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Review article

Childhood Trauma in Adult Depressive and Anxiety Disorders: An Integrated Review on Psychological and Biological Mechanisms in the NESDA Cohort

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ABSTRACT

Background: Childhood trauma (CT) has adverse consequences on mental health across the lifespan. The understanding of how CT increases vulnerability for psychiatric disorders is growing. However, lack of an integrative approach to psychological and biological mechanisms of CT hampers further advancement. This review integrates CT findings across explanatory levels from a longitudinal adult cohort – the Netherlands Study of Depression and Anxiety (NESDA).

Methods: We reviewed all studies ($k = 37$) from the NESDA cohort ($n = 2981$) published from 2009 to 2020 containing CT findings related to psychopathology and potential psychological and biological mechanisms of CT.

Results: CT was associated with a higher risk of anxiety and depressive disorders with the strongest associations in the comorbid group. CT predicted the onset of these disorders, recurrence, and poorer outcomes (more comorbidity and chronicity). CT was associated with maladaptive personality characteristics and cognitions (e.g., higher neuroticism and negative self-associations), mild stress systems dysregulations (heightened levels of cortisol and inflammation), advanced biological aging (increased epigenetic aging and telomere attrition), poorer lifestyle (higher smoking rate and body mass index), somatic health decline (e.g., increased metabolic syndrome dysregulations), and brain alterations (e.g., reduced mPFC volume and increased amygdala reactivity).

Limitations: Literature review of one cohort using mixed analytical approaches.

Conclusion: **:** CT impacts the functioning of the brain, mind, and body, which together may contribute to a higher vulnerability for affective disorders. It is essential to employ an integrative approach combining different sources of data to understand the mechanisms of CT better.

1. Introduction

Childhood trauma (CT) is one of the most robust and significant risk factors for depressive and anxiety disorders. CT is commonly defined as "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility,

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trust or power" [(World Health Organization (WHO) 1999), p.15]. CT is operationalized as emotional (or psychological) abuse, physical abuse, sexual abuse, and neglect (emotional or physical) before the age of 18 years (Butchart et al., 2006). There is uncertainty about the frequency and severity of CT worldwide, as it is mostly hidden and unreported due to fear, stigma, and societal acceptance of this type of violence (Pinheiro, 2006). Discrepancies between CT rates reported by child-protection agencies and community studies (self-report) suggest that most incidences of CT are underreported (Gilbert et al., 2009, Sedlak and Ellis, 2014). So far, sexual and physical abuse in childhood has been most frequently investigated, while emotional abuse and neglect the least (Gilbert et al., 2009, Moody et al., 2018). Unfortunately, CT is common in the clinical and general population. For instance, a recent systematic review on the international lifetime prevalence of self-reported CT combining clinical and general population revealed the rates of emotional abuse of approximately 21.7% in Europe and 23.9% in North America (Moody et al., 2018).

CT has severe and long-lasting effects on both mental and somatic health across the lifespan. About one-third of all adult-onset psychiatric disorders are related to CT (Sedlak and Ellis, 2014), with lifelong effects on morbidity and mortality (Gilbert et al., 2009, Chen et al., 2016). Moreover, CT increases the risk of negative life events, suicidality, sleep problems, and cognitive problems (Angelakis et al., 2019, Norman et al., 2012, van Harmelen et al., 2010). CT not only affects mental health but also increases the risk of obesity, diabetes, lung disease, and cardiovascular disorders (Widom et al., 2012, Danese and Tan, 2014). For instance, exposure to CT has not only been associated with three to four times increased risk for depression and anxiety but also with two to three times increased risk of adult cancer, respiratory and cardiovascular disease (Hughes et al., 2017). This is relevant as somatic health generally receives limited attention within psychiatry, notwithstanding higher mortality rates and a greatly reduced lifespan. There is increasing evidence that CT-related affective disorders represent a clinically distinct subtype of psychopathology (Teicher and Samson, 2013), characterized by earlier emergence, more severe and recurrent symptoms, as well as worse treatment outcomes be it psychotherapy, pharmacotherapy, or combined treatment (Teicher and Samson, 2013, Hovens et al., 2012, Miniati et al., 2010, Nanni et al., 2012, Nelson et al., 2017). Despite the severity and high prevalence of CT across affective disorders, it is largely unknown why and how CT is associated with persistently poor outcomes for both anxiety and depression, and no targeted treatments exist that reverse the detrimental effects of CT. CT is, therefore, a major public health problem, and arguably the most potent predictor of poor mental health across the lifespan.

Biological research findings suggest that severe stress in early life elevates cortisol levels that over-activate glucocorticoid receptor (GR). The consequence of this glucocorticoid overproduction during early life is the abnormal development of the stress systems (Lupien et al., 2009, Roberts and Lopez-Duran, 2019, van Bodegom et al., 2017). Although this response may be adaptive in the short-term, it comes at the cost of long-term maladaptation: a reduced capacity to adequately and dynamically respond to stress across the lifespan (McLaughlin et al., 2010, Daskalakis et al., 2013). Precise mechanisms of CT, leading to poorer outcomes across the lifespan are heterogeneous, spanning from psychological, environmental to the biological. Unraveling the mechanisms through which CT impacts mental health outcomes so far has been difficult, due to the methodological heterogeneity among the studies and the focus on one type of the mechanism. Hence, this review aims to summarize and integrate CT findings from a large longitudinal adult sample - The Netherlands Study of Depression and Anxiety (NESDA), in relation to psychopathology and discuss different psychological and biological mechanisms that may underlie the long-lasting impact of CT.

2. The Netherlands Study of Depression and Anxiety (NESDA)

The Netherlands Study of Depression and Anxiety (NESDA; $n = 2981$) is an ongoing longitudinal cohort study examining the course and consequences of depressive and anxiety disorders (Penninx et al., 2008). NESDA sample includes Dutch-fluent adults between 18 and 65 years old with a current or remitted depressive and/or anxiety disorder (78% Composite International Diagnostic Interview, CIDI) (Robins et al., 1988) and healthy controls (22%). Participants were recruited between September 2004 and February 2007 from three different settings: community (19%), primary health-care (54%), and specialized mental health-care (27%). Individuals with a primary clinical diagnosis of other psychiatric disorders, such as post-traumatic stress disorder, bipolar disorder, psychotic disorder, or obsessive-compulsive disorder, were excluded. All participants were assessed on various sociodemographic, lifestyle, (mental) health, and biological factors during a 4-hour clinic visit. A subgroup of NESDA participants ($n = 301$) with or without (healthy controls) depressive and/or anxiety disorder underwent magnetic resonance imaging (MRI) assessment at the baseline. These individuals aged between 18 and 55 years and had no history of major internal or neurological disorders. NESDA 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 detailed information on NESDA can be found in Penninx et al. (Penninx et al., 2008).

Within NESDA, CT was examined in 37 articles (identified from the list of all publications to date on the NESDA website: www.nesda.nl) focused on psychopathology as well as potential psychological and biological mechanisms underlying CT. Exposure to CT in NESDA was assessed twice: at the baseline using the structured Childhood Trauma Interview (CTI) (de Graaf et al., 2004), and at a 4-year follow-up using the self-reported Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Bernstein et al., 2003). Both the CTI and the CTQ-SF retrospectively assess different types of CT: emotional neglect, emotional abuse, physical abuse, sexual abuse, and/or physical neglect (additionally assessed by the CTQ-SF) before the age of 16, thus, while growing up. The strong correlation between the CTI and the CTQ-SF with a 4-year time difference (total score, $r = 0.77$; subscales, $r = 0.57$-0.61) indicated high consistency of retrospective reports (Kuzminskaite et al., 2020, Spinhoven et al., 2014). Due to the fact that it was assessed at the baseline and had the largest completeness (99.6%), the majority of research within NESDA focuses on the CTI. In the CTI, 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). In the case of CT, participants are asked about the perpetrator: biological father, biological mother, stepfather or friend of the mother, stepmother or friend of the father, siblings, other family member, or somebody else. Intercorrelations between different CT types ranged from modest to large, with the highest correlation between emotional neglect and emotional abuse ($r = .61, p < .001$) (see Fig. 1 for correlations and density plots). Hence, the sum of the number of CT types and frequency of exposure to CT (childhood trauma index, range 0-8) is often used as a gradient and has been particularly associated with the prevalence, chronicity, and development of psychopathology in a dose-response manner (Hovens et al., 2012, Hovens et al., 2010, Wiersma et al., 2009, Hovens et al., 2015).

3. Epidemiological Findings of CT Within NESDA

3.1. CT Prevalence and Impact on Affective Disorders

Concerning the prevalence rates of CT within NESDA ($n = 2970$; exposure of at least once as assessed by the CTI), emotional neglect and emotional abuse were the most common types (38.9% and 24.8%, respectively), followed by sexual (18.5%) and physical abuse (13.8%) with approximately half of participants (48.6%) having experienced at least one type of CT. Out of participants with CT, the majority scored in the mild childhood trauma index range (score 1-3; 55.5%), with 44.5% scoring in the more severe range (score $\geq$ 4). If emotional neglect or

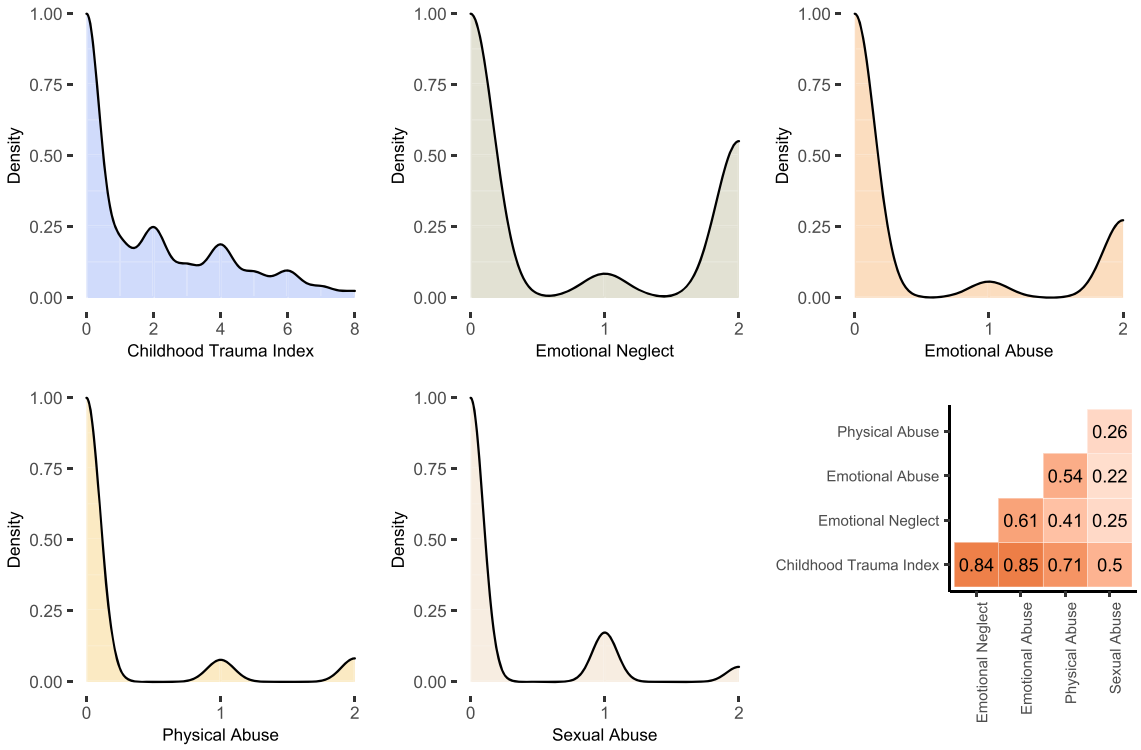

Fig. 1. Scaled density plots for childhood trauma index and each trauma type with corresponding intercorrelations (Pearson's *r*).
Note: all correlation p-values < .001

emotional abuse were present, more than 80% reported the frequency of "regularly, often, or very often". This was lower for physical (52%) and sexual abuse (23.3%). Emotional neglect, emotional abuse, and physical abuse were most often identified as perpetrated by family members (61-84%), while sexual abuse by someone else (71%). For additional details, also see Hovens et al. (Hovens et al., 2010).

Many previous studies that reported a relationship between CT and depressive or anxiety disorders in adulthood have focused on lifetime psychopathology (Kessler et al., 1997) and the more obvious forms of maltreatment, such as physical and sexual abuse. Within NESDA, the emphasis was on multiple types of CT (i.e., emotional neglect, emotional, physical, and sexual abuse), and the specificity of associations with psychopathology (depressive versus anxiety disorders) (Hovens et al., 2010). In a sample of 1931 participants, we demonstrated that exposure to any type of CT was associated with a higher risk of current anxiety and depressive disorders in increasing strength from current anxiety to current depressive to current comorbid disorder (OR = 2.3, 4.8, and 9.4, respectively, for CT score 4-8 versus 0). All types of CT were also consistently and strongly associated with the presence of current anxiety and depressive disorders in adulthood. These findings concurred with a previous meta-analysis (Norman et al., 2012) and showed robust evidence of the impact of emotional neglect, emotional and physical abuse on the presence of depressive and anxiety disorders in adulthood according to a robust dose-response gradient. For all CT types, strongest associations were found in the comorbid group. Since comorbidity is associated with an increased number and severity of symptoms, our results suggest that CT contributes to the severity of psychopathology. Childhood life events (i.e., divorce of parents, early parental loss, and placement in care) were not consistently associated with psychopathology (Hovens et al., 2010).

Some studies have additionally analyzed associations between different types of CT and various depressive and anxiety disorders, suggesting that different trauma types may be linked to somewhat different psychopathology manifestations (van Veen et al., 2013, Spinhoven et al., 2010). Although all CT types were significantly associated with almost all depressive and anxiety disorders (i.e., dysthymia, major depressive disorder (MDD), generalized anxiety disorder, social phobia, panic disorder, agoraphobia), when controlled for comorbidity of disorders and different trauma types, emotional neglect appeared to be particularly associated with dysthymia, MDD, and social phobia, while sexual abuse with dysthymia only (Spinhoven et al., 2010). Adjusting for CT types and psychopathology status, emotional neglect was also found to be independently associated with the general distress and anhedonic depression symptom profiles, while sexual abuse with the general distress and anxious arousal (van Veen et al., 2013). These findings suggest that maltreatment, especially, emotional neglect, seem to be stronger associated with manifestations of depression.

Moreover, CT often occurs within families, and recently also siblings of respondents with lifetime depression and/or anxiety were invited to participate in the NESDA study. In a subsample consisting of 256 families ($n = 636$), siblings showed the most similarity in their reports of emotional abuse and/or emotional neglect followed by physical abuse, whereas sexual abuse was mostly reported by one person within a family (Kullberg et al., 2020). In line with these observations, the mean family level of emotional maltreatment and physical abuse, but not sexual abuse, were associated with more depressive symptoms. Hence, particularly in the case of more visible forms of CT, findings implicate that in addition to individual maltreatment experiences, the context of siblings' experiences is another crucial risk factor for adult depressive symptomatology.

3.2. CT and the Course of Affective Disorders

Exposure to CT as a predictor of the 2-year course of depressive and anxiety disorders was studied in a follow-up sample of 1209 NESDA participants with a baseline diagnosis of depressive and/or anxiety disorder (Fig. 2) (Hovens et al., 2012). The results confirmed that a reported history of CT was associated with a poor outcome, characterized

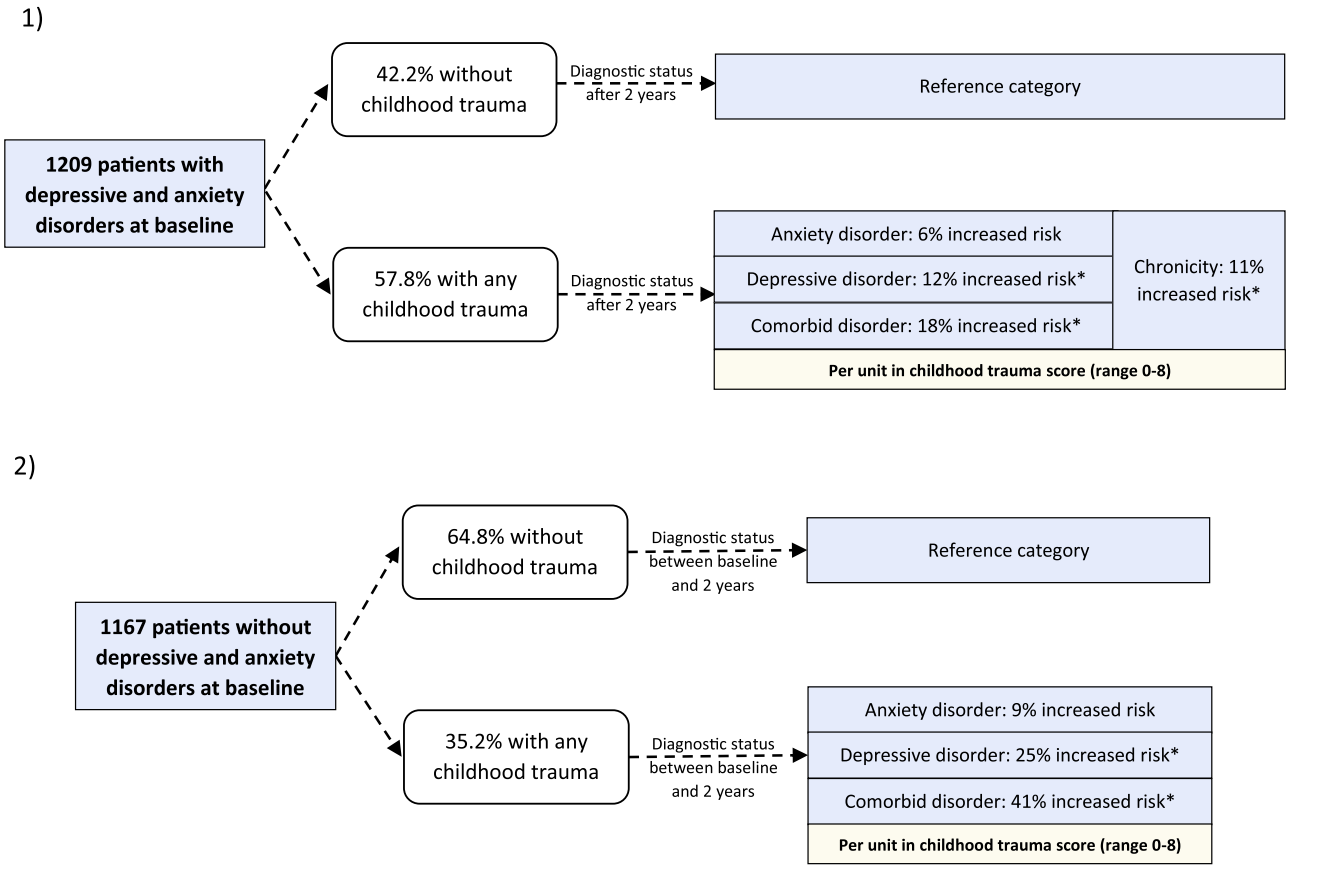

Fig. 2. The impact of childhood trauma on the 2-year course of depressive and/or anxiety disorders within the NESDA cohort with (1) and without (2) psychopathology at the baseline (see also: Hovens et al. (2012). Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatr Scand, 126*(3), 198-207; Hovens et al. (2015). Impact of childhood life events and childhood trauma on the onset and recurrence of depressive and anxiety disorders. *J Clin Psychiatry, 76*(7), 931-938).
*$p < .001$

by more comorbidity and chronicity (Wiersma et al., 2009, De Venter et al., 2017). This prospective study was different from the handful of previous studies in terms of considerably larger sample size and the inclusion of a range of CT types. We found that childhood emotional neglect, emotional abuse, and physical abuse were all (consistently and strongly) associated with the persistence of both depressive and comorbid depressive and anxiety disorders. Emotional neglect and emotional abuse were also associated with a higher occurrence of a chronic course. No significant associations were found between childhood sexual abuse and the course of anxiety and depressive disorders, which was surprising and counter-intuitive. This could partially be attributed to a somewhat lower statistical power for sexual abuse when compared to emotional neglect and abuse. The CT score was predictive of both depressive or comorbid disorder and a chronic course after a 2-year follow-up. The impact of CT on diagnostic status and course at a 2-year follow-up was not as strong for anxiety disorders.

Additionally, we explored the differential impact of different types of CT on the onset or recurrence of anxiety, depressive, and comorbid disorders in a sub-sample of 1167 NESDA participants without current baseline depressive and/or anxiety disorder followed over a 2-year time period (Fig. 2) (Hovens et al., 2015). Prospective evidence of CT predicting onset and recurrence of adult affective disorders is scarce and limited to children samples followed until (young) adulthood (Widom et al., 2007, Moffitt et al., 2007, Clark et al., 2010). We found that a history of CT significantly predicted the first onset and recurrence of depressive and comorbid disorders, but only slightly increased the risk for anxiety disorders. Among the CT types, emotional neglect was the main independent predictor of first onset and recurrence of any depressive or comorbid disorder at 2-year follow-up, suggesting that the relationship between CT and psychopathology is predominantly driven by emotional neglect. In line with NESDA previous cross-sectional studies (Hovens et al., 2010, Spinhoven et al., 2010), childhood life events were not associated with the 2-year onset and recurrence of depressive and/or anxiety disorders. Our findings on the course of depression in adults with reported CT were confirmed in a meta-analysis (Nanni et al., 2012), suggesting that maltreated individuals were twice more likely to develop both recurrent and persistent depressive episodes than those without a history of maltreatment. Altogether, NESDA findings indicate that individuals with the history of CT are at particular risk for depressive disorders and comorbid depression-anxiety, which further results in the personal and societal burden. For instance, findings within NESDA showed that individuals with severe childhood trauma had significantly reduced work functioning in terms of absenteeism and presenteeism, which was partially explained by current depressive and comorbid depressive and anxiety disorders (De Venter et al., 2020).

3.3. Psychological Mechanisms Linking CT and Psychopathology

3.3.1. Maladaptive Personality Characteristics and Cognitions

Exposure to CT may alter basic cognitive assumptions about the self and others, that over time may become ingrained in an individual's personality. The Five-Factor Model (FFM), in which individual personality differences are grouped to the five major dimensions of neuroticism, extraversion, openness, agreeableness, and conscientiousness, presently constitutes one of the dominant models comprehensively examining personality functioning (Kotov et al., 2010). The

development of the less adaptive personality characteristics has been proposed as a potential underlying mechanism explaining the link between CT and subsequent psychopathology (Kim et al., 2009). In line, within NESDA, the severity of CT corresponded with more maladaptive personality characteristics and cognitive reactivity styles, including higher levels of neuroticism, openness, hopelessness, rumination, and external locus of control and lower levels of extraversion, agreeableness, and conscientiousness (Table 1) (Hovens et al., 2016). Specifically, emotional neglect and abuse were associated with all personality characteristics in a detrimental direction, whereas physical and sexual abuse predicted only neuroticism, openness, rumination, hopelessness, and external locus of control (Hovens et al., 2016). Adopting a person-centered approach to personality, we have also identified five latent (mal)adaptive personality types, which primarily differed in the degree of neuroticism, extraversion, and, to a lower extent, conscientiousness and agreeableness with openness to experience not being related to a personality type (Spinhoven et al., 2016). In line with the findings by Hovens et al. (Hovens et al., 2016), individuals reporting more severe CT showed the most maladaptive personality types (Spinhoven et al., 2016). Additionally, individuals with high levels of neuroticism were found to be particularly vulnerable to the impact of cumulative stress (including CT) on depression outcomes (Vinkers et al., 2014), suggesting that personality is both a moderator and a potential mediator of psychopathology.

Within NESDA, CT has also been associated with lower levels of optimism with emotional abuse and/or emotional neglect showing the strongest association, even after adjustment for potential confounders (Broekhof et al., 2015). This is in line with a study among 20,000 Finnish workers, showing a dose-response association between childhood adversities and optimism (Korkeila et al., 2004). In addition, another NESDA study investigated the association between different types of abuse and negative self-associations and found that emotional abuse and/or emotional neglect, compared to other types of abuse, had the strongest association with both self-reported and automatic (implicit) negative self-associations to words such as "useless", "inadequate", or "insecure" (van Harmelen et al., 2010). One of the explanations for the particularly strong link between emotional maltreatment and negative cognitions is that in the case of emotional abuse or emotional neglect, negative self-associations are explicitly handed to the child by the parent (e.g., "you are worthless"). Moreover, automatic and explicit negative self-associations partially mediated the link between emotional abuse and/or neglect and depressive or anxious symptomatology (van Harmelen et al., 2010), and may also alter emotional regulation strategies that underlie optimistic outcome expectancies (Rose and Abramson, 1992). Overall, NESDA findings on potential psychological mechanisms of CT suggest that CT may generate maladaptive personality characteristics, including higher levels of neuroticism and negative self-associations, as well as lower levels of extraversion and optimism.

3.4. Biological Mechanisms Linking CT and Psychopathology

3.4.1. Dysregulated Biological Stress Systems

Alterations in the activity of the major stress systems, namely, the hypothalamic-pituitary-adrenal (HPA)-axis, the immune-inflammatory system, and the autonomic nervous system (ANS), are at the center of the biological psychiatry research seeking to explain the enduring impact of CT. Stressful life events can irreversibly dysregulate the functioning of stress systems by chronically stimulating the release of cortisol, the secretion of pro-inflammatory cytokines, and the alteration of sympathetic and parasympathetic nervous system activity (Danese and Baldwin, 2017, Koss and Gunnar, 2018, Young-Southward et al., 2019). These vital stress systems are also firmly connected by regulating each other's functioning, e.g., HPA-axis is involved in the regulation of inflammatory processes, which in turn stimulate the release of cortisol. Despite being inconclusive and generally suggesting small additive effects, a body of evidence indicates dysregulated stress systems as factors, at least partially explaining the enduring impact of CT (Ioannidis et al., 2020). Recent meta-analyses confirmed significant associations between CT and blunted wake-up cortisol as well as cortisol response to experimental social stress conditions (Bernard et al., 2017, Bunea et al., 2017). Nevertheless, the more static patterns of basal cortisol, cortisol awakening response (CAR), diurnal cortisol slope, or cortisol response to acute stress were not consistently associated with CT (Bernard et al., 2017, Fogelman and Canli, 2018). Meta-analytic evidence also concluded CT as being significantly linked to heightened levels of adult pro-inflammatory C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (Baumeister et al., 2016). Evidence on the autonomic dysregulation is rather inconsistent, but generally suggesting blunted heart rate (HR) and pre-ejection period (PEP) with inconclusive findings on respiratory sinus arrhythmia (RSA) in response to experimental psychological stress conditions (Young-Southward et al., 2019, Sijtsema et al., 2015, Lovallo et al., 2012).

Within NESDA, we not only examined associations between CT and separate commonly assessed markers of major stress systems, but also employed an integrative approach including cumulative markers within each stress system and across all systems (Table 1). Although higher retrospective CT scores in the NESDA cohort were generally associated with slightly elevated salivary cortisol and blood inflammation levels, the number of significant associations was very limited (Kuzminskaite et al., 2020, Holleman et al., 2012). Regression coefficients were small, but rather comparable to the effects observed in previous meta-analyses, both in terms of the direction and the magnitude, somewhat contradicting findings on blunted wake-up cortisol (Bernard et al., 2017, Fogelman and Canli, 2018, Baumeister et al., 2016). Direct associations between CT and stress systems within the total NESDA cohort could have been hard to discern due to the genetic moderation, at least within the HPA-axis (Gerritsen et al., 2017), or by an overrepresentation of psychopathology, characterized by significantly dysregulated stress systems within NESDA (Hu et al., 2016, Vogelzangs et al., 2016, Vreeburg et al., 2009). Consequently, to increase contrast, we compared individuals with severe CT (including those with and without psychopathology) to healthy controls without CT, resulting in significantly elevated levels of the CAR, cumulative HPA-axis markers, CRP, IL-6, cumulative inflammation, and cumulative stress markers across all systems, partially explained by unhealthy lifestyle and higher rates of chronic diseases (Kuzminskaite et al., 2020). Moreover, individuals with more occurrence of CT showed lower levels of CAR or evening cortisol when more demands, less control, and less social support at work was reported (Holleman et al., 2012), suggesting that a history of CT may be important in how the HPA-axis responds to recent life stress. Taken together, our findings suggest that the direct impact of CT on stress systems is small and may be influenced by the presence of psychopathology as well as poorer lifestyle, somatic health, and recent life stress.

3.4.2. Accelerated Biological Aging, Unhealthy Lifestyle, and Somatic Health Decline

CT not only affects the brain but also extends its effects to poor health behaviors and the functioning of our entire body. A recent meta-analysis has shown significant associations between multiple exposures to CT and poor adult lifestyle behaviors such as physical inactivity, obesity, smoking, sexual risk-taking, heavy alcohol and illicit drug use (Hughes et al., 2017). In line, within NESDA, we found that individuals with severe CT had significantly higher rates of smoking and body mass index (BMI) than healthy controls without CT (Table 1) (Kuzminskaite et al., 2020). This was also true when comparing those with and without CT whilst not excluding psychopathology, suggesting lifestyle as an essential factor for understanding the impact of CT on health outcomes. Moreover, meta-analytic findings on 38 studies confirmed that individuals with retrospectively reported CT showed a 40% increased risk of adult cardiometabolic disease, consisting of cardiovascular diseases, diabetes, and metabolic syndrome (Jakubowski et al., 2018). In line with these findings, within NESDA, we found that individuals with CT,

Table 1
Studies examining CT-related personality characteristics, cognitions, stress systems' functioning, biological aging, lifestyle, and somatic health in the NESDA cohort.

Study	Focus	Sample	CT	Outcome
			Personality Characteristics and Cognitions	
van Harmelen et al. (2010)	Negative self-associations	n = 2483 of which 48.3% with CT	CTI: multiple incidences per trauma type, and any trauma	CT was associated with (implicit and explicit) enhanced negative self-associations. When compared to physical and sexual abuse, emotional abuse and/or neglect had the strongest link to negative self-associations.
Vinkers et al. (2014)	Neuroticism	n = 2274 of which ~45% with CT	CTQ-SF and CTI: total severity scores of any trauma (as a part of the cumulative stress index including CT, major life events, and daily hassles)	The impact of the cumulative stress index, including CT and other stressors, on depression, was most pronounced in vulnerable individuals with high levels of trait neuroticism.
Broekhof et al. (2015)	Optimism	n = 2104 of which ~45% with CT	CTI: a sum of trauma frequency per CT type (range 0-2)	CT was associated with lower levels of optimism with emotional abuse and/or neglect showing the strongest association.
Hovens et al. (2016)	Personality characteristics and cognitive reactivity styles	n = 1474 of which 57.4% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8)	CT was associated with lower levels of extraversion, agreeableness, and conscientiousness, and higher levels of neuroticism, openness, hopelessness, rumination, and external locus of control. Emotional neglect and abuse were associated with all personality characteristics in detrimental direction, whereas physical and sexual abuse predicted only neuroticism, openness, rumination, hopelessness, and external locus of control.
Spinhoven et al. (2016)	Maladaptive personality types	n = 2938 of which 44.5% with CT	CTI: multiple incidences per CT type, and a total sum of the number of trauma (range 0-4)	CT severity was progressively associated with more maladaptive personality types. Prevalence rates of CT types were higher at higher levels of maladaptive personality functioning.
			Biological Stress Systems	
Holleman et al. (2012)	Salivary cortisol	n = 1995 of which ~45% with CT	CTI: multiple incidences of any type of trauma, and a total sum of the number and frequency of any trauma (range 0-8)	CT was not associated with saliva cortisol levels. Those reporting higher scores of total CT had a lower CAR or evening cortisol levels when reporting more demands, less control or less social support at work.
Gerritsen et al. (2017)	HPA-axis genes, salivary cortisol, hippocampal and amygdala volume	n = 2327 of which 50% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	NR3C2 gene (which codes for MR) AA (vs. G) allele carriers with CT showed higher cortisol levels after DST.
Kuzminskaite et al. (2020)*	Salivary cortisol, blood inflammatory markers, and ANS activity	n = 2778 of which 47.9% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8); CTQ-SF: total severity scores	No consistent associations between CT and cortisol, inflammation, or autonomic activity in the total sample. Those with severe CT as compared to healthy controls without CT showed the strongest evidence for slightly elevated levels of cortisol, inflammation, and cumulative stress systems' markers, partially explained by an unhealthier lifestyle and poorer health.
			Biological Aging, Lifestyle, and Somatic Health	
van Reedt Dortland et al. (2012)	Metabolic risk factors	n = 2755 of which ~45% with CT	CTI: a sum of trauma frequency per CT type (range 0-2)	Sexual, emotional, and physical abuse were associated with lower levels of HDL cholesterol, higher waist circumference, and overall increased metabolic risk. Emotional neglect was associated with lower SBP. Sexual abuse was the most unfavorable correlate of metabolic risk.
Verhoeven et al. (2014)	Telomere length	n = 1095 with current MDD from n=2407 of which ~45% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	CT was not associated with telomere length in individuals with current MDD.
Verhoeven et al. (2015)	Telomere length	n = 2936 of which ~45% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8); CTQ-SF: total severity scores	CT was not associated with shorter telomere length.
Bomhof-Roordink et al. (2015)	Subclinical cardiovascular disease	n = 650 of which 47.5% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8)	Increased central arterial stiffness was found in individuals with CT, especially in those with highest trauma score. Severity of depression and anxiety partially mediated this association. All CT types, except sexual abuse, showed significant associations with increased central arterial stiffness.
Generaal et al. (2016)	Musculoskeletal pain	n = 1646 of which ~45% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	CT was associated with both the presence and the severity of chronic pain. Associations remained significant after depression, anxiety, and antidepressant adjustment.
Révész et al. (2016)	Telomere attrition	n = 1860 of which ~45% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	Higher baseline CT score predicted larger 6-year telomere attrition.
Han et al. (2018)	DNA methylation	n = 811 with current MDD from 1130 of which ~45% with CT	CTI: a total sum of the number of any trauma (range 0-4)	CT was positively associated with epigenetic aging in individuals with current MDD.
Kuzminskaite et al. (2020)*	Smoking and BMI	n = 2778 of which 47.9% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	Individuals with severe CT had significantly higher rates of smoking and BMI than healthy controls without CT.

Note. * Same study.
Abbreviations: ANS, autonomic nervous system; BMI, body mass index; CT, childhood trauma; CTI, childhood trauma interview; CTQ-SF, childhood trauma questionnaire-short form; CAR, cortisol awakening response; DST, dexamethasone test; HDL, high-density lipoprotein; MDD, major depressive disorder; MR, mineralocorticoid receptor; SBP, systolic blood pressure.

especially those with severe CT, showed more subclinical cardiovascular disease symptoms as represented by the increased central arterial stiffness (Bomhof-Roordink et al., 2015). Exposure to CT, especially sexual abuse, was also associated with more metabolic syndrome dysregulations when compared to no CT exposure (van Reedt Dortland et al., 2012). These results were most clearly present for dyslipidemia and abdominal obesity, but not for hypertension and hyperglycemia components of the metabolic syndrome. Results could not be explained by a poorer lifestyle (e.g., smoking, alcohol use, or physical inactivity) in individuals with CT. The adverse health effect of CT is not limited to cardiovascular outcomes. In addition, within NESDA, CT has also been associated with more presence and severity of chronic musculoskeletal pain (Generaal et al., 2016).

Observational research shows that exposure to adverse childhood events leads to dramatically different life-course trajectories, including a two-times higher risk for premature mortality but also the increased onset of various somatic conditions (Bellis et al., 2013). Consequently, CT seems to be more generally linked to an increased risk for age-related health conditions. This leads to the suggestion that CT can more generally accelerate the aging process. Although chronological age is invariable, people differ in biological age, which may fall behind or outpace chronological age. Biological aging is a multi-faceted and complex process that manifests across multiple levels. Therefore, there is no single indicator that captures biological aging completely; multiple indicators exist (Han et al., 2019). Examples of molecular indicators of biological age are short telomere length, decrease in mitochondrial deoxyribonucleic acid (DNA) copy number, and more advanced epigenetic, transcriptomic, or metabolomic age. Within NESDA, we measured epigenetic aging (via sequencing of all DNA methylation sites) and telomere length (via quantitative polymerase chain reaction). Both DNA methylation and telomere length showed more accelerated aging in depressed individuals versus controls (Han et al., 2018, Verhoeven et al., 2016, Verhoeven et al., 2014). As compared to controls, most advanced epigenetic aging was present in depressed individuals with CT (Han et al., 2018). Although cross-sectionally CT was not associated with telomere length (Verhoeven et al., 2014, Verhoeven et al., 2015), more considerable telomere attrition from baseline to 6-year follow-up was found to be present in individuals with more severe CT (Révész et al., 2016). Overall, these NESDA findings support the hypothesis that CT may produce long-lasting biological "scars" that have an impact on advanced or premature aging processes later in life.

3.4.3. *Altered Brain Structure and Function*

CT has been hypothesized to alter brain development via sustained activation of the HPA-axis and the immune system. During stress, the sympathetic nervous system activates immune cells to stimulate the release of the pro-inflammatory markers (Pongratz and Straub, 2014). As such, chronic activation of the HPA-axis and immune system are thought to be one of the mechanisms through which CT may impact on the structure and function of the brain (Danese and Baldwin, 2017, Danese and van Harmelen, 2017).

Structural MRI studies. Within NESDA, studies on brain structure (Table 2) have predominantly focused on key emotional brain regions (medial prefrontal cortex, mPFC), the limbic regions (hippocampus and amygdala), and conducted exploratory whole-brain analyses. The findings showed reduced dorsal mPFC volume in both patients and healthy controls with emotional abuse and/or emotional neglect (van Harmelen et al., 2010). This is in line with a review suggesting that CT-related mPFC reductions may not be directly related to vulnerable emotional functioning (Moreno-López et al., 2019). Indeed, we observed that patients with CT reported significantly more negative life events than healthy controls with CT, which may, in turn, lead to depressive and anxiety disorders (van Harmelen et al., 2010). While reduced amygdala volume was linked to CT, hippocampal and anterior cingulate cortex (ACC) volumes were not directly related to CT in the NESDA sample (van Harmelen et al., 2010, Molendijk et al., 2012, Gerritsen et al., 2015, van Velzen et al., 2016). However, there were additional indications that genetic influences may play a role in reducing amygdala, ACC, and hippocampal volumes for individuals with CT (see the section below) (Gerritsen et al., 2017, Molendijk et al., 2012, van Velzen et al., 2016). The hippocampal effects may contribute to increased vulnerability to the development of psychopathology in the NESDA sample; as Gerritsen et al. (Gerritsen et al., 2015) showed that in those individuals with CT, a diagnosis of MDD was associated with smaller hippocampal volume.

Functional MRI (fMRI) studies. Concerning studies on brain function (Table 2), individuals reporting emotional abuse and/or emotional neglect showed amygdala hyperresponsivity to emotional faces (van Harmelen et al., 2013), suggesting persistent vigilance towards the detection of emotional facial expressions. CT was associated with hypoactivity in the mPFC during a task that required higher-order cognitive processing (van Harmelen et al., 2014). Hippocampal activity during emotional memory was not affected by CT (van Harmelen et al., 2014), although hippocampal activity to negative emotional words may be modulated by genetic influences (Molendijk et al., 2012) as well as CT-related amygdala and posterior cingulate cortex (PCC) responses to emotional faces (Opmeer et al., 2014). Finally, we examined emotional brain connectivity during rest using fMRI within the limbic, salience, and default networks associated with emotion regulation and self-reflective processing and found widespread reductions in connectivity patterns of these networks related to CT (van der Werff et al., 2013). For instance, a decrease in connectivity between the right amygdala and the precuneus in individuals with CT was reported, which is essential for emotion regulation and self-reflective processing. Reduced connectivity with the precuneus within the salience network may be related to the NESDA findings of more negative self-cognitions in individuals with CT (van Harmelen et al., 2010). In individuals with CT exposure, but no psychopathology, increased negative connectivity was found between the dorsal ACC and the lingual gyrus and occipital fusiform gyrus (van der Werff et al., 2013), suggesting that in resilient individuals with CT increased ability to downregulate emotional processing and responses in verbal declarative memory may play a role, leading to improved ability to re-appraise negative situations, or recall positive autobiographical memories (Ioannidis et al., 2020, Askelund et al., 2019).

In conclusion, findings from the NESDA study indicate that in individuals with emotional maltreatment reduced mPFC and amygdala volumes are found, as well as amygdala hyperactivity, mPFC hypoactivity, and reduced connectivity in limbic, salience, and default-mode networks.

3.4.4. *Is Everyone Similarly Vulnerable to the Impact of CT?*

Although CT is a major risk factor for depression and anxiety, considerable heterogeneity exists in outcomes after exposure to CT. Several theories posit that the impact of CT may be dependent on individual characteristics. However, these characteristics are generally difficult to identify due to methodological heterogeneity and lack of replicated findings.

Within NESDA, some individuals seemed to be particularly more vulnerable to the impact of CT. First, the impact of a cumulative stress index, including CT and other stressors, on depression was most pronounced in at-risk individuals with high levels of neuroticism (Vinkers et al., 2014), suggesting that the adverse effects of CT may primarily

Table 2
Studies examining CT-related brain structure and function in the NESDA cohort.

Study	Paradigm	Sample	CT	Approach	Outcome
			MRI Studies		
van Harmelen et al. (2010)	Structural	Emotional abuse/ neglect, yes (n = 84), no (n = 97)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: hippocampal, amygdala, mPFC volume + whole brain	Emotional abuse/neglect was associated with a reduction in left dorsal mPFC volume, independent of gender, psychiatric status, and other types of abuse. No effects of emotional abuse/neglect on amygdala or hippocampal volume.
Molendijk et al. (2012)*	Structural	Val^{66}val (n = 103; 79% with CT); val^{66}met allele (n = 54; 43% with CT)	CTI: a total sum of the number and frequency of any trauma (range 0-8)	ROI: hippocampal volume + whole brain	Smaller hippocampal volume in val^{66}met allele carriers. No main effect or moderation effect by CT. No effects of the BDNF genotype found in other brain areas.
Gerritsen et al. (2015)	Structural	n = 262 (50% with CT)	CTI: a total sum of the number of any trauma (range 0-4)	ROI: hippocampal volume	No main effect of CT on hippocampal volume. In those with CT, a diagnosis of MDD was associated with smaller hippocampal volume, but not in those without CT.
van Velzen et al. (2016)	Structural	CT, yes (n = 146), no (n = 143)	CTI: at least one type of CT	ROI: amygdala and hippocampal volume; rostral and caudal ACC cortical thickness and surface area	CT was associated with lower amygdala volume. This was more pronounced in maltreated BDNF vall^{66}met allele carriers. Decreased cortical thickness of the ACC in CT with val/val genotype.
Gerritsen et al. (2017)	Structural	n = 225 (from n = 2327 with genome data of which 50% with CT)	CTI: a total sum of the number and frequency of any trauma (range 0-8)	ROI: amygdala and hippocampal volume	NR3C2 gene (which codes for MR) AA (vs. G) allele carriers with CT had smaller hippocampal and amygdala volumes.
			fMRI Studies		
Molendijk et al. (2012)*	Emotional memory encoding and retrieval	Val^{66}val (n = 103; 79% with CT); val^{66}met allele (n = 54; 43% with CT)	CTI: a total sum of the number and frequency of any trauma (range 0-8)	ROI: hippocampus + whole brain	Hippocampal activity to negative and neutral (vs. baseline) word encoding higher in BDNF val^{66}met allele carriers. Hippocampal encoding activity in response to negative words was higher in those with CT (vs. no CT) and interacted with genotype: CT predicted increased hippocampal activation in those with val/val allele, but not in met allele carriers.
van Harmelen et al. (2013)	Emotional face processing	Emotional abuse/ neglect, yes (n = 60), no (n = 75)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: dorsal, ventral mPFC, ACC, and amygdala + whole brain	Emotional abuse/neglect was associated with enhanced bilateral amygdala reactivity to emotional faces in general, and independent of psychiatric status. No support for differential mPFC functioning.
van der Werff et al. (2013) *Psychological Medicine*	Resting-state functional MRI	Emotional abuse/ neglect, yes (n = 44), no (n = 44)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI (seed-based): bilateral amygdala (limbic network), bilateral dorsal ACC (salience network), and the PCC (DMN)	Emotional abuse/neglect was associated with decreased negative connectivity between the right amygdala and bilateral occipital cortex, decreased positive connectivity between right amygdala and OFC, insular to subcortical structures, including the hippocampus and putamen. Decreased negative connectivity between left dorsal ACC and angular cortex and precuneus. Decreased positive connectivity between the left dorsal ACC seed and a bilateral frontal cluster containing the mPFC, the paracingulate gyrus, and the frontal pole. No differences in the left dorsal mPFC seed in the DMN.
van der Werff et al. (2013) *Child abuse and Neglect*	Resting-state functional MRI	CT (n = 22), matched controls without CT (n = 11)	CTI: at least one type of CT; CTQ: total severity score of any trauma	ROI (seed-based): bilateral amygdala (limbic network), bilateral dorsal ACC (salience network) and the PCC (DMN)	CT was associated with an increase in negative connectivity between left dorsal ACC and the lingual gyrus and the occipital fusiform gyrus in the resilient group (healthy individuals with CT) when compared to the healthy controls (no psychopathology and no CT) and when compared to patients with MDD/anxiety with CT.
Opmeer et al. (2014)	Emotional face processing	Emotional abuse/ neglect, yes (n = 56), no (n = 62)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: amygdala + whole brain	Within carriers of the C-allele risk genotype, emotional abuse/neglect was associated with higher amygdala activation, but did not influence activation in non-risk carriers. In the PCC, lower activation was seen in those with emotional abuse/neglect and the risk genotype, whereas genotype did not influence PCC activation in those without trauma. Those carrying the risk genotype with experience of emotional abuse/neglect made a faster gender decision than those without trauma.

(*continued on next page*)

Table 2 (*continued*)

Study	Paradigm	Sample	CT	Approach	Outcome
van Harmelen et al. (2014)	Emotional memory encoding and retrieval	Emotional abuse/ neglect, yes (n = 96), no (n = 98)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: hippocampus, amygdala, dorsal, ventral mPFC, dorsolateral PFC, and the dorsal and pregenual ACC + whole brain	Dorsal mPFC hypoactivity during encoding and recognition of (subsequently) correctly recognized positive, negative, and neutral words in adults with emotional abuse/ neglect.

Note. * Same study.

Abbreviations: ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; CT, childhood trauma; CTI, childhood trauma interview; CTQ-SF, childhood trauma questionnaire-short form; DMN, default mode network; DST, dexamethasone test; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; MDD, major depressive disorder; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PCC, posterior cingulate cortex; ROI, regions of interest.

surface in those with personality traits linked to a vulnerability for psychopathology. Second, maltreated men carrying the CA haplotype of the mineralocorticoid receptor (MR) showed increased depressive symptoms, whereas those carrying the CG haplotype showed increased resilient mental health functioning, indicating important sex-dependent effects of MR on depression susceptibility following CT (Vinkers et al., 2015). Third, maltreated individuals who carried the AA allele of the NR3C2 gene, which codes for MR and mediates rapid cortisol effects in the limbic structures, showed reduced hippocampal and amygdala volumes as well as increased cortisol levels after the dexamethasone suppression test (Gerritsen et al., 2017). Hippocampal and amygdala volumes were also reduced in individuals reporting CT with the val^{66}met genotype of the brain-derived neurotrophic factor (BDNF), playing a critical role in the neural growth (Molendijk et al., 2012, van Velzen et al., 2016, Hariri et al., 2003), while the ACC thickness was reduced in the maltreated individuals carrying the val/val genotype (van Velzen et al., 2016). Individuals with the BDNF val^{66}met genotype also showed reduced serum BDNF levels when exposed to CT (Elzinga et al., 2011). Finally, individuals with BDNF val/val allele were characterized by increased hippocampal activity to negative emotional words (Molendijk et al., 2012), while those with C-allele of neuropeptide Y genotype (NPY) showed particularly increased behavioral responding, higher amygdala activity, and lower PCC activity in response to emotional faces (Opmeer et al., 2014).

Drawing firm conclusions about specific genes mentioned above is difficult, as they show small effects and, therefore, require considerable sample sizes. Consequently, findings on polygenic risk scores (PRS), reflecting a sum of the relevant risk alleles representing a cumulative genetic risk, could provide more conclusive evidence. In line, within NESDA, the effect of PRS on MDD was significantly increased in the presence of CT, suggesting that individuals with CT and high PRS are particularly at risk for developing depression (Peyrot et al., 2014). While some characteristics of individuals more sensitive to the impact of CT have been revealed, collaborative research, especially on genetic characteristics, is necessary to replicate findings and allow firmer conclusions.

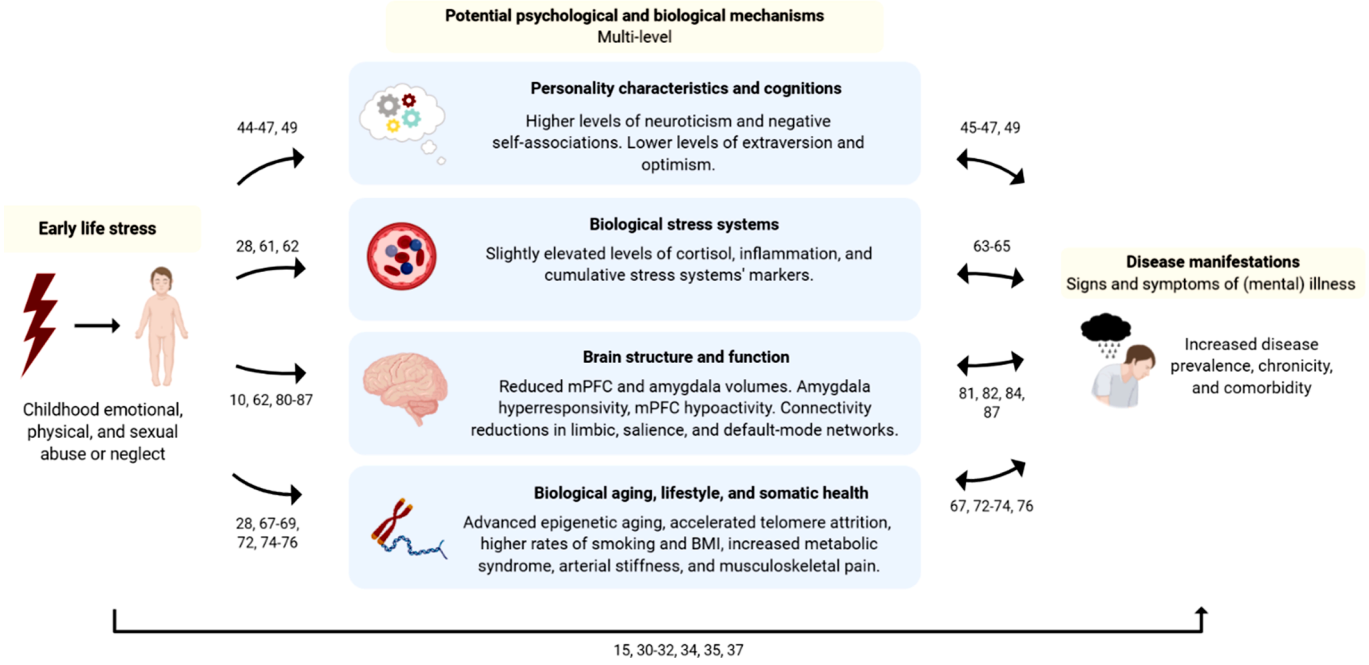

Fig. 3. CT-related psychological and biological changes involved in (mental) illness manifestations in the NESDA cohort (Created with BioRender.com).

Note: numbers indicate study reference, i.e. 10 van Harmelen et al. (2010), 15 Hovens et al. (2012), 28 Kuzminskaite et al. (2020), 30 Hovens et al. (2010), 31 Wiersma et al. (2009), 32 Hovens et al. (2015), 34 van Veen et al. (2013), 35 Spinhoven et al. (2010), 37 De Venter et al. (2017), 44 Hovens et al. (2016), 45 Spinhoven et al. (2016), 46 Vinkers et al. (2014), 47 Broekhof et al. (2015), 49 van Harmelen et al. (2010), 61 Holleman et al. (2012), 62 Gerritsen et al. (2017), 63 Hu et al. (2016), 64 Vogelzangs et al. (2016), 65 Vreeburg et al. (2009), 67 Bomhof-Roordink et al. (2015), 68 van Reedt Dortland et al. (2012), 69 Generaal et al. (2016), 72 Han et al. (2018), 73 Verhoeven et al. (2016), 74 Verhoeven et al. (2014), 75 Verhoeven et al. (2015), 76 Révész et al. (2016), 80 Molendijk et al. (2012), 81 Gerritsen et al. (2015), 82 van Velzen et al. (2016), 83 van Harmelen et al. (2013), 84 van Harmelen et al. (2014), 85 Opmeer et al. (2014), 86 van der Werff et al. (2013), 87 van der Werff et al. (2013).

Abbreviations: BMI, body mass index; CT, childhood trauma; mPFC, medial prefrontal cortex

4. Discussion

This review summarized and integrated the potential mechanisms through which CT exerts its adverse effects using findings from the large longitudinal adult NESDA cohort. NESDA results indicated that CT has a negative impact on the onset and the course of affective disorders, both for depression and/or anxiety disorders and their comorbidity. These findings are in line with a large and convincing body of literature, showing that CT negatively impacts mental health across the lifespan and is, therefore, one of the most prominent public health risks for poor mental outcomes (Angelakis et al., 2019, Norman et al., 2012, Widom et al., 2012, Danese and Tan, 2014, Hughes et al., 2017). Findings also suggested existing interindividual differences, with some individuals exposed to CT being at significant risk for psychopathology or further biological CT-related alterations.

To better understand who is at risk and, ultimately, develop personalized (preventative) interventions, it is essential to determine the mechanisms by which CT exerts its adverse outcomes. Our review suggested a wide range of possible pathways in the psychological and biological domains (Fig. 3). Specifically, within NESDA, CT was associated with more maladaptive personality characteristics and cognitions (higher levels of neuroticism and negative self-associations; lower levels of extraversion and optimism), stress systems' dysregulations (slightly elevated levels of cortisol and inflammation), advanced biological aging (accelerated epigenetic aging and telomere attrition over time), poorer lifestyle (higher rates of smoking and BMI), somatic health decline (increased metabolic syndrome dysregulations, arterial stiffness, and musculoskeletal pain), and brain alterations at the structural and functional level (reduced mPFC and amygdala volumes; amygdala hyperresponsivity and mPFC hypoactivity). CT was also linked to more negative life events and diminished work functioning, indicating additional personal and societal burden. From all CT types, emotional abuse and/or emotional neglect seemed to show the most profound effect. However, this was mostly true when all types of CT were considered together.

Our findings demonstrated the complexity of an organism, suggesting that the impact of CT on poor mental health outcomes is probably a result of a complex interaction of genes, brain processes, environment, and psychological factors (Teicher and Samson, 2013, Daskalakis et al., 2013, Ioannidis et al., 2020). Although most findings within NESDA on CT, impacting the brain, mind, and body, fit well with the key hypotheses and explanatory biological models, we have to be cautious of causal inferences of the succession of pathways (Danese, 2019, Danese and McEwen, 2012). It is currently unknown how different systems interact due to a lack of theoretic underpinnings and comprehensive longitudinal projects integrating psychological, environmental, and biological factors in the same samples in the context of CT. For instance, obesity is likely to mediate CT's impact on adult inflammation (Miller and Chen, 2010); however, other factors such as HPA-axis functioning are also likely playing a role in this relationship (Miller and Chen, 2010, Hewagalamulage et al., 2016). Considering longitudinal findings in NESDA, baseline maladaptive personality characteristics, predominantly, neuroticism mediated the relationship between CT and the course of depressive and anxiety disorders (De Venter et al., 2017, Hovens et al., 2016, Spinhoven et al., 2016). Most likely, CT results in increased neuroticism levels, leading to a higher vulnerability to psychopathology (Roy, 2002). However, it may well be that children with higher neuroticism levels are also more likely to experience and/or report CT. To disentangle the impact of CT, its potentially pre-existing factors, and succession of pathways leading to psychopathology, prospective-longitudinal studies are required. Nevertheless, most research to date relies on cross-sectional studies or longitudinal studies with factors such as neuroticism being assessed only at one-time point, forbidding the inference of change before the CT (Ioannidis et al., 2020, Moreno-López et al., 2019, Danese, 2019).

To advance our knowledge, there are currently several unmet needs in psychiatric research concerning CT and affective disorders: lack of comprehensive longitudinal projects investigating how multiple systems interact to result in affective disorders, and how these different interactions sustain and proliferate symptomatology. It is essential to elucidate the time path between CT, its underlying mechanisms, and psychopathology, as well as investigate how genes and environment are both involved in adverse CT outcomes. For instance, parenting behaviors can be well affected by the psychiatric state of the parent, resulting in more CT, especially, emotional maltreatment, and further child risk for affective disorders (Banyard et al., 2003). Therefore, the increased risk for psychopathology in individuals with CT may be partially related to genetic transmission. One valuable method would be to link findings from epidemiological child/adolescent studies to adult population studies in line with the ongoing Mood and Resilience in Offspring (MARIO; www.mario-project.nl) cohort study, investigating intergenerational transmission of mood disorders.

The current review has some limitations as it focuses on CT findings within one – albeit large and well-defined – cohort, and replications of integrative approaches related to CT are essential. At the same time, this is also a strength as the findings are comparable since the assessment of CT and other methodology were homogenous. We, therefore, encourage other large cohorts to employ a similar approach and integrate different CT findings from the same cohort. Moreover, we refrained from analyzing the associations and relations between the different CT findings as publications have used data from various waves, and sometimes only studied subsamples from the total NESDA cohort. Lastly, NESDA is an adult cohort with self-reported CT. Hence, it is unknown whether CT findings in adulthood are comparable to those in childhood and whether they would be different if CT was assessed prospectively.

This review has shown that CT impacts the functioning of the brain, mind, and body. All these aspects most likely work together and contribute to a higher vulnerability for affective disorders across the lifespan. An integration of mechanistic explanations at different psychological, biological, and environmental levels is essential to better understand the life-long adverse effects of CT in the context of affective disorders.

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Data Availability Statement

According to European law (GDPR) data containing potentially identifying or sensitive patient information are restricted; our data involving clinical participants are not freely available in a public repository. However, data are – under some specifications - available upon request via the NESDA Data Access Committee (nesda@ggzingeest.nl). See also our website: www.nesda.nl

CRediT authorship contribution statement

Erika Kuzminskaite: Conceptualization, Visualization, Project administration, Writing - original draft, Writing - review & editing. **Brenda W.J.H. Penninx:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Anne-Laura van Harmelen:** Writing - original draft, Writing - review & editing. **Bernet M. Elzinga:** Writing - original draft, Writing - review & editing.

Jacqueline G.F.M. Hovens: Writing - original draft. **Christiaan H. Vinkers:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

All authors declare no competing interests.

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