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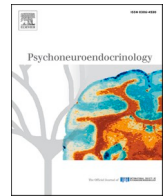
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Childhood trauma and dysregulation of multiple biological stress systems in adulthood: Results from the Netherlands Study of Depression and Anxiety (NESDA)

Erika Kuzminskaite [a,*], Christiaan H. Vinkers [a,b], Bernet M. Elzinga [c,d], Klaas J. Wardenaar [e], Erik J. Giltay [f], Brenda W.J.H. Penninx [a]

[a] Department of Psychiatry (GGZ inGeest), Amsterdam UMC (location VUmc), Vrije University, Amsterdam Public Health and Amsterdam Neuroscience Research Institutes, Amsterdam, the Netherlands
[b] Department of Anatomy and Neurosciences, Amsterdam UMC (location VUmc), Vrije University, Amsterdam, the Netherlands
[c] Institute of Psychology, Clinical Psychology Unit, Leiden University, Leiden, the Netherlands
[d] Leiden Institute for Brain and Cognition (LIBC), Leiden University, Leiden, the Netherlands
[e] University Medical Center Groningen, University of Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), Groningen, the Netherlands
[f] Leiden University Medical Center, Department of Psychiatry, Leiden, the Netherlands

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ABSTRACT

Background: Childhood trauma (CT) is a risk factor for depressive and anxiety disorders. Although dysregulated biological stress systems may underlie the enduring effect of CT, the relation between CT and separate and cumulative activity of the major stress systems, namely, the hypothalamic-pituitary-adrenal (HPA)-axis, the immune-inflammatory system, and the autonomic nervous system (ANS), remains inconclusive.
Methods: In the Netherlands Study of Depression and Anxiety (NESDA, $n = 2778$), we determined whether self-reported CT (as assessed by the Childhood Trauma Interview) was associated with separate and cumulative markers of the HPA-axis (cortisol awakening response, evening cortisol, dexamethasone suppression test cortisol), the immune-inflammatory system (C-reactive protein, interleukin-6, tumor necrosis factor-α), and the ANS (heart rate, respiratory sinus arrhythmia, pre-ejection period) in adulthood.
Results: Almost all individuals with CT ($n = 1330$) had either current or remitted depressive and/or anxiety disorder (88.6%). Total-sample analyses showed little evidence for CT being significantly associated with the separate or cumulative stress systems' activity in adulthood. These findings were true for individuals with and without depressive and/or anxiety disorders. To maximize contrast, individuals with severe CT were compared to healthy controls without CT. This yielded slight, but significantly higher levels of cortisol awakening response (AUCg, $\beta = .088$, $p = .007$; AUCi, $\beta = .084$, $p = .010$), cumulative HPA-axis markers ($\beta = .115$, $p = .001$), C-reactive protein ($\beta = .055$, $p = .032$), interleukin-6 ($\beta = .053$, $p = .038$), cumulative inflammation ($\beta = .060$, $p = .020$), and cumulative markers across all systems ($\beta = .125$, $p = .0003$) for those with severe CT, partially explained by higher rates of smoking, body mass index, and chronic diseases.
Conclusion: While our findings do not provide conclusive evidence on CT directly dysregulating stress systems, individuals with severe CT showed slight indications of dysregulations, partially explained by an unhealthy lifestyle and poorer health.

1. Introduction

Childhood trauma (CT), such as emotional and physical neglect or emotional, physical, and sexual abuse before the age of 18, has been increasingly recognized as a prominent risk factor for mental and somatic disorders occurring across the lifespan (Felitti et al., 2019; Hughes

et al., 2017; Teicher and Samson, 2013; Wegman and Stetler, 2009). With regard to depressive and anxiety disorders, adults with a history of CT have an earlier onset and chronic course, with higher rates of co-morbidity, and poorer treatment outcomes than those without CT (Hovens et al., 2012; Nanni et al., 2012; Wiersma et al., 2009). This long-lasting effect has been partially explained by biological stress-induced alterations such as dysregulation of stress systems (Berens et al., 2017; Otte et al., 2016). These bodily stress systems include the hypothalamic-pituitary-adrenal-axis (HPA-axis), the immune-inflammatory system, and the autonomic nervous system (ANS).

While the activation of stress systems is a natural response to acute stress, when prolonged, it can result in systematic dysregulations, leading to adverse health outcomes. Indeed, the hampered activity of major stress systems has been observed in both mental and somatic disorders (Fioranelli et al., 2018; Penninx et al., 2013). Although inconclusive, there is also evidence for dysregulations of stress systems as prominent factors associated with CT. For instance, CT has been significantly linked to HPA-axis dysregulation as represented by blunted wake-up cortisol and cortisol response to experimental social stress conditions in children and adults in recent meta-analyses (Bernard et al., 2017; Bunea et al., 2017). However, meta-analyses have not consistently confirmed significant associations with the more static measures of cortisol awakening response (CAR), diurnal cortisol slope, basal cortisol, or cortisol response to acute stress (among which dexamethasone suppression test, DST) (Bernard et al., 2017; Fogelman and Canli, 2018). Adult low-grade inflammation, marked by significantly elevated levels of pro-inflammatory markers, particularly, basal C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α, has been meta-analytically associated with CT as well (Baumeister et al., 2016). Research on CT and ANS has also suggested dysregulation within the sympathetic and parasympathetic activity as marked by significantly blunted heart rate (HR) and pre-ejection period (PEP), with rather inconclusive results on respiratory sinus arrhythmia (RSA) in response to experimental psychological stress conditions (Lovallo et al., 2012; Sijtsema et al., 2015; Young-Southward et al., 2019).

Although there have been promising findings on the biological CT correlates underlying the risk for future disorders, further research is necessary. Previous meta-analyses reporting mostly small effect sizes were based on a wide range of studies ($k = 5-29$) and participants ($n = 665-16{,}870$) (Baumeister et al., 2016; Bernard et al., 2017; Bunea et al., 2017; Fogelman and Canli, 2018). Synthesis of mixed findings from a variety of methodologically diverse studies also resulted in significant and large heterogeneity, and publication or selection biases. Besides, the majority of the single studies used relatively small samples with limited and diverse adjustment for confounding factors, likely undermining the accuracy of the results. Furthermore, earlier studies mainly focused on an individual marker within a specific stress system and did not examine the cumulative activity of stress systems together. Considering the existing interplay between these systems (Doolin et al., 2017; Hu et al., 2018; Rotenberg and McGrath, 2016), this is crucial. A comprehensive approach, including measures of all the major stress systems, is likely to provide a better picture of the pathophysiology of CT necessary to identify who is at risk for future disorders and, ultimately, to develop personalized (preventative) interventions.

The current study aimed to further examine associations between retrospectively reported CT and markers of HPA-axis (CAR, evening [basal] cortisol, and DST cortisol), immune-inflammatory system (CRP, IL-6, and TNF-α), and the ANS (HR, RSA, and PEP) in a large adult cohort – the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), adjusting for multiple potentially confounding factors. Previous studies on the NESDA cohort have revealed significant associations between many stress systems' markers and psychopathology (Hu et al., 2016; Vogelzangs et al., 2016; Vreeburg et al., 2009a). An attempt was also made to bridge CT and markers of the HPA-axis with no convincing associations revealed (Holleman et al., 2012). Since no studies have directly examined associations between CT,

immune-inflammatory system, and the ANS or focused on the cumulative activity of the stress systems in the context of CT, the current study conducted analyses focusing on separate markers of the three stress systems, cumulative markers within systems, and cumulative markers across all systems. As previous literature has inconsistent findings, no specific hypotheses were defined.

2. Methods

2.1. Sample

Data came from an ongoing longitudinal cohort (NESDA; $n = 2981$) (Penninx et al., 2008). Participants were Dutch-fluent adults (18–65 years) with or without depressive and/or anxiety disorder (current or remitted; Composite International Diagnostic Interview, CIDI) (Robins et al., 1988) recruited between September 2004 and February 2007 from three different settings: community, primary health care, and specialized mental health care. Patients with a primary diagnosis of other than depressive or anxiety disorder (e.g., post-traumatic stress disorder, bipolar disorder, psychotic disorder, obsessive-compulsive disorder) were excluded. At baseline, participants were assessed on various socio-demographic, lifestyle, (mental) health, and biological factors.

In the current study, baseline data of 2970 participants with available measure of CT and at least one of the stress systems' markers were used. Exclusion of participants who were pregnant/breastfeeding ($n = 27$, .9%) or used corticosteroids ($n = 165$, 5.6%) led to the total sample including 2778 participants. Missing data on stress systems' markers resulted in further exclusions for analyses on area under the curve with respect to the ground (AUCg; $n = 945$, 34%), area under the curve with respect to the increase (AUCi; $n = 945$, 34%), evening cortisol ($n = 784$, 28.2%), DST cortisol ($n = 893$, 32.1%), CRP ($n = 38$, 1.4%), IL-6 ($n = 38$, 1.4%), TNF-α ($n = 57$, 2.1%), HR ($n = 111$, 4.0%), RSA ($n = 111$, 4.0%), and PEP ($n = 133$, 4.8%). NESDA's protocol was approved by the ethical review board of each participating research center in Amsterdam, Leiden, and Groningen. All participants provided written informed consent. More information regarding NESDA can be found in Penninx et al. (2008).

2.2. Measures

2.2.1. Childhood trauma

To assess CT, trained research staff administered the Childhood Trauma Interview (CTI) previously used in the Netherlands Mental Health Survey and Incidence Study (de Graaf et al., 2004). The CTI is a structured interview, retrospectively assessing four types of CT before the age of 16 years: emotional neglect, emotional abuse, physical abuse, and sexual abuse. Each CT type is answered as "no" or "yes" with a further frequency indication as (0) - "never", (1) - "once or sometimes", and (2) - "regularly, often, or very often" (range 0–2). A continuous cumulative CT severity score (range 0–8) was calculated as a sum of the number of types and frequency of CT with a higher score indicating more severe CT (Hovens et al., 2010; Wiersma et al., 2009). The CTI has previously been shown to have good psychometric properties (Fink et al., 1995; Hovens et al., 2012; Spinhoven et al., 2014).

For sensitivity analysis, the consistency of findings was checked with an alternative CT variable, based on the self-reported Childhood Trauma Questionnaire (CTQ-SF) (Bernstein et al., 1994, 2003) assessed during the 4-year follow-up of NESDA. The CTQ-SF is a 25-item 5-point Likert questionnaire, retrospectively assessing five types of CT while growing up: emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse (five items per subscale). Due to the low validity and reliability (Spinhoven et al., 2014), physical neglect subscale was not used in the current study. The total score per CTQ-SF type ranges from 5 to 25, with the total CT severity score ranging from 20 to 100 (excluding the physical neglect subscale). Total CTQ-SF data were available for 2144 (72.2%)

participants of our initial sample. The CTQ-SF has been shown to have good psychometric properties (Bernstein et al., 2003; Spinhoven et al., 2014).

2.2.2. Hypothalamic-Pituitary-Adrenal (HPA)-Axis

For the HPA-axis, three salivary cortisol patterns were measured (Vreeburg et al., 2009): (1) CAR, reflecting 1-h cortisol secretion after awakening (AUCg) and changes over 1-h (AUCi) (Pruessner et al., 2003), (2) evening cortisol, reflecting basal cortisol secretion (Kirschbaum and Hellhammer, 1989), and (3) DST cortisol, reflecting the negative feedback of the HPA-axis (Carroll et al., 1981). Saliva samples were collected by participants on a regular day using Salivettes (Sarstedt, Nümbrecht, Germany) at seven time points: (T1) at awakening, (T2) 30 min after, (T3) 45 min after, (T4) 60 min after, (T5) at 10 PM, (T6) 11 PM, and (T7) the next morning at awakening after ingestion of .5 mg dexamethasone directly after the saliva sample at 11 PM (Vreeburg et al., 2009, Vreeburg et al., 2009). Participants were instructed not to eat, smoke, drink, or brush their teeth 15 min before sampling, and have no dental work 24 h before sampling. Competitive electrochemiluminescence was used for the cortisol analysis (Roche, Basel, Switzerland) (van Aken et al., 2003). The detection limit was 2.0 nanomoles per liter, and the intra- and inter-assay variability coefficients were <10%. For the CAR, AUCg and AUCi were calculated using values from the T1 to T4 as based on the formulas by Pruessner et al. (2003). For the evening cortisol, values from the T5 and T6 (correlated at $\rho = .74$, $p < .001$) were used to determine a mean estimate. For the DST cortisol, a cortisol suppression ratio was calculated (T1/T7).

2.2.3. Immune-inflammatory system

For the immune-inflammatory system, three inflammation markers in blood plasma were assessed: (1) CRP, (2) TNF-α, and (3) IL-6 (Vogelzangs et al., 2012). Participants' fasting morning (~8 AM) blood samples were obtained and kept frozen at −80 °C. Plasma levels of IL-6 were assessed by a high-sensitivity enzyme-linked immunosorbent assay (PeliKine-Compact ELISA, Sanquin, Amsterdam, the Netherlands). Plasma TNF-α levels were determined by a high-sensitivity solid-phase ELISA (Quantikine HS Human TNF-α Immunoassay, R&D Systems, Minneapolis, MN, USA). High-sensitivity plasma levels of CRP were assessed by an in-house ELISA based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). Intra- and inter-assay variability coefficients were 8% and 12%, 10% and 15%, 5% and 10% for IL-6, TNF-α, and CRP, respectively.

2.2.4. Autonomic nervous system (ANS)

For the ANS, three physiological measures were assessed: (1) HR, reflecting the combined effect of sympathetic and parasympathetic activity, (2) RSA, reflecting cardiac parasympathetic activity, and (3) PEP, reflecting cardiac sympathetic activity (Licht et al., 2010). ANS measures were assessed by the Vrije University Ambulatory Monitoring System (VU-AMS) – device recording an electrocardiogram (ECG) and changes in thorax impedance (dZ) through six surface electrodes placed on the chest and the back (Willemsen et al., 1996). HR was determined by extracting the inter-beat interval time series from the ECG signal, while the RSA and PEP were estimated from the combined dZ and ECG signals (Licht et al., 2010). Due to the confounding effect of postural changes on RSA and PEP (Houtveen et al., 2005), periods during which participants were nonstationary (~15 min), as registered via vertical accelerometry, were excluded. Visual inspection was used to verify the automated scoring of RSA and PEP, with valid data averaged over 98.0 ± 24 min (mean ± SD) to create single estimates of HR and RSA during rest (blood pressure measurement) and test (interviews and/or Implicit Association Task) conditions (correlated at $r = .86–.88$, $p < .001$). Only test values were used for PEP estimate, because rest values were too irregular.

2.2.5. Cumulative markers of stress systems

To assess the cumulative activity of stress systems, cumulative marker scores were created, reflecting the activity within each system and across all systems similar to previous papers (Black et al., 2017; Thesing et al., 2018). For the cumulative score, markers of DST cortisol, RSA, and PEP were reversed, as lower values represent higher disease risk. To standardize values across each marker, values were transformed into z-scores. The score for each system was calculated as the average score of the three markers within the system. Similarly, the score across systems was calculated as the average standardized score of all markers within all systems. These scores were estimated only for participants with complete data on all markers within each system or across all systems.

2.2.6. Covariates

Standard covariates for all analyses included age in years, sex, smoking, alcohol consumption, physical activity (International Physical Activity Questionnaire (IPAQ) (Hagströmer et al., 2007)), body mass index (BMI), and a number of chronic diseases. Stress-system-specific covariates were based on earlier studies using the same data. Awakening time, working status on the day of the sampling, and season on the day of the sampling were included for HPA-axis-focused analyses (Vreeburg et al., 2009b). Anti-inflammatory medication use was included for inflammation-focused analyses (Vogelzangs et al., 2012), while antidepressant use, cardiac medication use, respiratory rate (for RSA), and mean arterial pressure (for PEP) were included for ANS-focused analyses (Houtveen et al., 2005; Licht et al., 2012). Analyses of the cumulative occurrence of dysregulations included all relevant covariates. To examine whether the effect of CT is independent of the psychiatric status, presence of current (past 6 months) and remitted (lifetime, but not past 6 months) depressive and/or anxiety disorder and CT × current and remitted depressive and/or anxiety disorder were additionally included in the analyses. Diagnoses were based on the CIDI version 2.1 (Robins et al., 1988) assessing depressive (major depressive disorder, dysthymia) and anxiety disorders (social anxiety disorder, agoraphobia, generalized anxiety disorder, panic disorder with or without agoraphobia) as based on the criteria of DSM-IV (American Psychiatric Association (APA) (2001)).

2.3. Data-analyses

Sample characteristics were explored descriptively and presented as means with standard deviations, medians with interquartile ranges (for skewed outcome distributions), or numbers with percentages. Spearman's correlation (ρ) was used to examine the intercorrelations between CT and markers of stress systems. For further analyses, markers with skewed distributions (evening cortisol, DST cortisol, CRP, IL-6, and TNF-α) were log-transformed (ln).

To determine whether CT is significantly associated with stress systems, multiple linear regression analyses were performed. CT was included as a predictor variable and each of the stress systems' markers as an outcome variable. CT was examined as a total severity score (range 0–8) and as severity scores for different types of CT (range 0–2). The activity of stress systems was examined as markers of the HPA-axis (CAR, evening cortisol, and DST cortisol), inflammation (IL-6, TNF-α, and CRP), ANS (HR, RSA, and PEP), and a cumulative marker score within each stress system, as well as across all systems (average standardized score). Two models were created: Model 1, including basic adjustment for demographic and stress-system-specific covariates (see covariates section); and Model 2, additionally adjusting for lifestyle and health-related covariates that could partially explain the association between CT and dysregulation of stress systems. As a sensitivity analysis, the main analyses were rerun with the CTQ-SF as a measure of CT. For the secondary analysis, to fully disentangle the effect of the severity of CT and the potential influence of psychopathology in the sample, extreme-comparison analyses zooming in on the clearest contrasting

groups were performed. We compared: (1) individuals with mild CT (CTI score 1–3) versus healthy controls without CT (HC; CTI score 0 + no lifetime depressive and/or anxiety disorder), and (2) individuals with severe CT (CTI score ≥ 4) versus HC without CT. To avoid over-adjustment in latter analyses, psychiatric status was not included in Model 2.

For all analyses, the statistical significance was based on a *p*-value < .05. The Benjamini-Hochberg False Discovery Rate (FDR *p*-value < .05) was used to correct for multiple analyses (14 tests per model) (Benjamini and Hochberg, 1995). Based on 1409 participants (with complete data on all stress systems' markers and covariates), a post-hoc power to detect small to large effect size (f^2 = .02–.35) with 20 predictors in a model was high (92 %–100 %, α = .05, G*Power). All data were interpreted using IBM SPSS 25 and R Studio 1.3.959 software (IBM Corp, 2017; RStudio Team, 2020).

3. Results

3.1. Sample characteristics

The mean age of the sample (*n* = 2778) was 41.65 (*SD* = 13.1) years, with the majority of participants being female (65.6 %; Table 1). The average total CT score was 1.58 (*SD* = 2.11, CTI), with about half of the sample having experienced at least one type of CT (47.9 %, *n* = 1330). Of those with CT, almost all (88.6 %, *n* = 1178) had current or remitted depressive and/or anxiety disorder. Most of those without CT had a diagnosed current or remitted depressive and/or anxiety disorder as well (68.4%, *n* = 990). Weak but significant correlations (ρ = -.08 to .08, *p* < .05) were found between total CT score and the AUCg, evening cortisol, CRP, IL-6, and RSA (Table S1). All markers within each stress system were also significantly intercorrelated (ρ = -.28 to .44, *p* < .01), as were almost all markers between the immune-inflammatory system and ANS (ρ = -.20 to .18, *p* < .01). Besides, significant correlations were observed between the DST cortisol and IL-6, AUCg, and RSA, as well as of evening cortisol with CRP, RSA, and PEP (*p* < .05).

3.2. Associations between CT and stress systems

Slightly heightened levels of cortisol and inflammation in individuals with higher CT scores were observed (Table 2). The total CT score was significantly associated with IL-6 (β = .048, *p* = .012) and cumulative markers across all systems (β = .058, *p* = .025) in Model 1 controlling for demographic and stress-system-specific covariates; however, after the lifestyle and health-related adjustment in Model 2 significant associations disappeared (*p* > .05). Among the CT types, only emotional abuse was significantly associated with AUCi (β = .144, *p* = .049), CRP (β = -.135, *p* = .014), and cumulative inflammation (β = -.113, *p* = .044) (Model 2; Table 3). None of the significant associations between CT and stress systems' markers survived the multiple comparison adjustment (p_{FDR} > .05). The associations were also not modified by psychiatric status as indicated by non-significant CT × psychiatric status (current and remitted depressive and/or anxiety disorder) interactions. Only the interaction between emotional abuse and current disorder on inflammation was significant (CRP, β = .114, *p* = .028; cumulative inflammation, β = .111, *p* = .036); however, this was not consistent across analyses, did not survive the multiple comparison adjustment, and was not confirmed in the sensitivity analysis. Analysis of CT using a categorical approach rather than a continuous variable did not alter the results.

3.3. Sensitivity analysis – CTQ-SF

All correlations between parallel subscales of the CTI (baseline) and CTQ-SF (4-year follow-up) ranged from moderate to strong and were significant (*r* = .59–.70, *p* < .001; Table S2). The CTI and CTQ-SF total scores showed the strongest correlation (*r* = .77, *p* < .001). In line with

Table 1
Sample characteristics.

Characteristics	N	Mean (SD) / Median (IQR) / n (%)
Demographics		
Age in years, mean (SD)	2778	41.65 (13.10)
Sex, female, n (%)	2778	1823 (65.6)
Lifestyle and health		
Current smoker, yes, n (%)	2778	1077 (38.8)
Alcohol consumption (drinks per week), mean (SD)	2739	7.14 (10.03)
Physical activity (1000 MET-min/wk), mean (SD)	2778	3.70 (3.02)
BMI (kg/m²), mean (SD)	2776	25.49 (4.94)
Number of chronic diseases, mean (SD)	2778	.83 (1.02)
Current depressive and/or anxiety disorder (CIDI), yes, n (%)	2778	1585 (57.1)
Remitted depressive and/or anxiety disorder (CIDI), yes, n (%)	2778	583 (21.0)
Healthy controls (CIDI), yes, n (%)	2778	610 (21.9)
Childhood trauma		
CTI total severity score, mean (SD)	2778	1.58 (2.11)
CTI emotional neglect, mean (SD)	2778	.72 (.93)
CTI emotional abuse, mean (SD)	2778	.44 (.81)
CTI physical abuse, mean (SD)	2778	.20 (.55)
CTI sexual abuse, mean (SD)	2778	.22 (.50)
CTQ-SF total severity score, mean (SD)	2144	32.78 (11.74)
CTQ-SF emotional neglect, mean (SD)	2146	12.27 (5.10)
CTQ-SF emotional abuse, mean (SD)	2146	8.56 (4.34)
CTQ-SF physical abuse, mean (SD)	2148	5.94 (2.57)
CTQ-SF sexual abuse, mean (SD)	2148	6.03 (2.89)
Hypothalamic-Pituitary-Adrenal-axis		
Cortisol awakening response, mean (SD)	1833	
AUCg (nmol/L/hr)		18.91 (6.96)
AUCi (nmol/L/hr)		2.16 (6.23)
Evening cortisol (nmol/L), median (IQR)	1994	4.81 (3.22)
DST cortisol, median (IQR)	1885	2.39 (1.50)
Immune-inflammatory system		
C-reactive protein (mg/L), median (IQR)	2740	1.19 (2.38)
Interleukin-6 (pg/mL), median (IQR)	2740	.74 (.74)
Tumor necrosis factor-α (pg/mL), median (IQR)	2721	.80 (.50)
Autonomic Nervous System		
Heart rate (bpm), mean (SD)	2667	71.79 (9.60)
Respiratory sinus arrhythmia (ms), mean (SD)	2667	44.72 (25.88)
Pre-ejection period (ms), mean (SD)	2645	120.22 (17.76)
Stress-system-specific covariates		
Awakening time (00:00–23:59), mean (SD)	1868	7.46 (1.24)
Working on the sampling day, yes, n (%)	1871	1103 (59.0)
Season on the sampling day, n (%)	2778	
October-February (less daylight)		1207 (43.4)
March-September (more daylight)		1571 (56.6)
Anti-inflammatory medication use, yes, n (%)	2778	109 (3.9)
Antidepressant use, yes, n (%)	2778	682 (24.6)
Cardiac medication use, yes, n (%)	2778	333 (12.0)
Respiratory rate, mean (SD)	2667	17.08 (1.20)
Mean arterial pressure, mean (SD)	2773	99.57 (13.36)

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/m2, 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; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; Nmol/L/hr, nanomoles per liter per hour; Nmol/L, nanomoles per liter; Mg/L, milligrams per liter; Pg/mL, picograms per liter; Bpm, beats per minute; Ms, milliseconds.

the results obtained using the CTI, individuals with higher CTQ-SF scores showed slightly elevated levels of cortisol and inflammation (Table S3). The total CTQ-SF score was significantly associated with CRP (β = .049, *p* = .025) in Model 1; however, the significant association disappeared in Model 2. Magnitude of the associations with IL-6 (β = .036, *p* = .097) and cumulative stress systems' markers (β = .052, *p* = .060) was comparable to that obtained using the CTI, but

Table 2
Multiple regression results on standardized stress systems' markers associated with the total childhood trauma score (CTI).

	Childhood trauma (CTI) – Total severity score							
	Model 1 – Basic adjustment				Model 2 – Additional lifestyle/health adjustment			
	N	Beta[†]	SE[‡]	p	N	Beta[†]	SE[‡]	p
HPA-axis markers								
CAR - AUCg	1603	.022	.026	.380	1596	.016	.078	.831
CAR - AUCi	1603	.022	.027	.381	1596	.077	.080	.313
Evening cortisol	1733	.011	.024	.662	1725	.086	.068	.204
DST cortisol	1639	−.018	.026	.476	1632	.057	.083	.478
Cumulative HPA markers	1536	.037	.027	.151	1529	.038	.080	.626
Immune-inflammatory markers								
C-reactive protein	2739	.025	.019	.187	2700	−.092	.055	.096
Interleukin-6	2739	.048	.019	**.012**	2700	−.016	.059	.781
Tumor necrosis factor-α	2720	−.010	.019	.622	2681	−.038	.061	.536
Cumulative inflammation markers	2712	.032	.019	.094	2673	−.070	.056	.214
ANS markers								
Heart rate	2666	−.005	.019	.790	2627	.012	.060	.838
Respiratory sinus arrhythmia	2666	.001	.016	.965	2627	−.064	.050	.198
Pre-ejection period	2641	.005	.020	.794	2602	−.082	.060	.173
Cumulative ANS markers	2641	−.001	.019	.955	2602	.083	.058	.146
Cumulative stress markers	1416	.058	.026	**.025**	1409	.096	.079	.205

Note. Model 1: adjustment for age, sex, awakening time (for HPA-axis), working status on the day of the sampling (for HPA-axis), season on the day of the sampling (for HPA-axis), anti-inflammatory medication use (for inflammation), antidepressant use (for ANS), cardiac medication use (for ANS), respiratory rate (for RSA), and mean arterial pressure (for PEP). Model 2: additional adjustment for psychiatric status (current and remitted depressive and/or anxiety disorder), CT × psychiatric status, smoking, alcohol consumption, physical activity, BMI, and number of chronic diseases. Abbreviations: CTI, Childhood Trauma Interview; HPA-axis, hypothalamic-pituitary-adrenal-axis; CAR, cortisol awakening response; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; DST, dexamethasone suppression test; ANS, autonomic nervous system; RSA, respiratory sinus arrhythmia; PEP, pre-ejection period.
Boldface indicates statistical significance ($p < .05$) † Standardized beta. ‡ Standard error of the standardized beta.

only approaching significance. Sexual abuse was significantly associated with DST cortisol ($\beta = .215$, $p = .020$) in Model 2 (Table S4). Similar to CTI, none of the significant associations survived the multiple comparison adjustment ($p_{FDR} > .05$).
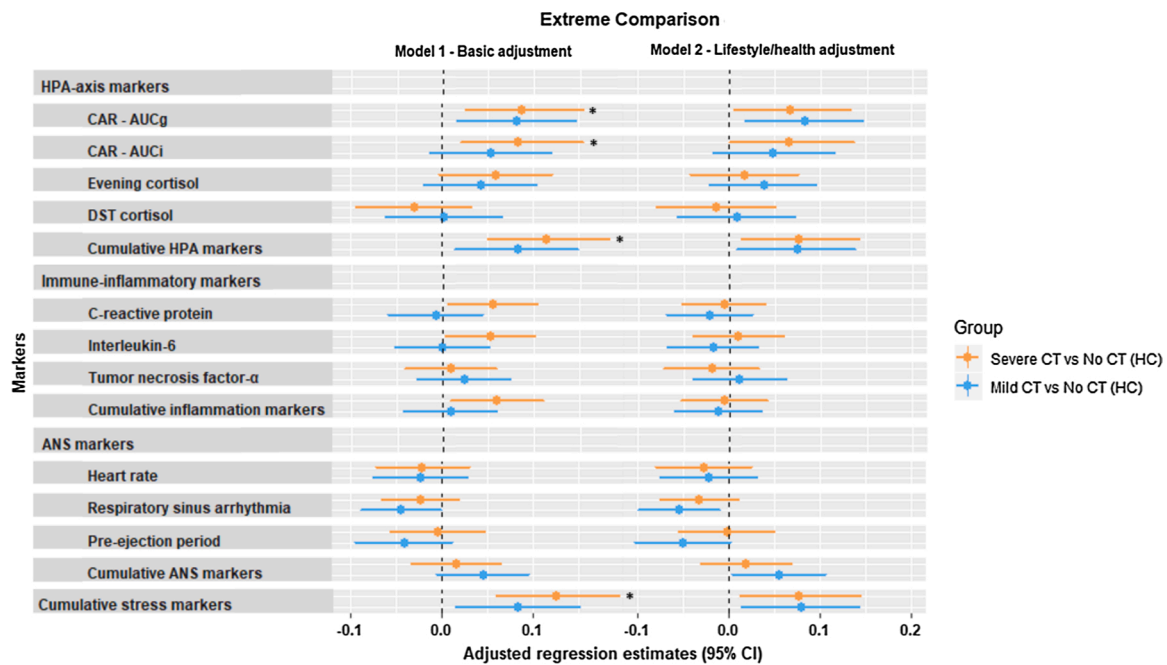
3.4. Extreme comparison analyses

Visual comparison of the regression estimates with corresponding 95 % confidence intervals (CIs) of stress systems' markers associated with mild and severe CT is shown in Fig. 1. Mild CT (CTI score 1–3, max $n = 748$, referenced to HC without CT and no lifetime depressive and/or anxiety disorder, max $n = 458$), was significantly associated with AUCg ($\beta = .082$, $p = .015$), cumulative HPA-axis markers ($\beta = .083$, $p = .017$), and cumulative markers across all systems ($\beta = .084$, $p = .017$) in Model 1 (Table S5). The associations remained significant in Model 2; however, in both models, significance levels did not survive the multiple

Table 3
Multiple regression results on standardized stress systems' markers associated with childhood trauma types (CTI).

	Childhood trauma types (CTI) – Model 2												
		Emotional neglect			Emotional abuse			Physical abuse			Sexual abuse		
	N	Beta[†]	SE[‡]	p	Beta[†]	SE[‡]	p	Beta[†]	SE[‡]	p	Beta[†]	SE[‡]	p
HPA-axis markers													
CAR - AUCg	1596	.068	.071	.334	.047	.073	.510	−.077	.109	.448	−.094	.069	.160
CAR - AUCi	1596	.033	.074	.650	.144	.076	**.049**	.104	.113	.316	−.046	.072	.505
Evening cortisol	1725	.084	.063	.192	.013	.066	.841	.126	.093	.160	.076	.063	.227
DST cortisol	1632	.038	.075	.614	.013	.075	.866	−.032	.124	.784	.118	.074	.097
Cumulative HPA markers	1529	.052	.073	.472	.068	.073	.341	.037	.118	.735	−.082	.071	.231
Immune-inflammatory markers													
C-reactive protein	2700	−.032	.051	.535	−.135	.054	**.014**	−.073	.062	.244	−.032	.050	.525
Interleukin-6	2700	−.051	.056	.354	−.008	.059	.890	−.027	.067	.692	.061	.055	.258
Tumor necrosis factor-α	2681	−.025	.057	.664	−.089	.060	.145	−.039	.069	.575	.061	.055	.280
Cumulative inflammation markers	2673	−.051	.053	.340	−.113	.056	**.044**	−.070	.064	.281	.045	.051	.387
ANS markers													
Heart rate	2627	<.001	.057	.996	−.016	.060	.786	−.023	.068	.735	.081	.055	.140
Respiratory sinus arrhythmia	2627	−.070	.047	.140	−.032	.050	.518	−.003	.057	.954	−.060	.046	.189
Pre-ejection period	2602	−.010	.057	.857	−.078	.060	.196	−.122	.068	.072	−.081	.055	.144
Cumulative ANS markers	2602	.049	.054	.368	.051	.057	.370	.057	.065	.375	.100	.053	.059
Cumulative stress markers	1409	.113	.072	.113	.047	.071	.507	.076	.114	.477	.023	.070	.728

Note. Model 2: adjustment for age, sex, awakening time (for HPA-axis), working status on the day of the sampling (for HPA-axis), season on the day of the sampling (for HPA-axis), anti-inflammatory medication use (for inflammation), antidepressant use (for ANS), cardiac medication use (for ANS), respiratory rate (for RSA), mean arterial pressure (for PEP), psychiatric status (current and remitted depressive and/or anxiety disorder), CT × psychiatric status, smoking, alcohol consumption, physical activity, BMI, and number of chronic diseases.
Abbreviations: CTI, Childhood Trauma Interview; HPA-axis, hypothalamic-pituitary-adrenal-axis; CAR, cortisol awakening response; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; DST, dexamethasone suppression test; ANS, autonomic nervous system; RSA, respiratory sinus arrhythmia; PEP, pre-ejection period.
Boldface indicates statistical significance ($p < .05$) † Standardized beta. ‡ Standard error of the standardized beta.

Fig. 1. Forest plot of adjusted standardized regression estimates with corresponding 95 % confidence intervals of stress systems' markers associated with mild and severe CT.

Note. Model 1:adjustment for age, sex, awakening time (for HPA-axis), working status on the day of the sampling (for HPA-axis), season on the day of the sampling (for HPA-axis), anti-inflammatory medication use (for inflammation), antidepressant use (for ANS), cardiac medication use (for ANS), respiratory rate (for RSA), and mean arterial pressure (for PEP). Model 2: additional adjustment for smoking, alcohol consumption, physical activity, BMI, and number of chronic diseases.

*FDR p-values $< .05$. Mild CT (total CTI score 1–3, max $n = 748$), severe CT (total CTI score ≥ 4, max $n = 582$), HC without CT (total CTI score $= 0 +$ no lifetime depressive and/or anxiety disorder, max $n = 458$), present lifetime depressive and/or anxiety disorder without CT (max $n = 990$). Abbreviations: HPA-axis, hypothalamic-pituitary-adrenal-axis; CAR, cortisol awakening response; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; DST, dexamethasone suppression test; ANS, autonomic nervous system; CT, childhood trauma; HC, healthy controls; RSA, respiratory sinus arrhythmia; PEP, pre-ejection period.

comparison adjustment ($p_{FDR} > .05$).

Severe CT (CTI score ≥ 4, max $n = 582$, referenced to HC without CT), was significantly associated with the AUCg ($\beta = .088$, $p = .007$), AUCi ($\beta = .084$, $p = .010$), cumulative HPA-axis markers ($\beta = .115$, $p = .001$), CRP ($\beta = .055$, $p = .032$), IL-6 ($\beta = .053$, $p = .038$), cumulative inflammation ($\beta = .060$, $p = .020$), and cumulative markers across all systems ($\beta = .125$, $p = .0003$) in Model 1. These associations were reduced in Model 2 by higher rates of smoking (more than 10% drop of the standardized regression estimate (beta, β) of severe CT on HPA-axis markers, inflammation markers, and cumulative markers across all systems), BMI (more than 10% drop of beta of severe CT on inflammation markers and cumulative markers across all systems), and number of chronic diseases (more than 10% drop of beta of severe CT on inflammation markers) which were more prevalent in those with severe CT (current smoker, 45.4% vs. 27.9%; BMI, $M = 26.48$, $SD = 5.36$ vs. $M = 25.00$, $SD = 4.59$, number of chronic diseases, $M = 1.12$, $SD = 1.18$ vs. $M = .53$, $SD = .79$, all p-values $< .001$). Significant Model 1 associations with HPA-axis markers and cumulative stress markers survived the multiple comparison adjustment; however, not in Model 2 ($p_{FDR} > .05$).

4. Discussion

The current study examined associations between CT and markers of the major stress systems in a large adult cohort, adjusting for multiple potentially confounding factors. The focus was on separate and cumulative markers within each stress system and across all systems. Generally, our results showed little evidence for CT being associated with separate or cumulative stress systems' dysregulations. These findings are in line with previous meta-analyses reporting no significant associations between CT and several static HPA-axis markers (Bernard et al., 2017;

Fogelman and Canli, 2018), but are in contrast with the meta-analytic findings on significant associations of CT with basal wake-up cortisol (Bernard et al., 2017) and inflammation (Baumeister et al., 2016). Standardized regression coefficients were small, generally suggesting slightly heightened levels of cortisol and inflammation in those with higher CT scores. This is rather comparable with the magnitude and direction of effect sizes reported in earlier meta-analyses (Baumeister et al., 2016; Fogelman and Canli, 2018), but in contrast with the meta-analytic findings on blunted wake-up cortisol (Bernard et al., 2017). Sensitivity analyses using a different CT measure, the self-reported CTQ-SF questionnaire, showed rather congruent results. Psychiatric status did not moderate associations between CT and stress systems. Zooming in on individuals with severe CT and contrasting them to HC without CT showed the strongest evidence for slight dysregulations within the HPA-axis (heightened CAR and cumulative HPA-axis markers), immune-inflammatory system (elevated CRP, IL-6, and cumulative inflammation), and cumulative markers across all stress systems. This was not the case for mild CT. However, these associations were partially explained by a pattern of higher rates of smoking, BMI, and number of chronic diseases in those with severe CT.

The lack of significant associations between CT and stress systems in NESDA cohort can be interpreted in a number of ways. First, these associations may have been diluted by an overrepresentation of the clinical population, characterized by dysregulated stress systems in our sample (Hu et al., 2016; Vogelzangs et al., 2016; Vreeburg et al., 2009a). This is in line with our significant findings from extreme contrast analyses comparing individuals with severe CT and HC without CT. Besides, previous meta-analyses have mostly focused on the general population, which possibly explains why our total-sample results do not align with theirs. Second, the association between CT and stress systems may be indirect and at least partially explained by other factors such as an

unhealthy lifestyle. For instance, our findings showed that significant associations between severe CT and stress systems' dysregulations were partially explained by higher rates of smoking and BMI. This may be interpreted as a confounding bias or a specific process via which CT impacts stress systems. In fact, a recent meta-analysis has concluded significant associations between multiple experiences of CT and adult lifestyle factors, among which smoking and obesity (Hughes et al., 2017), which, in turn, are linked to stress systems' dysregulation, and are likely to act as mechanisms of CT (Hostinar et al., 2015; Matthews et al., 2014). Consequently, lifestyle factors should not be ignored when examining CT and stress systems; however, this was not always addressed in previous meta-analyses. Third, CT may only have an impact on the stress systems depending on the genetic vulnerability of the person; thus, a direct effect may be hard to discern in the total sample. For instance, the mineralocorticoid receptor gene (MR, *NR3C2*; HPA-axis gene) was found to moderate the link between CT and DST cortisol (Gerritsen et al., 2017). These findings would explain the small or absent direct effects of CT on stress systems reported in earlier meta-analyses (Baumeister et al., 2016; Bernard et al., 2017; Fogelman and Canli, 2018). Fourth, the effect of CT on stress systems may be more prominent in response to acute stress (Bunea et al., 2017; Young--Southward et al., 2019) and not to the more static state used in our study. Therefore, studies comparing multiple static and dynamic measures of stress systems are needed. Fifth, although the markers used in the current study are common in trauma research and have been linked to both mental and somatic health outcomes (Fioranelli et al., 2018; Penninx et al., 2013), other stress systems' markers may be uniquely affected by CT. For instance, a recent study found a significant association between CT and soluble urokinase plasminogen activator receptor (suPAR; a marker of chronic inflammation), but no link with commonly assessed CRP and IL-6 after adjustment for lifestyle factors (Rasmussen et al., 2019). Finally, significant findings of previous meta-analyses could be overestimated due to the overrepresentation of the positive results in the published literature. Therefore, the dysregulation of stress systems may not be the primary mechanism of CT, and other neural, genetic, or metabolic mechanisms should be considered (Agorastos et al., 2019).

4.1. Strengths and limitations

With a large sample of adult participants, including individuals with and without psychopathology, the current study possesses adequate power to detect the effect of CT on stress systems. To address the interplay between the systems, the analyses were focused on separate and cumulative markers within and across the systems. Multiple variables were taken into account to provide the most accurate results. Although not all significant associations survived multiple comparison adjustment, they were generally in line with previous research, suggesting that false-positive findings are not very likely. The main limitation of the current study is the nature of its design. Reliance on the retrospective CT assessment may have been affected by recall bias, especially the negative recall bias considering the overrepresentation of psychopathology in our sample. Still, the strong correlation between the two measures of CT with a 4-year time difference suggested rather high consistency of retrospective reports. It has also been shown that the likelihood of CT being overreported is similar to being underreported (Baldwin et al., 2019) and that the reporting of CT is not explained by individual's psychiatric status (Fergusson et al., 2011). While overrepresentation of the clinical population in the current sample may have diluted the effect of CT, it appears to be a fact that many individuals with CT develop depressive and/or anxiety disorders in their adulthood. The cross-sectional design also limited examination of the temporal direction of the associations between variables. To disentangle causal associations between CT and stress systems, a longitudinal design more proximal to the occurrence of CT is necessary. Finally, stress systems' markers were mostly static and may not have been sensitive enough to detect the

dynamic activity of stress response.

4.2. Conclusion and future research

In the current study, little evidence for CT being significantly associated with the separate or cumulative stress systems' activity in adulthood was found. Only when zooming in on individuals with severe CT compared to healthy controls without CT, were most stress systems' dysregulations observed, which concerned slightly heightened levels of HPA-axis markers, inflammation markers, and cumulative markers across all systems. These dysregulations were partially due to smoking, BMI, and chronic disease patterns, indicating the relevance of considering lifestyle and health when interpreting the impact of CT on stress systems. Severe CT was also more strongly associated with cumulative stress markers than most of the separate markers, suggesting the importance of looking into cumulative dysregulations. Our comprehensive approach, including measures of the major stress systems, provided a better picture of the pathophysiology of CT, suggesting the heightened risk of stress systems' dysregulations for individuals with severe CT, and proposing lifestyle as a potential therapeutic target. Further large-scale longitudinal studies on multiple separate and cumulative stress markers are recommended to allow better comparison with existing evidence and to improve understanding of the pathophysiological mechanisms that bridge CT and health outcomes.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.10 4835.

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