as CTI score 1–3, and severe CT as CTI score $\geq$ 4. The CTI has good psychometric properties (Fink et al., 1995) (Spinhoven et al., 2014).

As a sensitivity analysis, the CTI score was replaced in the main analyses with the self-reported Childhood Trauma Questionnaire (CTQ-SF) score, which was assessed during the 4-year follow-up. CTQ data were available for 952 participants (77.0%) of our sample. The CTQ data includes the aforementioned trauma types and physical neglect (Bernstein et al., 1994). However, because the physical neglect subscale has been found to show insufficient internal consistency (Spinhoven et al., 2014), it was not used in the current study. In the current analysis, the cumulative score of the CTQ-SF ranged from 20 -100, and the subtype scores from 5 - 25. The CTQ-SF has good psychometric properties (Spinhoven et al., 2014). In the current study, correlations between CTQ and CTI were moderate to strong, with the strongest correlation between total CT scores ($\rho = 0.68$, $P < 0.001$) (Fig. S1).

2.3. LPS-stimulated cytokine levels

The immune response of 18 cytokines was assessed by stimulating blood with LPS *ex vivo*. Venous whole blood samples were obtained at baseline in a 7 mL heparin coated tube (Greiner Bio-One, Monroe, NC, USA). In 10–60 min after blood draw, 2.5 mL blood was transferred to a PAXgene tube (Qiagen, Valencia, CA, USA). The remaining 4.5 mL blood was stimulated by adding LPS (10 ng/ml − 1 blood; *Escherichia coli*, Sigma, St. Louis, MO, USA). LPS-stimulated samples were laid flat and incubated at a slow rotation for 5–6 h at 37 °C. A 2.5 mL sample of this LPS-stimulated blood was transferred into a PAXgene tube. This LPS procedure was carried out at four laboratories (Amsterdam, Leiden, Groningen, and Heerenveen, The Netherlands).

Levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), IFNγ, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-18, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β, matrix metalloproteinase-2 (MMP-2), TNFα and TNFβ were assayed simultaneously for all available samples, using a multi-analyte profile (Human Cytokine MAP A v 1.0; Myriad RBM, Austin, TX, USA). This commercial platform adheres to stringent guidelines of quality control and has Clinical Laboratory Improvement Amendments (CLIA) approval. GM-CSF, IL-3, IL-5 and IL-7 yielded too many values under the detection limit and were therefore excluded from further analyses, leaving a total of 13 cytokines.

All cytokines were checked for normality and if necessary, they were log-transformed to approach normal distributions, and subsequently standardized into *z*-scores. Cytokine levels were analysed individually and cumulatively. All 13 cytokine levels after LPS-challenge were positively intercorrelated (Fig. S2), and CT was positively associated with all cytokines (Fig. S2). We created two cumulative scores: the inflammation index score was calculated as the mean of all 13 standardized cytokines, which were standardized into a *z*-score again. Additionally, for each cytokine, the fourth quartile was calculated and defined as the HRQ. Then, the number of cytokines in a HRQ was determined per participant, yielding a score that could range from 0 - 13.

2.4. Covariates

Demographic factors, lifestyle/health factors, and psychiatric status were included in the analysis. Demographic factors included age, sex, and education level (years). Health-related and lifestyle factors comprised alcohol use (drinks per week), smoking status (former or current vs. no smoker), physical activity (in MET-minutes, using the International Physical Activity Questionnaire (Craig et al., 2003)), number of chronic diseases (self-reported, and for which treatment was received; diseases included heart disease, diabetes, stroke, lung disease, osteoarthritis, cancer, ulcer, intestinal problem, liver disease, epilepsy, and thyroid gland disease), BMI, frequent statin use (ATC code: C10AA), or anti-inflammatory, anti-rheumatic, or anti-inflammatory medication use (ATC codes: M01A, M01B, A07EB, A07EC), and whether the participant had a cold or fever in the week prior the blood draw.

Psychopathology was assessed using the Composite International Diagnostic Interview (CIDI WHO, version 2.1) for depressive disorders (major depressive disorder and dysthymia) and anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, and agoraphobia) based on the DSM-IV criteria. The psychometric properties of the CIDI are good (Wittchen, 1994). The CIDI was administered by trained research staff. Since previous LPS-stimulated inflammation analyses in the same cohort found no differences in the association for depression versus anxiety disorders, but did for remitted versus current disorders (Vogelzangs et al., 2016), the participants were classified as having 'no depressive/anxiety disorder', 'current depressive/anxiety disorder' (presence in the last 6 months), or 'remitted depressive/anxiety disorder' (lifetime presence but not in the past 6 months).

2.5. Data analyses

All data analysis was performed in R, version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Demographic and health characteristics were described as means with standard deviations (SD), medians with interquartile ranges (IQR), or percentages.

To determine whether CT was associated with LPS stimulated cytokine levels, linear regression analyses were conducted. CT total severity score and CT subtype severity scores were used as predictors in separate analyses. In subsequent analyses, we compared mild CT (CTI score 1–3) to no CT, and severe CT (CTI score $\geq$ 4) to no CT. Additionally, effect sizes of these analyses were calculated using Cohen's d. Separate cytokine levels and the two cumulative indices, the index score and the number of cytokines in a HRQ, were the outcome variables. The 13 separate cytokines and two cumulative indices (15 in total) were corrected for multiple testing using a false discovery rate adjustment (FDR p-value < 0.05) (Benjamini and Hochberg, 1995).

To assess whether demographic factors, anti-inflammatory medication use, lifestyle/health, and psychiatric status could explain the effect

of total CT severity on inflammation, two models were created. Model 1 included basic adjustment (demographic covariates), anti-inflammatory medication use, and a cold or fever in the past week. Model 2 additionally included the remaining health-related and lifestyle covariates as mentioned in 2.4 'covariates'. To investigate whether psychiatric status explains the relation between total CT severity and inflammation, all main analyses were additionally performed while adding psychiatric status (two dummy-coded variables: current depressive/anxiety disorder or remitted depressive/anxiety disorder) as a covariate to model 2. To examine whether psychiatric status could moderate the association between total CT severity and cytokines, we additionally included two interaction terms between total CT severity and current depressive/anxiety disorder (yes/no), and total CT severity and remitted depressive/anxiety disorder (yes/no). Lastly, as a sensitivity analysis, the CTI score was replaced in the main analyses with the CTQ-SF score.

3. Results

3.1. Sample characteristics

The mean age of the sample (N = 1237) was 42.7 years (SD = 12.7). Most (65.6%) were female (Table 1). About half of the participants (47.8%, N = 591), experienced at least one type of CT. Of these, 331 (26.8%) experienced mild CT and 260 (21.0%) experienced severe CT. Most individuals with CT had a current or remitted anxiety/depressive disorder (87.8%, N = 519), which was also true for those without CT (65.0%, N = 420). Total CT severity correlated with IL-2 (Pearson correlation (R) = 0.075, P = 0.009), IL-6 (R = 0.083, P = 0.003), IL-8 (R = 0.117, P < 0.001), IL-10 (R = 0.093, P = 0.001), MCP-1 (R = 0.115, P < 0.001), MIP-1α (R = 0.069, P = 0.015), MIP-1β (R = 0.004, P = 0.004), MMP-2 (R = 0.086, P = 0.002), TNFβ (R = 0.078, P = 0.006), and the inflammation index (R = 0.093, P = 0.001) (Fig. S2). Sex, age, socioeconomic status, alcohol consumption, smoking, BMI, number of chronic diseases, and current depression were significantly associated with the inflammation index (Table S1).

3.2. Total CT severity

In model 1 (basic adjustment), there was a significant association between total CT severity and the LPS-stimulated inflammation index (β = 0.100, P_{FDR} = 0.001) and the number of cytokines in HRQ (β = 0.079, P_{FDR} = 0.008) (Table 2). Moreover, total CT severity was significantly associated with IL-2, IL-6, IL-8, IL-10, MCP-1, MIP-1α, MIP-1β, MMP-2 and TNFβ (β = 0.066–0.110, all P_{FDR} < 0.05). In model 2 (additional adjustment for lifestyle and health), total CT severity remained significantly associated with the inflammation index score and the number of cytokines in a high-risk quartile (β = 0.085, P_{FDR} = 0.011; β = 0.063, P_{FDR} = 0.036, respectively). Also, the individual cytokines significant in model 1 remained significant in model 2 (β = 0.061–0.094, all P_{FDR} < 0.05), although βs were slightly attenuated. This was mainly due to adjustment for smoking and BMI, which caused a drop in the effect of total CT severity on cytokine measures of at least 10%. When psychiatric status was added to model 2, IL-6, IL-8, IL-10, MCP-1, and the inflammation index remained significantly associated. No moderation by psychiatric status was observed (interaction terms: P_{FDR} > 0.05).

3.3. CT types

In model 1 (basic adjustment), severity of all four CT types was associated with cumulative and individual cytokine measures (Table S2). In model 2 (additional adjustment for lifestyle and health), emotional abuse severity was associated with the inflammation index score (β = 0.077, P_{FDR} = 0.024), the number of cytokines in HRQ (β = 0.062, P_{FDR} = 0.040) and 8 individual cytokines (β = 0.064–0.084, P_{FDR} < 0.05) (Table S3, Fig. 1). Although emotional abuse severity showed somewhat stronger associations, effects were very similar in magnitude across different CT types.

Table 1
Sample characteristics.

Characteristics	N	Mean (SD)/Median (IQR)/n (%)
Demographics		
Age in years, mean (SD)	1237	42.72 (12.68)
Sex, female, n (%)	1237	812 (65.64)
Lifestyle and Health		
Socio-economic status (years of education), mean (SD)	1237	12.27 (3.30)
Current smoker, yes, n (%)	1237	459 (37.11)
Alcohol consumption (drinks per week), median (IQR)	1237	3.74 (8.54)
Physical activity (1000 MET-min/wk), median (IQR)	1237	3.07 (3.42)
BMI (kg/m^3), median (IQR)	1237	24.74 (6.31)
Sickness prior to interview, yes (%)	1237	369 (29.83)
Number of chronic diseases, median (IQR)	1237	1.00 (1.00)
Current depressive and/or anxiety disorder (CIDI), yes, n (%)	1237	692 (55.94)
Remitted depressive and/or anxiety disorder (CIDI), yes, n (%)	1237	390 (31.53)
Frequent use of anti-inflammatory medication, yes, n (%)	1237	64 (5.17)
Frequent use of anti-depressant medication, yes, n (%)	1237	299 (24.17)
Childhood Trauma		
CTI total severity score, mean (SD)	1237	1.57 (2.08)
CTI emotional neglect, mean (SD)	1237	0.72 (0.93)
CTI emotional abuse, mean (SD)	1237	0.45 (0.81)
CTI physical abuse, mean (SD)	1237	0.19 (0.53)
CTI sexual abuse, mean (SD)	1237	0.21 (0.49)
CTQ-SF total severity score, mean (SD)	952	39.39 (14.34)
CTQ-SF emotional neglect, mean (SD)	952	12.38 (5.19)
CTQ-SF emotional abuse, mean (SD)	953	8.68 (4.58)
CTQ-SF physical abuse, mean (SD)	953	5.99 (2.71)
CTQ-SF sexual abuse, mean (SD)	953	4.89 (2.78)
Cytokines after LPS induction		
IFNγ (pg/mL), median (IQR)	1237	10 (7.63)
IL-2 (pg/mL), mean (SD)	1237	9.55 (5.18)
IL-4 (pg/mL), median (IQR)	1237	8.61 (9.67)
IL-6 (ng/mL), median (IQR)	1237	25.70 (18)
IL-8 (ng/mL), median (IQR)	1237	10.40 (8.56)
IL-10 (pg/mL), median (IQR)	1237	204 (280)
IL-18 (pg/mL), median (IQR)	1237	249 (102)
MCP-1 (ng/mL), median (IQR)	1237	1.50 (1.26)
MIP-1α (ng/mL), median (IQR)	1237	17.70 (13.00)
MIP-1β (ng/mL), median (IQR)	1237	234.00 (147.00)
MMP-2 (pg/mL), median (IQR)	1237	72.90 (20.40)
TNFα (ng/mL), median (IQR)	1237	2.80 (2.31)
TNFβ (pg/mL), mean (SD)	1237	314.22 (135.66)

Note. Not-normally distributed outcome variables are presented as medians with interquartile ranges. Abbreviations: SD: standard deviation; IQR: interquartile range; 1000 MET-min/wk: 1000 metabolic equivalent minutes in the past week; BMI: body mass index kg/m^2, kilograms divided by the square of the height in meters; CIDI: Composite International Diagnostic Interview; CTI: Childhood Trauma Interview; CTQ-SF: Childhood Trauma Questionnaire – Short Form; IFN: interferon; IL: interleukin; MCP: monocyte chemotactic protein; MIP: macrophage inflammatory protein; MMP: matrix metalloproteinase; TNF: tumour necrosis factor; Ng/L: nanograms per liter; Pg/mL: picograms per liter.

3.4. Mild and severe CT versus no CT

In models 1 (basic adjustment) and 2 (additional adjustment for lifestyle and health), mild CT was neither significantly associated with the individual nor the cumulative measures of cytokines (Tables S4 and S5, Fig. 2). In contrast, severe CT was associated with the inflammation index score, the number of cytokines in HRQ and almost all individual

Table 2
Regression results of total childhood trauma score (CTI) associated with standardized cytokine levels.

	Model 1 (Basic adjustment)				Model 2 (Additional lifestyle/health adjustment)			
	β[†]	SE[‡]	P	P_{FDR}	β[†]	SE[‡]	P	P_{FDR}
IFNγ	0.058	0.029	**0.044**	0.055	0.057	0.029	0.052	0.065
IL-2	0.066	0.029	**0.021**	**0.029**	0.067	0.029	**0.022**	**0.036**
IL-4	−0.008	0.029	0.780	0.780	−0.008	0.029	0.781	0.781
IL-6	0.104	0.028	**<0.001**	**0.001**	0.091	0.029	**0.002**	**0.011**
IL-8	0.110	0.028	**<0.001**	**0.001**	0.085	0.028	**0.003**	**0.011**
IL-10	0.106	0.029	**<0.001**	**0.001**	0.094	0.029	**0.001**	**0.011**
IL-18	0.047	0.028	0.092	0.098	0.025	0.028	0.373	0.400
MCP-1	0.108	0.028	**<0.001**	**0.001**	0.081	0.028	**0.004**	**0.011**
MIP-1α	0.073	0.028	**0.011**	**0.016**	0.061	0.029	**0.034**	**0.047**
MIP-1β	0.095	0.028	**0.001**	**0.002**	0.077	0.028	**0.007**	**0.016**
MMP-2	0.085	0.028	**0.003**	**0.006**	0.070	0.029	**0.014**	**0.027**
TNFα	0.051	0.028	0.070	0.080	0.051	0.029	0.073	0.085
TNFβ	0.086	0.029	**0.003**	**0.006**	0.078	0.029	**0.007**	**0.016**
High-risk Q	0.079	0.028	**0.005**	**0.008**	0.063	0.028	**0.024**	**0.036**
Inflammation index	0.100	0.028	**<0.001**	**0.001**	0.085	0.028	**0.003**	**0.011**

Note: model 1: adjusted for age, sex, years of education, and anti-inflammatory medication use, and a cold or fever in the past week. Model 2: adjusted for age, sex, years of education, anti-inflammatory medication use, alcohol consumption, smoking, physical activity, body mass index, and number of chronic diseases. Abbreviations: CTI: Childhood Trauma Interview; Q: quartile; SE: standard error; FDR: false discovery rate; IFN: interferon; IL: interleukin; MCP: monocyte chemotactic protein; MIP: macrophage inflammatory protein; MMP: matrix metalloproteinase; TNF: tumour necrosis factor. Boldface indicates statistical significance ($p < 0.05$).
[†] Standardized beta.
[‡] Standard error of the standardized beta.

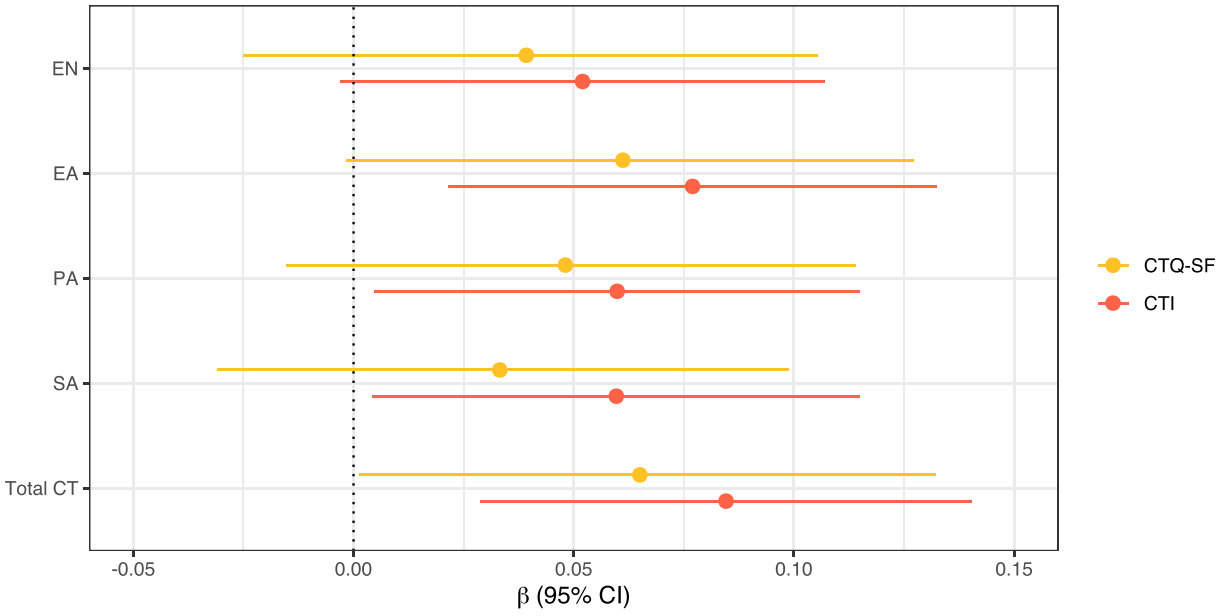

Fig. 1. Forest plot of β and corresponding 95% confidence intervals of the associations of CT subtypes as measured with the CTI and CTQ-SF, and the inflammation index in model 2. Note: model 2: adjusted for age, sex, years of education, anti-inflammatory medication use, a cold or fever in the past week, alcohol consumption, smoking, physical activity, body mass index, and number of chronic diseases. Abbreviations: CT: Childhood Trauma; CTI: Childhood Trauma Interview; CTQ-SF: Childhood Trauma Questionnaire Short Form; EN: Emotional Neglect; EA: Emotional Abuse; PA: Physical Abuse; SA: Sexual Abuse. * P_{FDR} of $\beta < 0.05$.

cytokines (in model 2, individual cytokines: β = 0.062–0.097, $P_{FDR} < 0.05$, d = 0.138–0.214; inflammation index score: β = 0.084, $P_{FDR} = 0.019$, d = 0.187; number of cytokines in HRQ: β = 0.067, $P_{FDR} = 0.041$, d = 0.148).

3.5. Sensitivity analysis

In sensitivity analysis, all main analyses were rerun using the CTQ-SF-score as a measure for CT (n = 952). Although most effects of total CT severity and subtypes measured by the CTQ after FDR adjustment were not significant in model 1 and model 2, they were very similar in magnitude to the results obtained with the CTI (Fig. 1). For instance, in model 2, the β value of CT (CTI) with the inflammation index was 0.085, and 0.065 in the sensitivity analysis (CTQ). The β value of the association between CT (CTI) and the number of cytokines in a HRQ was 0.063, and 0.065 in the sensitivity analysis (CTQ) (Table 2, Table S6).

4. Discussion

To our knowledge, this study was the first to investigate a large variety of LPS-stimulated cytokine levels in adults with a history of CT. We analysed thirteen cytokines, among which some have not been researched in the context of CT before, and two indices that integrated all cytokines. Higher total CT severity was associated with higher levels of the LPS-stimulated inflammation index, the number of cytokines in HRQ, and individual cytokines of IL-2, IL-6, IL-8, IL-10, MCP-1, MIP-1α,

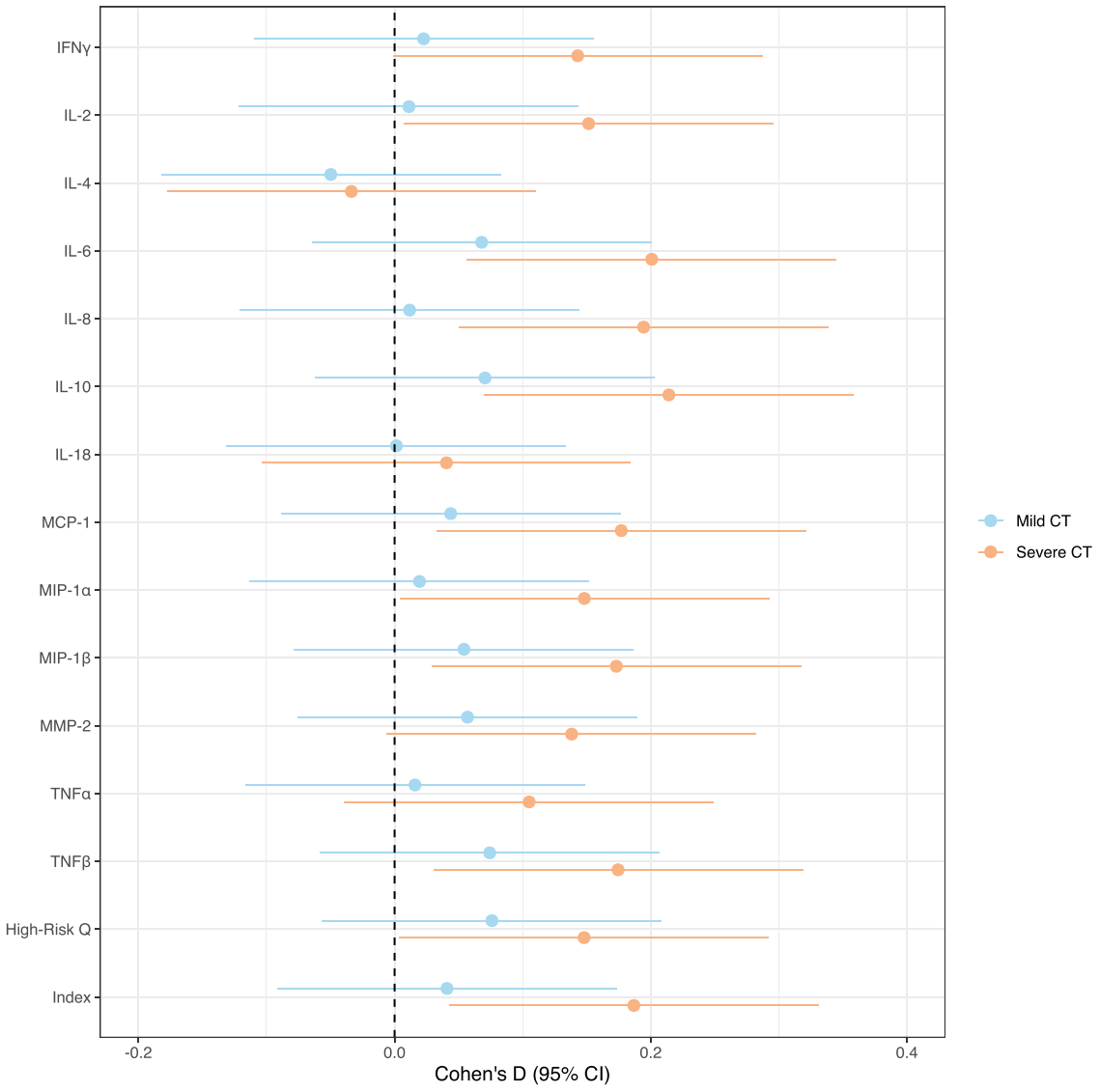

Fig. 2. Forest plot of Cohen's D and corresponding 95% confidence interval of mild and severe CT and individual and cumulative measures of cytokines in model 2. Note: model 2: adjusted for age, sex, years of education, anti-inflammatory medication use, a cold or fever in the past week, alcohol consumption, smoking, physical activity, body mass index, and number of chronic diseases. Abbreviations: CT: Childhood Trauma, IFN: interferon; IL: interleukin; MCP: monocyte chemotactic protein; MIP: macrophage inflammatory protein; MMP: matrix metalloproteinase; TNF: tumour necrosis factor; Q: quartile; Index: the inflammation index. * P_{FDR} of $\beta < 0.05$.

MIP-1β, MMP-2, and TNFβ, even after adjustment for demographic, lifestyle, and health factors. Effects were consistent across CT types and strongest for individuals with severe CT, reporting multiple types or frequencies of trauma. Half of the associations were not explained by psychiatric status as they remained significant after adjustment for psychiatric status, and no associations were moderated by psychiatric status as no interactions between CT and psychiatric status were observed. Overall, associations were statistically significant but with small effect sizes (between-group effect sizes for severe CT below 0.22). We, therefore, conclude that CT, especially severe CT, is associated with a slightly increased cytokine production capacity.

Our results regarding the association of CT with cytokine levels in adulthood were generally comparable to the findings of a previous *meta*-analysis and systematic review on basal (non-stimulated) cytokine levels outside of NESDA (Baumeister et al., 2016; Gill et al., 2020). Our sensitivity analyses showed that the results translate to other CT measures, at least in effect sizes. The lack of significance for our CTQ analyses might have been due to power differences, since the CTQ data had a lower sample size. Kuzminskaite et al. (2020) studied the association between CT and basal CRP, IL-6, and TNFα levels within the same NESDA cohort. For the cumulative index, much smaller effects were found compared to our study ($\beta = 0.032$ vs. $\beta = 0.100$ with basic adjustment, and $\beta = -0.070$ vs. $\beta = 0.085$ with lifestyle/health adjustment). This suggests that LPS-stimulated cytokine levels indeed capture more effects of CT than basal levels do, a finding supported by previous research comparing basal and LPS-stimulated cytokine levels in anxiety and depression (van Eeden et al., 2021; Vogelzangs et al., 2016). Furthermore, our result that CT is associated with increased LPS-stimulated cytokine levels is in accordance with previous findings (Hohmann et al., 2017; King et al., 2021; Miller and Chen, 2010). King et al. (2021) found a significant bivariate (unadjusted) correlation between CT (CTQ total score) and LPS-stimulated IL-6 in a population of which more than half was diagnosed with schizophrenia or schizoaffective disorder. In comparison, our standardized regression coefficients for IL-6 were rather smaller ($\beta = 0.104$ with basic adjustment, and $\beta = 0.091$ with lifestyle/health adjustment). One explanation for the difference in results is that we adjusted extensively for demographics, lifestyle and health-related factors, such as sex, BMI, and smoking,

whereas the association found by King et al. (2021) is not adjusted for such covariates.

CT-immune marker associations in our study were partially explained by poorer health, unhealthier lifestyle, and higher prevalence of current depressive or anxiety disorders in individuals with higher CT scores. Behaviours such as smoking and over-eating might help to cope with stress in the aftermath of CT (Felitti et al., 1998), but are also known to have pro-inflammatory effects (Lee et al., 2012; Pahwa et al., 2021; Shoelson et al., 2007). Half of the associations remained significant after adjustment for demographics, health, lifestyle and psychiatric status suggesting that there is an additional direct effect of CT over and above differences in these factors between individuals with and without CT, even though other unknown mediating factors might still exist. Precisely how this effect of CT on the immune system comes about is not known, although there is evidence that the glucocorticoid receptor is involved (Miller et al., 2009).

We analyzed a large variety of cytokines and two cumulative indices. To date, research mainly focussed on basal levels of individual cytokines, such as IL-6 (e.g. (de Punder et al., 2018; Kiecolt-Glaser et al., 2011), and has mainly been heterogeneous in which cytokine was mostly elevated. However, we found that effect sizes across cytokines were rather similar, and that CT predicted a relatively large increase in the inflammation index. Moreover, the intercorrelations between LPS-stimulated cytokine levels have been found to be much stronger than those between basal cytokine levels (Vogelzangs et al., 2016). Taken together, stimulated cytokine levels might be generally increased in adults with a history of CT, and therefore, focusing on individual cytokines might be of less relevance. Instead, a cumulative score might be a more suitable measure to assess the immune system of individuals with CT and should be explored further in future research. It is of note that some of the investigated cytokines have anti-inflammatory properties as well, most notably IL-10 (Opal and DePalo, 2000). However, LPS-stimulation gives a very general boost to the immune system, which upregulates cytokines independent of their anti- or pro-inflammatory nature.

Our finding that emotional abuse had slightly stronger effects on inflammation than other types of CT is not supported by a *meta*-analysis and review (Baumeister et al., 2016; Brown et al., 2021), but is consistent with the findings of some individual studies, showing rather higher levels of inflammation in the context of emotional abuse (Grosse et al., 2016; Munjiza et al., 2018). Moreover, emotional abuse has been most strongly associated with depression in three *meta*-analyses (Infurna et al., 2016; Mandelli et al., 2015; Norman et al., 2012). However, there is much heterogeneity in the findings of previous studies, and our findings did not differ considerably between the CT types. Therefore, we cannot conclude that one CT type is specifically associated with inflammation, and there is a clear indication that the severity and number of CTs seems more important than the specific type of CT.

There are several potential implications with clinical and scientific relevance. Cytokines can exert effects on nearly every cell type in the human body and can regulate not only the immune system but also the endocrine and nervous system (Saito, 2001). Whereas the relevance of basal cytokine levels in somatic and psychiatric disease is established, the clinical implications of LPS-stimulated cytokine levels are less so. It is thought that LPS-challenged cytokine levels represent the body's innate immune system reaction to eliminate invading infectious agents and to promote the repair of tissue damage after injury (van den Biggelaar et al., 2007). Anti-inflammatory cytokines that damp down inflammation, such as IL-4 and IL-10, are also involved in the inflammatory cascade (Opal and DePalo, 2000). When the immune response is too weak, infection may occur, but in the case of a chronic pro-inflammatory milieu, the body is at risk for diverse diseases (John-Henderson et al., 2016). Such diseases range from (auto)immune-mediated disorders (Sompayrac, 2019), atherosclerosis (Libby et al., 2018), metabolic syndrome (Jin et al., 2013), neurodegeneration (Heneka et al., 2014), and cancer (Taniguchi and Karin, 2018), to depression (Miller and Raison, 2016). The latter relates to affective symptoms, such as those present in sickness behaviour, including lethargy, loss of appetite, sleepiness, and concentration problems (van Eeden et al., 2020).

Our study has some limitations. First, the CT measure was based on retrospective self-report. CT is sensitive in nature, and its report is prone to several kinds of biases. Indeed, retrospective assessment of CT has been shown to identify a different group of individuals than prospective assessment (Baldwin et al., 2019). Factors that may reduce reliability of retrospective self-report include feelings of shame and memory bias (Baldwin et al., 2019). Memory bias may occur due to negative recall bias in, for example, depression (Mathews and MacLeod, 2005). This is of specific concern in the current research, because it might inflate correlations since depression was found to be associated with increased LPS-stimulated inflammation as well (Vogelzangs et al., 2016). However, it has been found that recall bias in CT accounts for <1% of report variance and that psychiatric status is not related to reporting errors of CT (Fergusson et al., 2000, 2011). In addition, our findings were rather similar to another CT assessment, the CTQ-SF, four years later. Second, the effects were significant but small, limiting the clinical relevance in everyday practice. Perhaps, a dysregulated immune system is part of a broader alteration of systems and pathways in individuals with CT, in which smaller and larger disturbances each play their role (Agorastos et al., 2019). Third, due to methodological limitations, we did not consider physical neglect in the current study, although it is a common subtype of CT and is important to be researched in the context of inflammation as well. Conversely, our study has some important strengths. First, we were one of the first to analyse a large variety of LPS-stimulated cytokines in individuals with a history of CT. The LPS challenge has both methodological and functional advantages over circulating levels of inflammatory markers. Second, we analysed thirteen different cytokines, among which novel ones in this context. This allowed us to get a broader view of cytokine dysregulation. Third, we extensively adjusted for demographics, lifestyle, health, and psychiatric status to provide the most accurate results. Fourth, we calculated two cumulative scores: the index score and the number of cytokines in HRQs. Especially the index score seems to be affected more by CT than the individual cytokines. Last, our sample size was large compared to most studies, decreasing the likelihood of coincidental findings.

In conclusion, the current study found an association between CT, especially severe forms of CT, and increased LPS-stimulated cytokine levels regardless of current psychopathology. This suggests an increased innate immune capacity in adults with CT, likely contributing to higher vulnerability for psychopathology and somatic diseases. We did not find clinically relevant differences in effect between the CT types. Overall, the effects were modest, but CT predicted a rather large increase in the inflammation index compared to individual cytokines. Therefore, exploration of cumulative measures of inflammation in the context of CT and (mental) health outcomes is recommended.

Declaration of Competing Interest

BP has received unrestricted research funding from Boehringer Ingelheim and Jansen Research b.v. Other 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.

Funding

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number: 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of

Groningen, Lentis, GGZ Friesland, Dimence, GGZ Drenthe, Rob Giel Onderzoekscentrum). BP is supported through the European Union's Horizon 2020 research and innovation programme (EARLYCAUSEgrant n° 848158). CV is supported by a Dutch Research Council (NWO) Vidi grant (09150171910042).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.07.158.

References

Agorastos, A., Pervanidou, P., Chrousos, G.P., Baker, D.G., 2019. Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects Beyond Stress System Dysregulation. Frontiers in Psychiatry 10, 118.

Alberts, B. 2015. Molecular biology of the cell. Garland Science. Taylor and Francis Group, New York, NY.

Baldwin, J.R., Reuben, A., Newbury, J.B., Danese, A., 2019. Agreement Between Prospective and Retrospective Measures of Childhood Maltreatment: A Systematic Review and Meta-analysis. JAMA Psychiatry 76, 584–593.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry 21, 642–649.

Baumeister, D., Russell, A., Pariante, C.M., Mondelli, V., 2014. Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors. Soc Psychiatry Psychiatr Epidemiol 49, 841–849.

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, 289–300.

Bernstein, D., 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, 1132–1136.

Bock, B.B., Bastos, C.R., Ardais, A.P., Grellert, M., de Carvalho, H.W., Farias, C.P., Jansen, K., Oses, J.P., da Silva, R.A., Portela, L.V., Kaster, M.P., Lara, D.R., Ghisleni, G., 2020. Temperament traits moderate the relationship between Childhood Trauma and Interleukin 1β profile in young adults. Psychoneuroendocrinology 116, 104671.

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.

Cakir, S., Tasdelen Durak, R., Ozyildirim, I., Ince, E., Sar, V., 2016. Childhood trauma and treatment outcome in bipolar disorder. Journal of Trauma & Dissociation 17, 397–409.

Campbell, J.A., Walker, R.J., Egede, L.E., 2016. Associations Between Adverse Childhood Experiences, High-Risk Behaviors, and Morbidity in Adulthood. Am J Prev Med 50, 344–352.

Coppack, S.W., 2001. Pro-inflammatory cytokines and adipose tissue. Proceedings of the Nutrition Society 60, 349–356.

Craig, C.L., Marshall, A.L., Sjöström, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., 2003. International physical activity questionnaire: 12-country reliability and validity. Medicine & science in sports & exercise 35, 1381–1395.

Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A 104, 1319–1324.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9, 46–56.

De Graaf, R., Bijl, R.V., Ten Have, M., Beekman, A.T.F., Vollebergh, W.A.M., 2004. Rapid onset of comorbidity of common mental disorders: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatrica Scandinavica 109, 55–63.

De Miguel, C., Obi, I.E., Ho, D.H., Loria, A.S., Pollock, J.S., 2018. Early life stress induces immune priming in kidneys of adult male rats. Am J Physiol Renal Physiol 314, F343–F355.

De Punder, K., Entringer, S., Heim, C., Deuter, C.E., Otte, C., Wingenfeld, K., Kuehl, L.K. 2018. Inflammatory Measures in Depressed Patients With and Without a History of Adverse Childhood Experiences. Frontiers in Psychiatry. 9. https://doi.org/10.3389/fpsyt.2018.00610.

Elwenspoek, M.M., Hengesch, X., Leenen, F.A., Schritz, A., Sias, K., Schaan, V.K., Mériaux, S.B., Schmitz, S., Bonnemberger, F., Schächinger, H., 2017. Proinflammatory T cell status associated with early life adversity. The Journal of Immunology 199, 4046–4055.

Engel, M.L., Coe, C.L., Reid, B.M., Donzella, B., Gunnar, M.R., 2021. Selective inflammatory propensities in adopted adolescents institutionalized as infants. Psychoneuroendocrinology 124, 105065.

Felitti, V.J.M.D., Facp, Anda, R.F.M.D., Ms, Nordenberg, D.M.D., Williamson, D.F.M.S., PhD, Spitz, A.M.M.S., Mph, Edwards, V.B.A., Koss, M.P.P., Marks, J.S.M.D., Mph. 1998. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine. 14. 245-258. https://doi.org/10.1016/s0749-3797(98)00017-8.

Fergusson, D.M., Horwood, L.J., Boden, J.M., 2011. Structural equation modeling of repeated retrospective reports of childhood maltreatment. Int J Methods Psychiatr Res 20, 93–104.

Fergusson, D.M., Horwood, L.J., Woodward, L.J., 2000. The stability of child abuse reports: a longitudinal study of the reporting behaviour of young adults. Psychological Medicine 30, 529–544.

Ferrante Jr., A.W., 2007. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. J Intern Med 262, 408–414.

Fink, L.A., Bernstein, D., Handelsman, L., Foote, J., Lovejoy, M., 1995. Initial reliability and validity of the childhood trauma interview: a new multidimensional measure of childhood interpersonal trauma. The American journal of psychiatry 152, 1329–1335.

Gill, H., El-Halabi, S., Majeed, A., Gill, B., Lui, L.M.W., Mansur, R.B., Lipsitz, O., Rodrigues, N.B., Phan, L., Chen-Li, D., McIntyre, R.S., Rosenblat, J.D., 2020. The Association Between Adverse Childhood Experiences and Inflammation in Patients with Major Depressive Disorder: A Systematic Review. Journal of Affective Disorders 272, 1–7.

Goodwin, R.D., Stein, M.B., 2004. Association between childhood trauma and physical disorders among adults in the United States. Psychol Med 34, 509–520.

Grosse, L., Ambrée, O., Jörgens, S., Jawahar, M.C., Singhal, G., Stacey, D., Arolt, V., Baune, B.T., 2016. Cytokine levels in major depression are related to childhood trauma but not to recent stressors. Psychoneuroendocrinology 73, 24–31.

Heneka, M.T., Kummer, M.P., Latz, E., 2014. Innate immune activation in neurodegenerative disease. Nature Reviews Immunology 14, 463–477.

Hohmann, C.F., Odebode, G., Naidu, L., Koban, M., 2017. Early Life Stress Alters Adult Inflammatory Responses in a Mouse Model for Depression. Ann Psychiatry Ment Health 5, 1095.

Hovens, J.G.F.M., Giltay, E.J., Wiersma, J.E., Spinhoven, P., Penninx, B.W.J.H., Zitman, F.G., 2012. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatrica Scandinavica 126, 198–207.

Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., Dunne, M.P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. The Lancet Public Health 2, e356 e366.

Infurna, M.R., Reichl, C., Parzer, P., Schimmenti, A., Bifulco, A., Kaess, M., 2016. Associations between depression and specific childhood experiences of abuse and neglect: A meta-analysis. Journal of Affective Disorders 190, 47–55.

Jakubowski, K.P., Cundiff, J.M., Matthews, K.A., 2018. Cumulative childhood adversity and adult cardiometabolic disease: A meta-analysis. Health Psychol 37, 701–715.

Jin, C., Henao-Mejia, J., Flavell, R.A., 2013. Innate Immune Receptors: Key Regulators of Metabolic Disease Progression. Cell Metabolism 17, 873–882.

John-Henderson, N.A., Marsland, A.L., Kamarck, T.W., Muldoon, M.F., Manuck, S.B., 2016. Childhood Socioeconomic Status and the Occurrence of Recent Negative Life Events as Predictors of Circulating and Stimulated Levels of Interleukin-6. Psychosom Med 78, 91–101.

Kiecolt-Glaser, J.K., Gouin, J.-P., Weng, N.-P., Malarkey, W.B., Beversdorf, D.Q., Glaser, R., 2011. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom Med 73, 16–22.

King, S., Holleran, L., Mothersill, D., Patlola, S., Rokita, K., McManus, R., Kenyon, M., McDonald, C., Hallahan, B., Corvin, A., Morris, D., Kelly, J., McKernan, D., Donohoe, G., 2021. Early life Adversity, functional connectivity and cognitive performance in Schizophrenia: The mediating role of IL-6. Brain, Behavior, and Immunity 98, 388–396.

Kuzminskaite, E., Penninx, B.W.J.H., van Harmelen, A.-L., Elzinga, B.M., Hovens, J.G.F.M., Vinkers, C.H., 2021. Childhood Trauma in Adult Depressive and Anxiety Disorders: An Integrated Review on Psychological and Biological Mechanisms in the NESDA Cohort. Journal of Affective Disorders 283, 179–191.

Kuzminskaite, E., Vinkers, C.H., Elzinga, B.M., Wardenaar, K.J., Giltay, E.J., Penninx, B. W.J.H., 2020. Childhood trauma and dysregulation of multiple biological stress systems in adulthood: Results from the Netherlands Study of Depression and Anxiety (NESDA). Psychoneuroendocrinology 121, 104835.

Lee, J., Taneja, V., Vassallo, R., 2012. Cigarette smoking and inflammation: cellular and molecular mechanisms. Journal of dental research 91, 142–149.

Libby, P., Loscalzo, J., Ridker, P.M., Farkouh, M.E., Hsue, P.Y., Fuster, V., Hasan, A.A., Amar, S., 2018. Inflammation, Immunity, and Infection in Atherothrombosis. Journal of the American College of Cardiology 72, 2071–2081.

Mandelli, L., Petrelli, C., Serretti, A., 2015. The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. European Psychiatry 30, 665–680.

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature reviews immunology 16, 22.

Mathews, A., MacLeod, C., 2005. Cognitive Vulnerability to Emotional Disorders. Annual Review of Clinical Psychology 1, 167–195.

Miller, G.E., Chen, E., 2010. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci 21, 848–856.

Miller, G.E., Chen, E., Fok, A.K., Walker, H., Lim, A., Nicholls, E.F., Cole, S., Kobor, M.S., 2009. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A 106, 14716–14721.

Munjiza, A., Kostic, M., Pesic, D., Gajic, M., Markovic, I., Tosevski, D.L., 2018. Higher concentration of interleukin 6 – A possible link between major depressive disorder and childhood abuse. Psychiatry Research 264, 26–30.

Nanni, V., Uher, R., Danese, A., 2012. Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis. American Journal of Psychiatry 169, 141–151.
Norman, R.E., Byambaa, M., De, R., Butchart, A., Scott, J., Vos, T., 2012. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med 9, e1001349.
O'Mahony, S.M., Marchesi, J.R., Scully, P., Codling, C., Ceolho, A.-M., Quigley, E.M., Cryan, J.F., Dinan, T.G., 2009. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. Biological psychiatry 65, 263–267.
Opal, S.M., DePalo, V.A., 2000. Anti-inflammatory cytokines. Chest 117, 1162–1172.
Pahwa, R., Goyal, A., Bansal, P., Jialal, I., 2021. Chronic Inflammation. StatPearls. StatPearls Publishing. Treasure Island (FL). PMID: 29630225.
Parent, C., Nguyen, H.-B., Wen, X., Diorio, J., Meaney, M.J., Zhang, T.Y., 2017. Maternal care modulates the febrile response to lipopolysaccharide through differences in glucocorticoid receptor sensitivity in the rat. Brain, Behavior, and Immunity 65, 239–250.
Penninx, B.W.J.H., Beekman, A.T.F., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W.J., Assendelft, W.J.J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W.J., Ormel, J., Van Dyck, R., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International Journal of Methods in Psychiatric Research 17, 121–140.
Pilowsky, D.J., Keyes, K.M., Hasin, D.S., 2009. Adverse childhood events and lifetime alcohol dependence. Am J Public Health 99, 258–263.
Saito, S., 2001. Cytokine cross-talk between mother and the embryo/placenta. Journal of Reproductive Immunology 52, 15–33.
Shoelson, S.E., Herrero, L., Naaz, A., 2007. Obesity, inflammation, and insulin resistance. Gastroenterology 132, 2169–2180.
Sompayrac, L.M., 2019. How the Immune System Works. John Wiley & Sons.
Spinhoven, P., Penninx, B.W., Hickendorff, M., van Hemert, A.M., Bernstein, D.P., Elzinga, B.M., 2014. Childhood Trauma Questionnaire: factor structure, measurement invariance, and validity across emotional disorders. Psychological assessment 26, 717.
Taniguchi, K., Karin, M., 2018. NF-κB, inflammation, immunity and cancer: coming of age. Nature Reviews Immunology 18, 309–324.
Tawfik, D.M., Lankelma, J.M., Vachot, L., Cerrato, E., Pachot, A., Wiersinga, W.J., Textoris, J., 2020. Comparison of host immune responses to LPS in human using an immune profiling panel, in vivo endotoxemia versus ex vivo stimulation. Scientific Reports 10, 9918.
Van den Biggelaar, A.H., Gussekloo, J., de Craen, A.J., Frölich, M., Stek, M.L., van der Mast, R.C., Westendorp, R.G., 2007. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. Exp Gerontol 42, 693–701.
Van der Linden, M.W., Huizinga, T.W.J., Stoeken, D.-J., Sturk, A., Westendorp, R.G.J., 1998. Determination of tumour necrosis factor-α and interleukin-10 production in a whole blood stimulation system: assessment of laboratory error and individual variation. Journal of Immunological Methods 218, 63–71.
Van Eeden, W.A., El Filali, E., van Hemert, A.M., Carlier, I.V.E., Penninx, B.W.J.H., Lamers, F., Schoevers, R., Giltay, E.J., 2021. Basal and LPS-stimulated inflammatory markers and the course of anxiety symptoms. Brain, Behavior, and Immunity 98, 378–387.
Van Eeden, W.A., van Hemert, A.M., Carlier, I.V.E., Penninx, B., Lamers, F., Fried, E.I., Schoevers, R., Giltay, E.J., 2020. Basal and LPS-stimulated inflammatory markers and the course of individual symptoms of depression. Transl Psychiatry 10, 235.
Van Exel, E., Eikelenboom, P., Comijs, H., Frölich, M., Smit, J.H., Stek, M.L., Scheltens, P., Eefsting, J.E., Westendorp, R.G.J., 2009. Vascular Factors and Markers of Inflammation in Offspring With a Parental History of Late-Onset Alzheimer Disease. Archives of General Psychiatry 66, 1263–1270.
Van Lier, D., Geven, C., Leijte, G.P., Pickkers, P., 2019. Experimental human endotoxemia as a model of systemic inflammation. Biochimie 159, 99–106.
Vogelzangs, N., de Jonge, P., Smit, J.H., Bahn, S., Penninx, B.W., 2016. Cytokine production capacity in depression and anxiety. Translational Psychiatry 6, e825–e.
Wittchen, H.U., 1994. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): A critical review. Journal of Psychiatric Research 28, 57–84.
Zielen, S., Trischler, J., Schubert, R., 2015. Lipopolysaccharide challenge: immunological effects and safety in humans. Expert Review of Clinical Immunology 11, 409–418.