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Proefschrift

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Jacqueline Gerarda Francisca Maria Hovens

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Prof. dr. kol. H.G.J.M. Vermetten
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I have learned that people will
forget what you said,
people will forget what you did,
but people will never forget
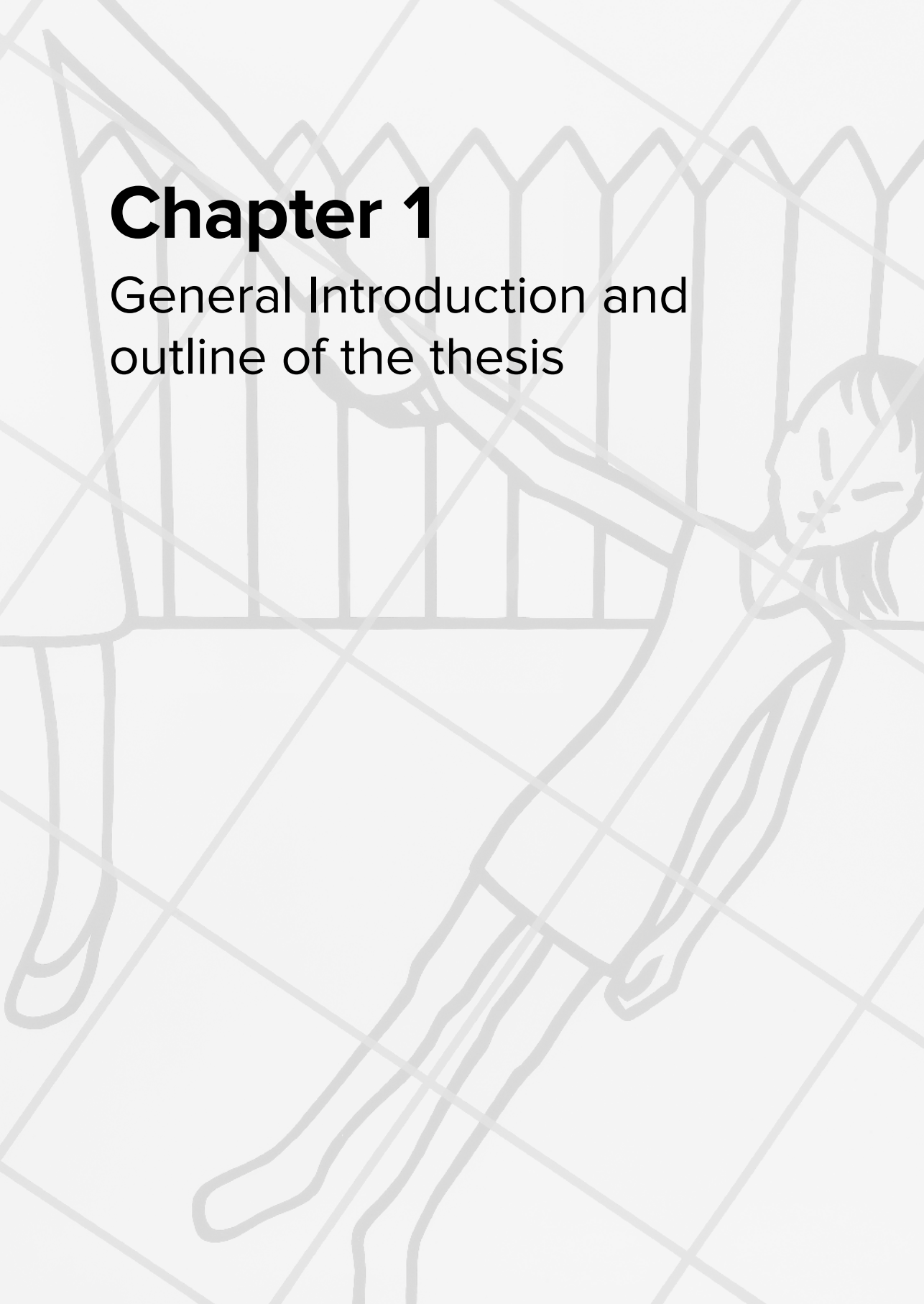how you make them feel.

Maya Angelou (1928-2014)

Voor Frans, Fabienne en Juliette

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Chapter 1

General Introduction and
outline of the thesis

Background

Almost on a weekly basis, we are confronted by horrific images of children enduring inconceivable traumas, such as the frequent school shootings in the US, the reports of abducted girls being held captive for years, and the many children exposed to war in the Middle East. On those days, we hug our children a little closer. We feel grateful for what we have, and mourn what others have lost. What we do not think about are the countless children who experience trauma just as distressing, but far too common to make headlines. Everyday, children are victims of emotional neglect, face physical and sexual abuse, domestic violence, loss of family members, poverty and mental illness; about 1 in 8 American children will experience some form of childhood trauma serious enough to be confirmed by government authorities. Many more go unreported. These traumas can have disastrous effects on children's physical and mental health and mark them for the rest of their lives as victims.

"Tragedies are covered daily in the news, but the commonplace domestic abuse and neglect of our youngest citizens often goes overlooked and unnoticed. That needs to change." wrote Beth Finkestein in the Daily Beast of 6/10/13.

While examining our adult patients and listening to their biographical stories, we are witnessing and confronted with their painful childhoods and hidden memories on a daily basis. What about our patients suffering from depression or anxiety? Which adverse childhood memories relate to their current feelings of despair? How can depression and/or anxiety be related to their 'unhealed wounds'? What is the effect of 'a painful past' on the course of their depressive and anxiety illness? And which are the potential risk factors for a disabling chronic course?

Increasing insight into the long-term effects of childhood trauma is of great public relevance and important for our clinical practice. Although the link between childhood trauma and adult psychopathology is well established, less is known about the exact nature of this relationship and the underlying mechanisms. Therefore, our research focuses on specific associations between childhood trauma and depressive and anxiety disorders, and on specific risk indicators of incidence and course of depressive and anxiety disorders. We take a broad perspective by exploring if, and which, potential mediating factors play a role in the association between childhood trauma and depressive and/or anxiety disorders. A more in-depth understanding of this interrelationship may help to develop and extend personalized prevention and treatment programs. In this introduction, we present background information on childhood trauma, depressive and/or anxiety disorders, and the Netherlands Study of Depression and Anxiety (NESDA), followed by the general aims and an outline of this thesis.

1. Childhood trauma

"Childhood trauma is a complex phenomenon, not only defined by the type of outside incident that causes it, but also by the meaning the child or adolescent affixes to it; how the mental condition is manifest comes directly from the meaning" (1).

1.1 Childhood trauma – Definition

A framework for childhood trauma, first described by Lenore Terr (1991), distinguishes between single-incident trauma (Type I) and repeated or chronic trauma occurring in interpersonal relationships (Type II) (2). The latter is the focus of this thesis. In the literature, this is often referred to as childhood maltreatment. Childhood maltreatment is defined as all forms of emotional and/or physical maltreatment, sexual abuse, neglect or negligent treatment, commercial or other exploitation of children that results in actual or potential harm to a child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power (3). In this thesis, we use the terms childhood trauma (i.e. type II) and childhood maltreatment in an interchangeable manner. Four types of maltreatment are commonly recognized: psychological (or emotional) abuse, physical abuse, sexual abuse and neglect (4):

Psychological or emotional abuse: any type of intentional behaviour by the parent or caregiver that conveys to a child that he/she is worthless, unloved, unwanted, flawed, endangered, or valued only in meeting another's needs. Involves both isolated incidents as well as episodic or a continuing pattern and may have a high probability of damaging the child's physical, mental or social development. Abuse of this type includes blaming, belittling, degrading, threatening, frightening, discriminating against, isolating and other non-physical forms of rejection or hostile treatment. Witnessing intimate partner-violence is also regarded as a form of child maltreatment, which can be classified as exposure to psychological abuse (5).

Physical abuse: the intentional use of force against a child that results in, or has a high likelihood of resulting in, harm for the child's health, survival, development or dignity. This includes hitting, beating, kicking, shaking, biting, strangling, burning, poisoning and suffocating.

Sexual abuse: the involvement of a child in a sexual activity, that he or she does not fully comprehend, is unable to give informed consent to, or for which the child is not developmentally prepared and violates the law or social taboos of society. This includes completed or attempted sexual act, sexual contact or non-contact sexual interaction. Children can be sexually abused by both adults and other children who are - by virtue of their age or stage of development - in a position of responsibility, trust, or power over the child.

Neglect: failure to meet a child's basic physical, emotional, medical/dental or educational needs; failure to provide adequate nutrition, hygiene, shelter or ensure a child's safety.

The above consensus definitions place responsibility for safeguarding children from maltreatment on all caregivers, including teachers, trainers or child minders. In practice, 80% or more of maltreatment is perpetrated by parents or parental guardians, with the exception of sexual abuse, which is mostly perpetrated by acquaintances or other relatives (5). For most children, childhood trauma is a pattern of ongoing or multiple abusive acts in a troubled context (5). Children exposed to one type of abuse are most likely to experience other types of abuse (6, 7). A single episode of abuse is highly related to repeated abuse and the frequency of abuse is positively associated with the severity of abuse (5-7).

1.2 Childhood trauma – Prevalence

There is a great deal of uncertainty about estimates of the frequency and severity of child maltreatment worldwide. Childhood trauma remains largely hidden and unreported because of fear and stigma and the societal acceptance of this type of violence (11). Discrepancies between child abuse rates reported by official statistics (child-protection agencies) and community studies (self-report) suggest that most incidences of child abuse are not reported to the authorities (5). Prevalence rates from large population-based random samples are probably closest to the true, unobservable rate of childhood abuse (5). The majority of studies providing prevalence figures for the different types of childhood abuse have been conducted in the USA. Comparing these rates is difficult as they differ in methodology, trauma instruments and populations sampled. So far, sexual abuse in childhood has been investigated most often and emotional abuse least (5, 8). A recent meta-analysis of the prevalence of child sexual abuse in community and student samples across the world reported that 19.7% of women had suffered some form of sexual abuse prior to the age of 18 years (9). A review in *The Lancet's* series on child maltreatment reported that around 10% of women had experienced severe emotional abuse during childhood and 4–16% physical abuse (5). A recent meta-analysis indicated a prevalence rate of 18.4% for emotional neglect among the few studies (majority originating from North America and only few from Asia, Australia and Europe) that examined childhood emotional neglect between 1980 and 2008 (10).

1.3 Childhood trauma – Assessment

In this thesis, data on childhood trauma have been obtained through interviews in adult life that rely on retrospective recall. Many researchers have questioned the validity of retrospective recall of adverse childhood experiences. Studies have shown some bias in retrospective reports; problems such as forgetting, suppression, denial (recall bias) and embarrassement (report bias) lead to under-reporting rather than over-reporting of childhood abuse (12-14). The available evidence on abuse and neglect indicates that when abuse or

neglect is retrospectively reported, these positive reports are likely to be correct (i.e., there is a low rate of false positives). The main concern over validity stems from the fact that, even with well-documented serious childhood abuse or neglect, about a third of adults do not report its occurrence when specifically asked about (substantial rate of false negatives) (12). Therefore, retrospective reports are more likely to provide underestimates of the incidence of childhood abuse. Retrospective reports are not necessarily dependent on the individual having personal memories of the specific events, but also rely on what other people (relatives) have told the individual. Adults are therefore able to accurately report parental death or divorce, even if these events happened when they were infants. Specific mood-congruent memory biases associated with psychopathology have been suggested, as individuals with current disorders may be more likely to recall negative life events due to increased cognitive appraisal. The controversial debate on recovered memory and false memory has reached consensus on the fact that a memory report on a traumatic event may be accurate as well as inaccurate (15).

Although the tradition of relying on patients' memories to obtain childhood information has been questioned, most research instruments use this approach, as does the clinical situation (16, 17). The retrospective recall of serious, readily operationalized, adverse experiences in childhood is sufficiently valid, even though there is significant under-reporting and some bias (12). The recall of experiences that rely heavily on judgment and interpretation (i.e. more subtle aspects of family life and relationships) have not been found to have sufficient validity (12). A variety of instruments have been used to measure interpersonal trauma, varying from one category of childhood trauma to several types of trauma. They can be divided into the categories of observer rated (interview) and self-report (questionnaire) retrospective trauma instruments. To assist the reader, these trauma instruments are listed in Table 1.

1.4 Childhood trauma – Negative consequences
Childhood trauma may have serious consequences in childhood/adolescence and also later on in adulthood.

In childhood/adolescence: The most tragic manifestation of the burden of childhood trauma is child mortality, which is 12.7% of deaths due to any injury (< age 15 years) (11). Although child homicide has decreased substantially over the past decennia, this occurs most frequently during infancy (29). In the UK, 35% of child homicide victims are younger than 1 year (30). Health and physical effects can include the immediate effects of bruises, burns, broken bones, and malnutrition and also long-term effects of brain injury, hemorrhages, and permanent disabilities. Psychosocial, behavioral and emotional problems are widespread in children, of all developmental ages, who have experienced maltreatment in their early years (31). Some studies find evidence of lowered intellectual and cognitive functioning in abused

Table 1. Description of trauma instruments.

Trauma Instruments	Authors	Type of trauma	Format	Parameters	Ages	Duration	Interrater reliability
Interviews							
Childhood Experience of Care and Abuse (CECA) [18]	Bifulco et al. 1994	EA, PA, SA, EN, PN, O	SS, T	Sev scale 1 - 4, SA: Freq, Top, Nop	<17 y	1 hour	Fair
Childhood Trauma Interview (CTI) [19]	Fink et al. 1995	EA, PA, SA, EN, PN, WV, Sep, Lo	SS, M	Sev, Freq scale 1 - 6, Top, Nop, Top, Dur	<18 y	20-30 min	Fair
Early Trauma Inventory (ETI) [20]	Bremner et al. 2000	EA, PA, SA, WV, Sep, Lo, O	SS, T	Freq, Dur, Top, Aoo, Impact	<18 y	45 min	Substantial
Trauma Antecedents Interview (TAI) [21]	Herman et al. 1989	EA, PA, SA, EN, PN, WV, Sep, Lo, O	SS, M, T	Most items: Nop, other rated Y/N	developmental stage	1-2 hours	Fair
Structured Trauma Interview (STI) [22]	Drayer and Langeland 1999	EA, PA, SA, EN, PN, WV, Sep, Lo, O	SS, M, T	PN and EN: Sev, Freq scale 1 - 7, Top, SA: Aoo, Sev 1 - 5, impact	<16 y	30 min	Fair
NEMESIS Trauma Interview [23]	de Graaf et al. 2002	EA, PA, SA, EN, Sep, Lo, O	SS, M, T	Freq scale 1 - 5, Top, Nop, SA; duration	<16 y	15-30 min	Unknown
Family Experience Interview (FEI) [24]	Ogata et al 1990	PA, SA, WV, PN, Sep, Lo, O	SS	Freq, Sev, Top, Aoo, Dur, impact	<18 y	30 min	Substantial
Questionnaires							
Childhood Trauma Questionnaire (CTQ) [25]	Bernstein et al 1994	EA, PA, SA, EN, PN, WV, Sep, O	70 items	5 point scale from 'never true' to 'very often true'	<18 y	10-15 min	Substantial
Early Trauma inventory (ETI-SR) [20]	Bremner et al 2000	EA, PA, SA, WV, Sep, Lo, O	62 items	Freq	<18 y	45 min	Fair
Adverse Childhood Experience (ACE) [26]	Felitti et al. 1998	EA, PA, SA, EN, PN, WN, O	10 items	Y/N	<18 y	10 min	High correlation with CTQ [28]

Type of trauma: emotional abuse (EA) physical abuse (PA) sexual abuse (SA), emotional neglect (EN), physical neglect (PN), witnessing interpersonal violence (WV), signifi-cant separations from caregivers (Sep) and loss of caregiver (Lo)(e.g., death of parent). Many interviews also measure adverse childhood events that are not always consi-dered trauma by wide consensus and/or not commonly measured: category other (O) such as domestic chaos, parental discord, severe illness in a parent and suffering a major medical illness during childhood.

Parameters used to quantify the trauma: absence or presence of trauma (Y/N), frequency of traumatic event (Freq), severity of trauma (Sev), type of perpetrator (Top), num-ber of perpetrators (Nop), duration (Dur), age of onset, of the trauma (Aoo) and the effects that trauma had on the victim (impact).
Format: SS: semi-structured, T: training required, M: manual.
Interrater reliability kappa > 0.6 fair, kappa >0.8 substantial [27]

children as compared to children who have not been abused (32). Maltreatment increases the risk of lower academic achievement and problematic school performance (33).

The presence of emotional and psychological problems among many maltreated children is well documented and include low self-esteem, depression and anxiety, post-traumatic stress disorder (PTSD), self-injurious behavior (e.g., suicide attempts), and eating disorders (5). Clinicians and researchers report behaviors that range from passive and withdrawn to active and aggressive. Physically and sexually abused children often exhibit both internalizing and externalizing problems (5). Maltreated children who develop insecure attachments to caregivers may become more mistrustful of others and less ready to learn from adults. They may also experience difficulties in understanding the emotions of others, regulating their own emotions and affect, and in forming and maintaining relationships with peers (34).

In adulthood: The starting point in understanding the role of trauma in medical and psychiatric pathology goes back to Freud, who explored the internal worlds of adults and attributed their unusual behavior to histories of trauma rather than to underlying biomedical pathology (35). It is clear that childhood trauma may have a profound and long-lasting effect on emotional state, whether measured by depression or suicide attempts, by protective unconscious defenses, like somatization and dissociation, or by unhealthy and dysfunctional coping behavior (substance abuse, eating disorders, acting out). Childhood trauma may have long lasting effects on mental and physical health, which persists into adulthood. Child abuse forms a prelude to the development of psychopathology in later life; 45% of all childhood onset and 30% of adult onset psychopathology is related to childhood maltreatment (36). Individuals with reported childhood trauma are more likely to develop a wide variety of mental disorders, such as major depression (5, 36, 37), bipolar disorder (38, 39), anxiety disorders (36, 37, 40), posttraumatic stress disorder (36, 37), substance abuse (37, 41), eating disorders (42), dissociative disorders (43), personality disorders (44, 45), and psychosis (46). Childhood trauma is also linked to a wide range of health risk behaviors (47), medical disorders (48), and shortened life expectancy (49). Both prospective and retrospective studies show an association between childhood trauma and adverse health outcomes (8). A recent meta-analysis of studies published between 1993 and 2011, showed robust evidence of significant associations between exposure to non-sexual child abuse and a range of mental disorders (i.e., depression and anxiety disorders), substance use disorders, suicide attempts, sexually transmitted diseases and risky sexual behaviour. An increase in the likelihood of alcohol problems was not consistently seen. There is weak but limited evidence suggesting a relationship with non-sexual child abuse and certain physical disorders, such as cardio-vascular diseases, obesity and type 2 diabetes, and lifestyle risk factors, such as smoking (8).

2. Depressive and/or anxiety disorders

2.1 Diagnostic criteria

In this thesis, depressive disorders include major depressive disorder and dysthymic disorder, defined according to the fourth edition of the Diagnostic and Statistical Manual of mental disorder (DSM IV-TR) (50), the world's leading diagnostic classification system of mental disorders. Major Depressive Disorder (MDD) is characterized by the presence of 5 or more MDD symptoms for at least 2 weeks, during which period minimally a depressed mood and/or a diminished interest or pleasure in nearly all activities should be present. Further MDD symptoms include weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, inability to concentrate, and recurrent thoughts about death or suicide. A diagnosis of MDD is only applicable if symptoms cause significant distress or impairment in everyday functioning. Dysthymic disorder (chronic depression) is characterized by a depressed mood, but less severe than MDD, with a duration of at least 2 years and no period longer than 2 months, during which the individual reports no symptoms. MDD is further characterized by specifiers, such as severity (e.g. remission, mild, moderate, severe), course characteristics (e.g. single episode, recurrent, chronic), and the presence of psychotic, catatonic, melancholic or atypical features. Dysthymic disorder can be further specified as early versus late onset and according to the presence of atypical features. Epidemiological and longitudinal studies show that approximately 20% of patients with MDD in the general population and up to 47% of patients with MDD treated in primary or secondary care suffer from chronic forms of depression, broadly defined as 2 years of continuous symptoms (51).

Anxiety disorders relevant for this thesis are classified according to the DSM-IV-TR as follows. Social phobia refers to a marked and persistent fear of certain social or performance situations in which one fears being embarrassed or humiliated, typically lasting for 6 months or more. A generalized anxiety disorder (GAD) is an excessive anxiety and worry about various every-day situations for at least 6 months. Panic disorder with or without agoraphobia is characterized by recurrent unexpected panic attacks, followed by 1 month (or more) of persistent concern or worry about additional panic attacks or agoraphobia. Agoraphobia is defined as a form of anxiety experienced in situations from which escape might be difficult or embarrassing, or in which help may not be available in case of panic (being outside, in a crowd or standing in line, travelling by bus, train or car), typically lasting for 6 months or more. Specific phobia, acute stress disorder, posttraumatic stress disorder, and obsessive-compulsive disorder were beyond the scope of this thesis.

2.2 Epidemiology

Depressive and anxiety disorders are highly prevalent worldwide. In the Netherlands, 6.1% of the adult population suffers from a mood disorder and 10.1% from an anxiety disorder.

Lifetime prevalence estimates in NEMESIS-2 are 20.2% for depressive and 19.6% for anxiety disorders (52). According to the World Health Organization (WHO), depressive disorders will be the second leading cause of disability by 2020 and it is expected to be the largest contributor to disease burden in 2030 (53). Depressive disorders have a large impact on well-being and daily functioning similar to or even exceeding the impact noted in common medical illnesses (54, 55). As a consequence of their negative effects on individual and public health, depressive and anxiety disorders have important economic consequences. The costs of these disorders are comparable to those of physical illnesses, mainly due to substantial disability and loss of production (56).

2.3 Risk factors
The predominant model to study etiological factors in depression and anxiety is the dynamic stress-vulnerability model (57). According to this model, long-lasting vulnerability factors (e.g., genetic and biological factors, personality characteristics and adverse childhood experiences) and short-term environmental stressors (e.g., stressful life events), are important causal factors in the development of depressive and anxiety disorders (58-60). Depressive and anxiety disorders share common risk factors, including female gender, high neuroticism, stressful negative life events and poor interpersonal functioning (61, 62). Numerous risk factors for depression have been identified; social factors such as low family support (63), loneliness (64), low self-steem (65), and negative attributional style (66) as cognitive variables. A cognitive risk factor associated with anxiety disorders is tendency to worry (67).

2.4 Comorbidity
Large population based studies in the US (68, 69) and the Netherlands (70, 71) show high comorbidity between depressive and anxiety disorders, ranging from 30 to 60%. In particular, a large overlap between GAD and MDD and/or Dysthymia is remarkable (72). These findings have questioned the validity of a categorical distinction between specific depressive and anxiety categories, with critics suggesting that a dimensional approach may be more appropriate than a categorical classification (73). The recognition of high comorbidity between depression and anxiety has resulted in the rating of panic attacks as a dimension across all mental disorders in DSM-V (74). Comorbidity of depressive and anxiety disorders is associated with greater disability, increased symptom severity, and higher health care utilization and is less likely to respond to treatment than pure depressive or pure anxiety disorders (75, 76).

2.5 Course
Longitudinal cohort studies indicate that the mean duration of depressive episodes ranges between 3-6 months, 20% of these episodes become chronic (> 2 years), and the course of depressive disorders is often characterized by recurrences (30-50%) (77-79). In anxiety disorders fewer large-scale prognostic studies indicate similar (or even worse) outcomes.

The course of panic disorders shows little to no improvement in approximately 40% of the subjects (80). Only 35% of patients with social phobia recover over 10 years, with a recurrence rate after recovery of 34% (81). A 2-year follow-up NESDA study cohort found that anxiety disorders have a longer time to first remission and a more chronic course than depressive disorders (82).

Prognostic studies have demonstrated that basic clinical factors, such as earlier age of onset, severity of the index episode and comorbidity of anxiety and depression are associated with a poor course outcome, referring to chronic and recurrent episodes (82-84). In addition, the presence of an anxiety disorder seems to have a larger negative effect on the course of a depressive disorder than vice versa (76, 84).

3. Childhood trauma and depressive and anxiety disorders

"Traumatic events of the earliest years of infancy and childhood are not lost but, like a child's footprints in wet cement, are often preserved life-long. Time does not heal the wounds that occur in those earliest years; time conceals them. They are not lost; they are embodied" (85).

Our understanding of the connection between childhood trauma and the pathways to pathology in adulthood is still being developed. It has become evident that traumatic life experiences during childhood and adolescence, often 'forgotten', hidden by shame, secrecy, and social taboo, are far more common than generally recognized (85). Moreover, they are associated with considerable mental health consequences in later life, in particular depressive and anxiety disorders, which are the focus of this thesis (5, 36, 86).

3.1 Depressive disorders

Strong evidence for an association between exposure to childhood trauma and the development of major depression was found in the Adverse Childhood Experience (ACE) study (47-49), which showed that risk for depression increased in a graded, dose-dependent relationship with the number of adverse childhood experiences. Individuals with exposure to one adverse childhood experience are twice as likely to develop a depressive disorder (26). Long-term prospective studies also indicate a twofold greater risk attributable to childhood trauma (87, 88). Childhood adversity explains in a predictive sense 26.2% of mood disorders (population attributable risk fraction) (36). Depressive disorders emerge earlier and have a more persistent course in individuals with childhood trauma (36, 89-91). These individuals also have more severe mood and neurovegetative symptoms and more comorbidity, in particular anxiety and substance abuse (92, 93). A recent meta-analysis of depression outcome studies confirmed that childhood trauma predicts a poor treatment response (91).

3.2 Anxiety disorders

The impact of childhood trauma on the development of anxiety disorders in adults has not been studied as much. The National Comorbidity Replication Study showed that childhood sexual and physical abuse was associated with a 2.0- to 3.8-fold increase in risk for specific phobias, social phobia, generalized anxiety disorder and panic disorder with and without agoraphobia (40). Childhood adversity accounted for 32.4% of the population attributable risk fraction for anxiety disorders (36). Exposure to multiple types of childhood adversity increases the likelihood of receiving a prescription for an anxiolytic by 2-fold (26). Increasing severity of various types of abuse was associated with advancing severity of social phobia, reduced quality of life and increased disability (94). In particular, emotional neglect and abuse were especially salient risk factors for social phobia.

3.3 Epidemiology issues/limitations in previous studies

The majority of studies, addressing the relationship between childhood trauma and psycho-pathology, are cross-sectional and based on adult retrospective reports of abuse and neglect in childhood (8). These studies cannot provide evidence of causality between childhood trauma exposure and the onset and course of depressive and/or anxiety disorders. The limited number of available prospective studies demonstrates an objective measure of exposure to abuse and give insight into the temporal relationship between childhood trauma and psychopathology. However, these studies are usually conducted in non-representative samples (8) as official cases of childhood abuse may only detect those who come to professional attention and generally reflect the lower end of the socioeconomic spectrum (95). The samples that most studies rely on are heterogeneous, varying from college students, high risk youth, patients in clinical treatments or population based community cohorts. Few include adequate control groups of equivalent non-traumatized individuals (8). Furthermore, the attrition bias in these studies (i.e. decreasing response rates with time in respondents with highest risk of mental disorders) can lead to errors in estimates that could be as great as those due to recall bias (36). In light of the above limitations of these studies, we use both a retrospective and a prospective approach in this thesis.

Most previous epidemiological studies have examined the associations between only one or a small number of childhood adversities and only one or a small number of adult psychiatric disorders, predominantly depression. This has compromised the usefulness of prior findings due to over-estimating associations (36) since childhood adversities commonly overlap and co-occur (7, 96) and considerable lifetime comorbidity occurs among adult psychiatric disorders (97). Remarkably, the main focus in the literature has been on the more obvious forms of maltreatment, such as physical and sexual abuse. Emotional neglect or emotional abuse is at least as damaging as physical or sexual abuse in the long term, but has received the least scientific and public attention (5). In this thesis, we will focus on multiple types of childhood trauma in the context of depressive and/or anxiety disorders. A clear distinction is

made between either separate depressive and anxiety disorders or the combination of both (comorbidity).

3.4 Mechanisms linking childhood trauma to depression and anxiety
Both psychological and biological mechanisms have been hypothesized as causal pathways of how childhood abuse increases vulnerability to later depressive and anxiety disorders. In this thesis, we focus on psychological mechanisms.

Attachment theorists (98, 99) proposed that a child develops an attachment bond with a primary caregiver based on the child's comfort-seeking behaviors (e.g., crying) toward the caregiver, who is most likely to provide comfort and protection. Children develop representations of attachment figures, based on their attachment relationship, which are crucial for the child's development and relative stable over time. Based on these *attachment representations*, they form a complementary model of themselves (e.g. as valuable, lovable and worthy of support and attention). Based on the work of Bowlby (98), it has been suggested that early childhood trauma may damage the child's attachment to parents or caretakers due to early experiences with an inconsistent caregiver and exposure to an attachment relationship in which nurturing is comingled with abuse. Children exposed to childhood trauma develop a model of caretakers as unavailable, unsympathetic, and unsafe and fail to develop a competent sense of self. Childhood trauma, occurring in interpersonal dependency, disrupts a child's normal development and impairs the child's ability to develop adaptive emotional regulation skills, self-esteem, and the ability to trust others (34). An adult attachment style is insecure if it is characterized by attachment anxiety (i.e., a tendency to worry about availability and responsiveness of significant others, fear of interpersonal rejection or abandonment), an excessive need for approval from others, and attachment avoidance (i.e., a tendency to feel uncomfortable with interpersonal intimacy and dependency, an excessive need for self-reliance, reluctance to self-disclose) (100).

Beck (101) subsequently developed a cognitive theory of differential susceptibility to depression following stressful life events. He proposed that an individual develops a self-concept which reflects their representations of the self, world, and future based on the attitudes and opinions communicated to them by important others during childhood. Aspects of Beck's theory have been incorporated in a more specific account of vulnerability to depression: helplessness theory (66). Helplessness arises when an individual makes stable, internal, and global attributions about negative experiences. These maladaptive explanations for success and failure lead an individual to believe that they have little control over future experiences, creating a vulnerability to depression.

The relationship between childhood trauma and psychopathology in adulthood is a complex interplay of multiple psychological and environmental factors and requires incorporation of

contextual and life course changes. Given the large time lag between childhood trauma and adult psychopathology, a number of possible intermediate pathways should be considered. In this thesis, we elucidate this complex relationship by analyzing several mediating risk factors.

3.5 Risk factors/mediating factors

In this thesis we explore and address the risk factors in adulthood that mediate the relationships between childhood trauma and adult depressive and anxiety disorders (36). A mediating risk factor is one that explains the association between childhood trauma and psychopathology, which developed after childhood trauma has occurred.

The following risk factors were studied as potential mediators:
(1) Clinical characteristics: severity of depressive and anxiety symptoms, age of onset, baseline psychiatric status and lifetime depressive and/or anxiety disorders (Chapter 4 and 5).
(2) Personality dimensions: neuroticism, extraversion, openness, agreeableness, conscientiousness and external locus of control (Chapter 6).
(3) Cognitive reactivity styles such as rumination and hopelessness (Chapter 6).

We tried to identify mediators with potential as causal risk factors and to provide insight in possible explanatory pathways. At the end of this thesis, we will integrate our findings into an integrative mechanistic model explaining the relation between childhood trauma and adult depressive and anxiety disorders.

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

The studies in this thesis are based on data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA was designed to investigate the long-term course and consequences of depressive and anxiety disorders in different health care settings (102). NESDA is an ongoing multi-center longitudinal cohort study of adults recruited from the general population (19%), primary care (54%) and mental health organizations (27%) in the Netherlands. The total sample consisted of 2,981 adults (18-65 years). The baseline assessments were done between 2004 and 2007. The NESDA sample contains individuals with a current or remitted depression and/or anxiety disorder, people at increased risk because of family history or sub-threshold symptoms of depression and anxiety, and healthy controls without a present or past diagnosis depressive or anxiety disorders. Because of the specific focus on depression and/or anxiety disorders, individuals with an apparent clinical diagnosis of other disorders, such as bipolar disorder, psychotic disorder or severe substance disorders were excluded in the NESDA. Assessments included a face-to-face interview,

written questionnaires and biological measurements. At the 2- and 4-year follow-up assessments respectively, 2,596 (87.1%) and 2,402 (80.6%) individuals responded. Baseline, 2-year and 4-year follow-up data were available for the present analyses described in this thesis. NESDA data offers the opportunity to study the longitudinal characteristics of depressive and anxiety disorders among individuals with and without childhood trauma in a large sample.

Lifespan

| Childhood trauma | | NESDA baseline: Adulthood Mean age 42 y | | ···· Prospective ···► | Follow-up 2 yr | Follow-up 4 yr |

Retrospective

Assessment: Recall bias
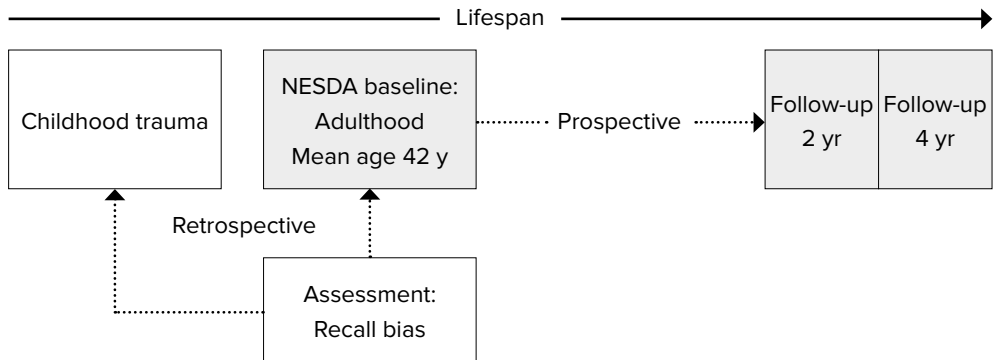
5. Aims and outline of this thesis

5.1 Aims
This thesis aims to uncover the patterns and pathways between childhood trauma and the clinical field of psychiatry, in particular depressive and anxiety disorders. The main objectives of this thesis are:
1. To examine whether and to what extent childhood trauma and childhood life events are associated with depressive and anxiety disorders in adulthood (Chapter 2 and 3).
2. To enhance our understanding of the longitudinal associations between childhood trauma, childhood life events and the course (Chapter 4), and the onset and recurrence (Chapter 5) of depressive and anxiety disorders.
3. To investigate the effect of childhood trauma on psychosocial characteristics, personality dimensions and cognitive reactivity styles, and examine whether these factors mediate the unfavourable course of depressive and anxiety disorders in patients with a history of childhood trauma (Chapter 6).

The findings reported in this thesis contribute to the exploration of how childhood trauma, depressive and anxiety disorders are interrelated. They increase our understanding of the characteristics of childhood trauma that make individuals vulnerable for the development of anxiety and depressive disorders in later life, and demonstrate how childhood trauma will

affect the course of their illness. This awareness may contribute to increasing insight into the underlying mechanisms between childhood trauma and depressive and anxiety disorders, and may tailor future preventative measures and treatment for patients.

5.2 Outline

Chapters 2 and 3 comprise research on cross-sectional associations of childhood trauma with depressive and/or anxiety disorders. In Chapter 2, we describe the risk of childhood trauma and childhood life events among individuals with pure depressive, pure anxiety disorders, and comorbid depressive and anxiety disorders, as compared to individuals without such disorders (i.e., controls). Next, we address the question of specificity between types of childhood trauma and childhood life events and pure depressive, pure anxiety, and the comorbid disorders. Chapter 3 outlines the importance of childhood trauma and childhood life events for chronicity of depression.

In Chapter 4, longitudinal associations of childhood trauma and childhood life events with depressive and anxiety disorders are described. We address the question whether childhood trauma and childhood life events predict the 2-year course of depressive and/or anxiety disorders in individuals with a baseline diagnosis of depressive and/or anxiety disorder. We also determine which clinical factors are possible mediators of the relationship between childhood trauma and the course of depressive and/or anxiety disorders.

In Chapter 5, we focus on the associations between childhood trauma and the onset and recurrence of depressive and anxiety disorders. For this purpose, we studied the effect of childhood trauma, in individuals without a baseline depressive and/or anxiety disorder, over a 2-year follow-up period.

In Chapter 6, we describe various psychosocial characteristics, personality dimensions and cognitive reactivity styles in traumatized versus non-traumatized individuals, with a baseline diagnosis of depressive and/or anxiety disorder. The predictive power of childhood trauma on the 4-year course of depressive and anxiety disorders is assessed in more detail. Next, personality dimensions and cognitive reactivity styles are studied as possible mediating factors in the 4-year course of expressive and anxiety disorders in patients with a history of childhood trauma.

Finally, in Chapter 7, we discuss the main findings, the methodological aspects and clinical implications of the studies included in this thesis and present suggestions for future research.

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Chapter 2

Childhood Life Events and Childhood Trauma in Adult Patients with Depressive, Anxiety and Comorbid Disorders vs Controls

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Abstract

Objective: To investigate the association between childhood life events, childhood trauma and the presence of anxiety, depressive or comorbid anxiety and depressive disorders in adulthood.

Method: Data are from 1,931 adult participants in the Netherlands Study of Depression and Anxiety (NESDA). Childhood life events included divorce of parents, early parental loss and 'placed in care', whereas childhood trauma was assessed as experienced emotional neglect, psychological, physical and sexual abuse prior to age 16.

Results: Childhood life events were not associated with psychopathology, except for 'placed in care' in the comorbid group. All types of childhood trauma were increasingly prevalent in the following order: controls, anxiety, depression, and comorbid group ($P < 0.001$). The higher the score was on the childhood trauma index, the stronger the association with psychopathology ($P < 0.001$).

Conclusion: Childhood trauma rather than childhood life events are related to anxiety and depressive disorders. The strong associations with the comorbid group suggest that childhood trauma contributes to the severity of psychopathology. Our study underscores the importance of heightened awareness of the possible presence of childhood trauma, especially in adult patients with comorbid anxiety and depressive disorders.

Introduction

Childhood abuse and other adverse childhood experiences have been linked to the later emergence of psychopathology, in particular depressive and anxiety disorders in adulthood (1-3). Adverse childhood experiences may alter the child's belief system and subsequently contribute to the development of cognitive vulnerability, in particular learned helplessness and an external locus of control (4). Consistent with these theoretical expectations (5, 6), childhood loss events were found to be more strongly related with subsequent onset of depressive disorders than with anxiety disorders (7, 8). In addition, it has been hypothesized that adverse childhood experiences affect this risk through their impact on neurobiology and neurochemistry (9).

Although depression and anxiety are closely related and frequently co-occur (10, 11), different environmental antecedents and specific vulnerability factors have been suggested in past research (4, 12, 13). Comorbidity of depression and anxiety has been associated with a distinct risk profile compared to pure depression and pure anxiety, usually involving more severe symptoms and longstanding vulnerability factors such as family history (10).

Considering adverse childhood life events, domestic conflict and parental psychopathology (over and above the genetic effects) are the most common childhood adversities in the Western world (1, 14). Considering childhood trauma, most studies have focused on the sequela of childhood sexual abuse into adulthood (2, 15-20). The association between childhood physical or sexual abuse and psychopathology appears stronger for women than men (19, 21). The association between emotional neglect and psychological abuse in childhood and subsequent vulnerability to the development of depressive and anxiety disorders has received much less attention (22-26). Most studies found that the different forms of childhood trauma were rather non-specific risk factors for adult psychiatric disorders (1, 2, 16).

Limited research has been done on the differential effects of emotional neglect, psychological, physical and sexual abuse on the onset and development of either anxiety disorders, depressive disorders or comorbid anxiety and depressive disorders (25, 26).

Aims of the study
The primary aims of the present study were: (i) to identify and describe the associations between reported childhood life events and childhood trauma and the presence of either pure anxiety, pure depressive or comorbid disorders and (ii) to explore which types of childhood life events and childhood trauma predominate in the prediction of pure anxiety, pure depressive or comorbid disorders.

Patients and methods

Sample

Data were obtained from baseline data of the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal cohort study that includes 2,981 participants, aged 18 through 65 years. A detailed description of the study design and sample has been previously published (27). Participants were stratified for different settings (general population, primary care and mental health care) and for different phases of illness (controls, high familial risk, first and recurrent episodes of depression and anxiety). Participants were recruited from different locations in the Netherlands (Amsterdam, Leiden and Groningen). For the current study, data were used from the baseline interviews conducted between September 2004 and February 2007. All interviews were tape-recorded to control the quality of the data. Analyses were carried out on 1,931 (64.7%) of 2,981 participants (213 from the general population, 1,012 from primary care and 706 from mental health care). Participants with a lifetime diagnosis of any anxiety and/or depressive disorder, which was not currently present, were excluded to maximize the likelihood of detecting contrast between anxiety and depressive disorders and thus be able to better differentiate the specific effects of childhood life events and childhood trauma on psychopathology. The exclusion of these subjects was thought to reduce the potential confounding influence of prevalent lifetime depressive disorders in the group of current anxiety disorders, and vice versa of prevalent lifetime anxiety disorders in the group of current depressive disorders. In other words, we used strict case definitions.

Diagnosis

During a 4-h baseline assessment, including written questionnaires, a face-to-face interview, a medical exam, an experimental computer task and blood and saliva collection, extensive information was gathered about psychopathology, demographic and psychosocial characteristics and clinical, biological and genetic determinants. Demographic data used in our study were gender, age and attained education level based on years of education. Depressive and anxiety disorders were defined according to DSM-IV criteria and diagnosed with the Composite International Diagnostic Interview (CIDI) (WHO version 2.1), a fully structured diagnostic interview. The CIDI is used worldwide and WHO field research has found high interrater reliability, high test-retest reliability and high validity for depressive and anxiety disorders (28, 29). The CIDI was conducted by specially trained clinical staff.

In the present study current diagnosis of major depressive disorder, dysthymia, panic disorder with or without agoraphobia, agoraphobia without history of panic, social phobia, and generalized anxiety disorder were used. Having a 'current' disorder was defined by the presence of a diagnosis within the preceding 12 months. Controls (n=520) were defined as participants, who were neither having a current nor a lifetime anxiety or depressive disorder, nor a current or lifetime alcohol abuse or dependence. The number of subjects with current

diagnoses in this sample was 252 with a pure anxiety disorder, 314 with a pure depressive disorder and 845 with both a current anxiety and depressive disorder.

Trauma assessment

Childhood life events and childhood trauma were assessed retrospectively by a Dutch semi-structured interview, previously used in the Netherlands Mental health Survey and Incidence Study (30-32).

Childhood life events. Participants were asked if any of the following life events had happened before the age of 16 years: death of either biological father or mother, divorce of the parents, being placed in a children's home, being placed in a juvenile prison or being brought up in a foster family. Each childhood life event was coded in a dichotomous format (0 absent / 1 present). Because of low prevalence rates, whether someone was placed in a children's home, in juvenile prison or brought up in a foster family was collapsed to a single life event in analyses, further referred to as 'placed in care'. The childhood life events were analysed per item separately, as well as cumulative. The childhood life event index (i.e. sum score ranging from 0 to 3), which we constructed ourselves, reflects the number of life events experienced.

Childhood trauma. The participants were asked whether they had experienced any kind of emotional neglect, psychological, physical or sexual abuse before the age of 16. The definition of emotional neglect included lack of parental attention or support and ignorance of one's problems and experiences. Psychological abuse was defined as being verbally abused, undeserved punishment, subordinated to siblings and being blackmailed. Physical abuse was defined as being kicked or hit with hands or an object, beaten up or physical abuse in any other way. Sexual abuse was defined as being sexually approached against your will, meaning being touched or having to touch someone in a sexual way. Participants answered 'yes' or 'no' to each of the 4 forms of childhood trauma and were asked to give an indication about the frequency on a five-point scale, '1' once, '2' sometimes, '3' regularly, '4' often and '5' very often. In the analyses, the frequencies were categorized into three groups (0: absent, 1: once or sometimes, 2: regularly, often, and very often). Subsequently, if any abuse had happened, the participants were asked for the perpetrator: biological father, biological mother, step-father or friend of mother, step-mother or friend of father, siblings, any other relative or someone else. For the analyses, the perpetrators were categorized as parents or others. In case of repeated sexual abuse, the duration in months was asked for and specified as: 0 until 11 months, 12 until 35 months and longer than 36 months. The self constructed childhood trauma index (sum scores of frequency ranging from 0-8) was calculated with a higher score indicating more types and a higher frequency of childhood trauma.

Statistical analyses

The four study groups (controls, anxiety disorder, depressive disorder, comorbid group) were compared by analysis of variance for continuous variables and X^2-tests for categorical variables. Variables used in the main analysis included childhood trauma and childhood life events. Odds ratios for having anxiety, depressive or comorbid disorders according to trauma and life event status were calculated by multinomial logistic regression analysis adjusted for age, sex and education. The control group was regarded as reference and P-values were derived by the likelihood ratio tests. Odds ratios were also analysed for each gender separately and the interaction term of gender*trauma was added to the analyses to assess whether the strength of associations differed between gender. A two-tailed $P < 0.05$ was considered statistically significant; the statistical software used was SPSS 14.0.

Results

Characteristics of the four study groups are summarized in Table 1. The sample consisted of 66.6% women and 33.4% men, equally distributed over the four groups. Mean age was about 41 years and did not significantly vary between the groups. The level of education was highest in the controls and lowest in the comorbid group ($P < 0.001$). The controls originated predominantly from the general population or primary care, whereas the majority of the participants with current anxiety and/or depressive disorders came from mental health settings ($P < 0.001$) (Table 1). Among the life events, divorce of parents was the most common (14.2 %), whereas 'placed in care' was the least common (6.6%). Emotional neglect and psychological abuse were the most prevalent types of childhood trauma reported in the study, with a prevalence of 38.3% and 25.1% respectively. Sexual abuse was more prevalent (18.5%) than physical abuse (14.4%). More females were found in the emotional neglect ($P = 0.014$), psychological ($P = 0.002$) and sexual abuse ($P < 0.001$) domains.

Correlations between emotional neglect, psychological abuse, physical abuse and sexual abuse were modest to large in magnitude. The highest correlations were found between emotional neglect and psychological abuse (Spearman $r = 0.63$, $P < 0.001$) and the lowest correlations were found with sexual abuse. The correlation between the childhood life event index and the childhood trauma index was weak ($r = 0.22$) illustrating that life events and trauma largely represent separate childhood indicators.

Childhood life-events

The prevalence of parental divorce and early parental loss did not differ between the groups, whereas 'placed in care' was lowest in controls and highest in the comorbid group ($P = 0.03$) (Table 1). No significant associations were found between childhood life events and pure current anxiety, pure current depression and current depression and anxiety, except for 'placed in care' in the latter group (Table 2).

Table 1. Childhood trauma according to diagnosis in 1,931 study participants.

	Controls (n=520)	'Pure' current anxiety (n=252)	'Pure' current depression (n=314)	Current depression *and* anxiety (n=845)	*P*-value*
Female gender (n, %)	349 (67.1%)	163 (64.7%)	196 (62.4%)	579 (68.5%)	.54
Age (years, ± SD)	41.8 ± 14.6	40.7 ± 13.5	40.2 ± 12.5	40.8 ± 12.0	.16
Education level attained (years, ± SD)	12.7 ± 3.2	12.1 ± 3.3	12.1 ± 3.3	11.4 ± 3.3	< .001
Setting:					
General population	107 (20.6%)	18 (7.1%)	27 (8.6%)	61 (7.2%)	< .001
Primary care	413 (79.4%)	140 (55.6%)	138 (43.9%)	321 (38.0%)	
Mental health care	0 (0.0%)	94 (37.3%)	149 (47.5%)	463 (54.8%)	
Childhood life-events before age 16:					
Divorce parents	66 (12.7%)	40 (15.9%)	43 (13.7%)	125 (14.8%)	.39
Early parental loss	35 (6.7%)	15 (6.0%)	20 (6.4%)	69 (8.2%)	.26
Placed in care	23 (4.4%)	18 (7.1%)	21 (6.7%)	65 (7.7%)	.03
Childhood trauma before age 16:					
Emotional neglect:					
No	437 (84.0%)	176 (69.8%)	184 (58.6%)	393 (46.4%)	< .001
Once or sometimes	45 (8.7%)	45 (17.9%)	67 (21.3%)	182 (21.5%)	
Regularly, often or very often	38 (7.3%)	31 (12.3%)	63 (20.1%)	269 (31.9%)	
Psychological abuse:					
No	470 (90.4%)	211 (83.7%)	234 (74.5%)	530 (62.8%)	< .001
Once or sometimes	32 (6.2%)	28 (11.1%)	48 (15.3%)	158 (18.7%)	
Regularly, often or very often	18 (3.5%)	13 (5.2%)	32 (10.2%)	156 (18.5%)	
Physical abuse:					
No	490 (94.2%)	221 (88.1%)	274 (87.3%)	666 (78.9%)	< .001
Once or sometimes	19 (3.7%)	15 (6.0%)	21 (6.7%)	69 (8.2%)	
Regularly, often or very often	11 (2.1%)	15 (6.0%)	19 (6.1%)	109 (12.9%)	
Sexual abuse:					
No	463 (89.0%)	209 (82.9%)	264 (84.1%)	636 (75.4%)	< .001
Once or sometimes	30 (5.8%)	14 (5.6%)	27 (8.6%)	80 (9.5%)	
Regularly, often or very often	27 (5.2%)	29 (11.5%)	23 (7.3%)	128 (15.2%)	

Data are number (percentage) or mean (± SD), when appropriate. 'Pure' current anxiety indicates patients with anxiety disorders during the last 12 months without lifetime depression. 'Pure' current depression indicates patients with depressive disorders during the last 12 months without lifetime anxiety. *: *P*-values by ANOVA linear term or Chi square tests (for linear association).

Table 2. Odds ratio's for risk of having 'pure' current anxiety, 'pure' current depression or 'pure' current comorbid anxiety and depression versus no disorder according to trauma status in 1,931 participants.

	A: 'Pure' current anxiety (n=252)	B: 'Pure' current depression (n=314)	C: Current depression *and* anxiety (n=845)	Over-all *P* *	*P* B *vs.* A	*P* C *vs.* B
Childhood life events before age 16:						
Divorce parents	1.25 (0.81-1.92)	1.04 (0.68-1.57)	1.11 (0.80-1.54)	.76	.44	.67
Early parental loss	1.07 (0.57-2.01)	0.99 (0.56-1.75)	0.73 (0.47-1.12)	.33	.85	.22
Placing in care	1.60 (0.84-3.06)	1.54 (0.83-2.87)	1.67 (1.01-2.76)	.21	.91	.73
Childhood trauma before age 16:						
Emotional neglect:						
No				< .001	.006	<.001
Once or sometimes	2.65 (1.68-4.17)	3.90 (2.56-5.94)	4.88 (3.40-7.02)			
Regularly, often or very often	2.23 (1.34-3.72)	4.56 (2.92-7.13)	9.03 (6.19-13.2)			
Psychological abuse:						
No				< .001	.01	.001
Once or sometimes	2.03 (1.19-3.47)	3.23 (2.00-5.21)	4.59 (3.06-6.89)			
Regularly, often or very often	1.61 (0.77-3.36)	3.79 (2.07-6.95)	7.50 (4.50-12.5)			
Physical abuse:						
No				< .001	.93	.004
Once or sometimes	1.78 (0.89-3.57)	2.03 (1.07-3.86)	2.73 (1.61-4.62)			
Regularly, often or very often	2.90 (1.31-6.45)	3.06 (1.43-6.56)	6.69 (3.54-12.6)			
Sexual abuse:						
No				< .001	.13	.006
Once or sometimes	1.07 (0.55-2.06)	1.65 (0.96-2.85)	1.95 (1.25-3.03)			
Regularly, often or very often	2.48 (1.42-4.34)	1.66 (0.92-2.98)	3.41 (2.19-5.31)			

Reference=controls
Odds-ratios were adjusted for age, sex, and education.
*: Chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model.

Childhood trauma

Emotional neglect was the most frequent type of abuse (Table 1). Compared to the controls, the prevalence of emotional neglect, psychological and physical abuse was about twice as high in the anxiety and depression groups and more than three times as high in the comorbid group. If emotional neglect, psychological or physical abuse were present, approximately 40% reported a frequency of 'regularly, often or very often', with the highest frequency (approximately 60%) in the comorbid group. In comparison with the controls, the prevalence of sexual abuse was only slightly higher in the anxiety and depression groups,

but twice as high in the comorbid group. If sexual abuse was present, 45-65% reported a frequency of 'regularly, often or very often'.

In case of emotional neglect, psychological and physical abuse, over 80% of the identified perpetrators were the parents, whereas in sexual abuse the identified perpetrator was most often (86.4%) someone else than the parents. These findings did not differ among the four groups. The duration of sexual abuse was also similar among the four groups (mean 10.2 months, range 0-52 months).

In age, sex and education adjusted multinomial regression analysis, emotional neglect, psychological and physical abuse were associated with pure current anxiety, pure current depression and current depression and anxiety in increasing order (all P values <0.001) (Table 2). The odds ratios were higher in the comorbid depression and anxiety group. Associations were also stronger in the depression group than in the anxiety group, as shown by the post hoc P-values (P = 0.006 for emotional neglect and P = 0.01 for psychological abuse).

The associations between sexual abuse and pure current anxiety, pure current depression and current depression and anxiety appeared not as strong as for other types of abuse. However, the overall P-value shows a highly statistical difference. The associations were again strongest in the comorbid depression and anxiety group, whereas those for the depression and anxiety group were of equal strength.

To investigate whether gender played an important role, the adjusted odds ratio's for men and women were analyzed separately using multinomial regression analysis. Emotional neglect, psychological, physical and sexual abuse was associated with pure current anxiety, pure current depression and current depression and anxiety, for both men and women (P < 0.001). Subsequently, the interaction term of gender*trauma was added to the analyses. For all types of abuse, no significant effect of the interaction term was found in the anxiety, depression and comorbid groups.

Childhood life event and childhood trauma indices
For all groups, higher childhood trauma indices corresponded with higher odds ratios for psychopathology (all P values <0.001), suggesting a dose-response relationship (Figure 1). The dose was defined as the frequency of exposure to childhood trauma and the number of childhood trauma types. The strongest associations were found with current comorbid anxiety and depression. In contrast, the childhood life event index did not show any significant relationship with psychopathology (Figure 1).

Figure 1. Odds ratios (with bars representing 95% confidence intervals) for 'pure' anxiety, 'pure' depression, and comorbid depression and anxiety versus controls according to the childhood life event and childhood trauma indices in 1,931 subjects, adjusted for age, gender and education.
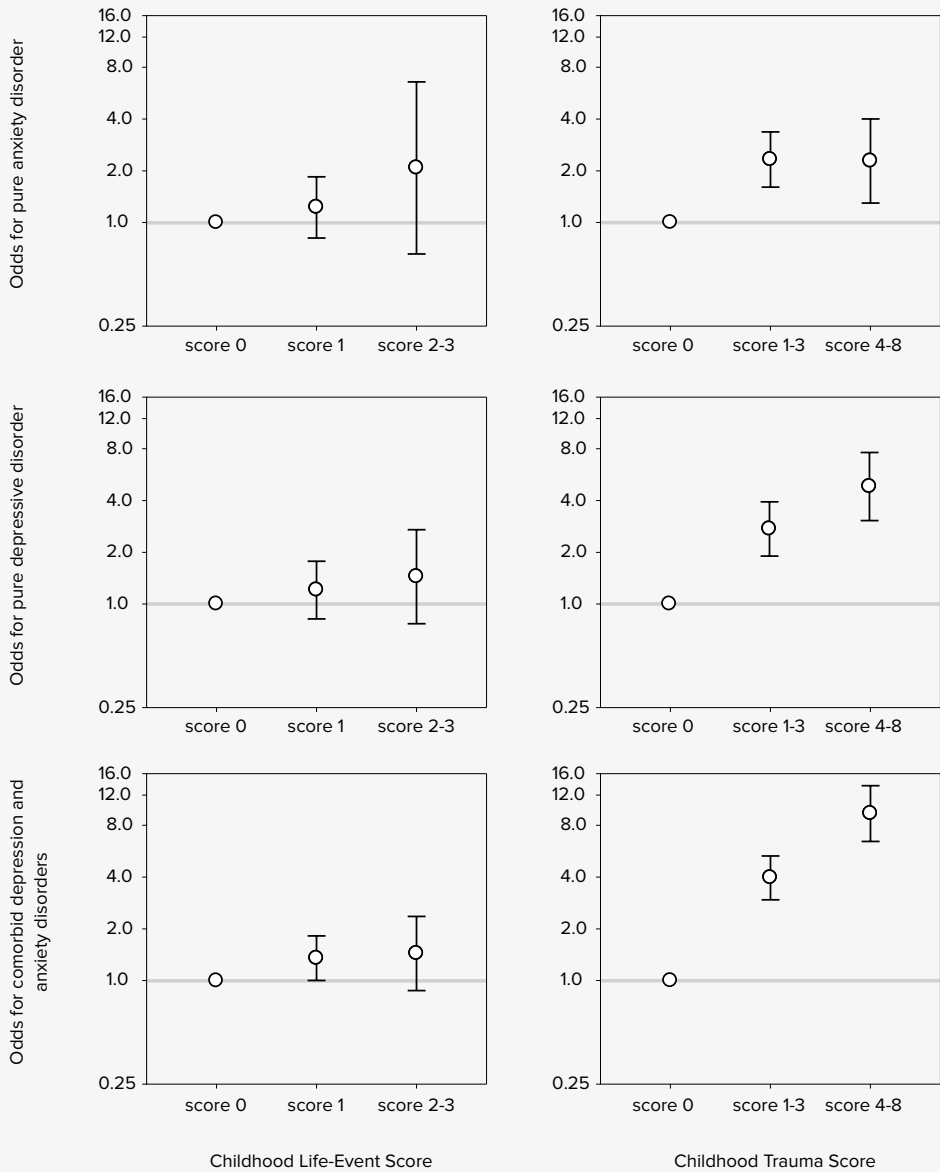
Discussion

Our study demonstrates that a reported history of childhood trauma is associated with a higher risk of anxiety and depressive disorders in adulthood and with an increasing order from anxiety to depressive to comorbid anxiety and depressive disorders. Emotional neglect and psychological, physical and sexual abuse in childhood were all associated with the presence of anxiety and depressive disorders in adulthood. The results showed a strong dose-response relationship between the types and frequency of exposure to childhood trauma and the presence of psychopathology. The magnitude of the risk associated with childhood trauma was substantially larger than with childhood life events such as early parental loss, parental divorce and 'placed in care'. Emotional neglect and psychological abuse had a stronger correlation with pure current depression than pure current anxiety. In all trauma domains, the strongest associations were found in the comorbid group.

Our findings are consistent with previous studies reporting a relationship between a history of childhood trauma and anxiety and depressive disorders in adulthood (15-25). Both clinical (3, 20) and population-based community studies (15-19, 23) have examined the relationship between child abuse and lifetime psychopathology among adults. However, most studies focus on lifetime psychopathology only (3, 16-19). In the US National Comorbidity Study (1), Kessler et al. investigated the persistence of psychopathology until the year preceding the CIDI diagnostic interview. The effects of childhood adversities were consistently associated with risk of onset, but not with recency of disorders. The US National Comorbidity Study assessed childhood trauma emphasizing only physical and sexual abuse items, but did not address emotional neglect and psychological abuse. Considering a mean age in our population of 41 years, the presence of current anxiety or depressive disorders suggests that the effects of childhood trauma are indeed longstanding. Our findings are in line with two studies investigating current symptoms of psychopathology (23, 24), but in contrast with our study, without use of diagnostic interviews.

This study puts emphasis on testing the specificity of various types of abuse to different psychiatric diagnoses. Only one study has compared the differential effects on psycho-pathology across the subtypes of childhood trauma. Gibb et al. described a cohort of 857 adult psychiatric outpatients focussing on current diagnosis, using the Childhood Trauma Questionnaire (CTQ), which investigates childhood emotional, physical and sexual abuse (25, 26). In line with our findings, childhood emotional abuse was more strongly related to depressive than anxiety disorders, whereas childhood physical and sexual abuse showed an association with anxiety and depressive disorders of equal strength. To address the issue of specificity, in our analyses we adjusted for lifetime comorbidity, because many studies have documented pervasive lifetime and current comorbidity among anxiety and depressive disorders (10-12). The different types of childhood trauma have frequently been identified as non-specific risk factors for adult psychiatric disorders (1, 2, 16). Emotional neglect and

psychological, physical and sexual abuse were all consistently and strongly associated with adult psychopathology. The lack of specific interrelationships between childhood trauma and psychopathology supports the hypothesis of general vulnerability for psychopathology among individuals exposed to early childhood trauma. The childhood trauma index, which reflects the number and frequency of childhood trauma, is indicative of the emergence of psychopathology. This observation agrees with previous studies linking the number and severity of abuse to increased risk of psychopathology (1, 16-19). In all trauma domains, the results of the current study are compelling with respect to the strong relation between childhood trauma and comorbidity and may imply that childhood trauma contributes to the severity of psychopathology.

The observation that childhood life events were not associated with anxiety, depressive or comorbid disorders, is a remarkable finding and (partially) inconsistent with both theoretical expectations (5, 6) and past research (7, 8). Childhood loss events (death of a parent, divorce parents) in the US National Comorbidity Study (1) were more strongly associated with the subsequent onset of mood disorders than anxiety disorders. However, these loss events were found to predict only mania and dysthymia and not major depression. Parental loss in childhood is associated with an increased likelihood of a depressive disorder in adulthood only if the quality of the surviving family relationship is poor (33). Previous studies (1, 34) have shown that parental divorce is a stronger predictor of subsequent psychopathology than other loss events and more likely to cause depression than anxiety. In our study the prevalence of parental divorce was relative low, which may affect our findings. In a high-risk cohort of children from parents with bipolar disorder, Hillegers et al. found that stressful life events increase the liability to mood disorders, but the effects slowly diminish with time (35). If we extrapolate this finding, the impact of adverse childhood life events could have been extinguished with advancing age, as shown in our adult population in which we focused on current diagnoses. Furthermore, our results support the assumption that life events per se are not pivotal, but rather the quality of the childhood holding environment. In this per-spective, a suggestion for future research may be to examine the impact of more subjectively perceived life events such as family dysfunction and the quality of the relationship with either the parents or other principal caregivers.

Rosenman et al. described the phenomenon "context of abuse", referring to the frequent co-occurrence of adverse childhood life events and various types of childhood abuse (14). However, the overlap and co-existence of adverse childhood life events and childhood trauma in our study was relatively low, which suggests that these variables represent separate and rather independent adverse childhood indicators for adult psychopathology.

Strengths of the current study include a large representative sample in which childhood life events and different types of childhood trauma have been considered, use of a structured diagnostic interview, a control group and a focus on pure current depressive and pure current anxiety disorders to test the specificity of the relationship of adverse life events and

trauma with psychopathology. The use of a semi-structured interview to question childhood trauma is favourable, because the relationship between childhood trauma and psychiatric disorders is frequently underestimated by researcher's reliance on records rather than direct questioning (36).

Methodological limitations include the retrospective, cross-sectional design and the substantial colinearity between the various types of trauma which precluded the use of multivariate analyses. The cross-sectional design may incur the possibility of reverse causation: patients with current anxiety and/or depressive disorders might perceive and report more childhood trauma in retrospection, which may be secondary to their mental problems. Although studies of retrospective reports of childhood trauma conclude that there is little evidence that psychopathology is associated with less reliable or less valid recollections (37, 38), caution is still necessary. The definition of sexual abuse was rather broad and we speculate that this might explain why sexual abuse was not the adversity with the largest impact on adult mental disorders. Given the cross-sectional design, we can not draw any conclusions about the causal role of childhood trauma in the onset and development of anxiety and depressive disorders. Longitudinal studies are needed to understand the biological and psychological mechanisms by which the different types of childhood trauma may contribute to the development and course of psychopathology.

In conclusion, this cross-sectional study demonstrates that childhood trauma rather than childhood life events appears to be an important risk factor for depressive and anxiety disorders, in particularly in cases of comorbid depression and anxiety. Emotional neglect and psychological abuse may play a more pivotal role in the emergence of pure current depression compared to pure current anxiety. Nevertheless there does not appear to be a unique predictive relationship between types of childhood trauma and specific psychiatric disorders.

Implications

Clinical practice may benefit from early interventions aimed at prevention of the negative impact of childhood trauma in later life. Current evidence-based treatments of anxiety and depressive disorders take little notice of childhood trauma. Depressive and anxiety disorders associated with a history of childhood trauma may respond differently to treatment (39) or are associated with treatment resistance (40). Among those with a history of early childhood trauma, psychotherapy alone was superior to antidepressant monotherapy (39). These results suggest that psychotherapy may be an essential element in the treatment of patients with a history of childhood trauma. Interventions that focus on childhood trauma may contribute to the development of more effective treatments for a subgroup of anxiety and depressive disorders, preceded by childhood trauma. Our study underscores the importance of heightened awareness of the possible presence of childhood trauma, especially in adult patients with comorbid anxiety and depressive disorders.

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Chapter 3

The Importance of Childhood Trauma and Childhood Life Events for Chronicity of Depression in Adults

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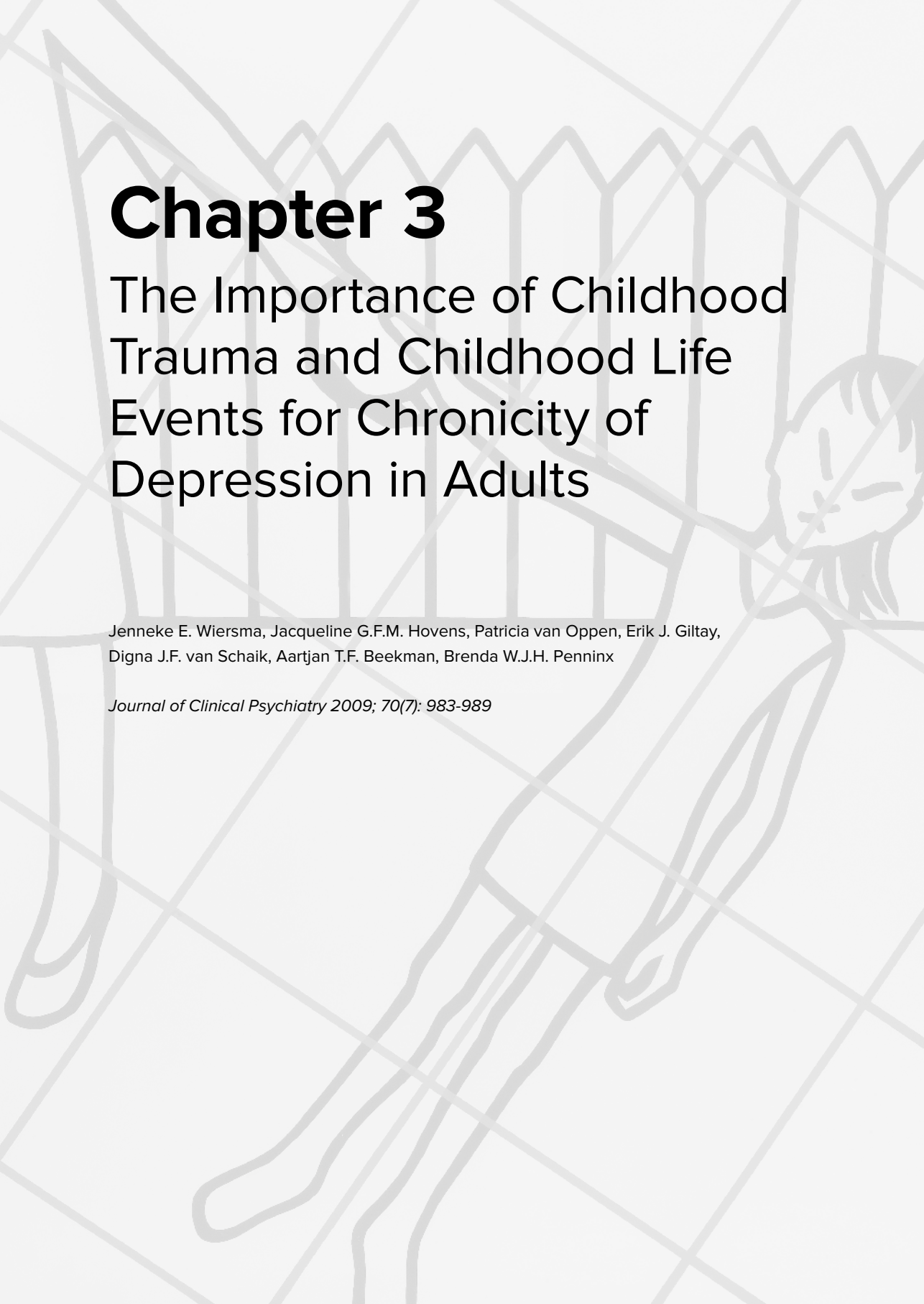
Abstract

Background: Childhood trauma is linked to adult depression and might be a risk factor for a more chronic course of depression. However, the link between childhood trauma and chronicity of depression has not been investigated using a large and representative sample in which other depression characteristics, such as severity, age of onset, and comorbid psychopathology were taken into account.

Method: Baseline data, collected during 2004 through 2007, were drawn from the Netherlands Study of Depression and Anxiety (NESDA). Participants had a current DSM-IV-TR diagnosis of Major Depressive Disorder (MDD) and were recruited from the community, primary care settings, and specialized mental health care facilities (N=1,230). Relationships between both childhood trauma and childhood life events and chronicity of depression were examined using multiple logistic regression models. *Chronicity of depression* was defined as being depressed for 24 months or more in the past four years.

Results: Chronicity of depression was associated with a significantly higher prevalence of childhood trauma, but was not associated with childhood life events. We found the strongest association for those with the highest score on a cumulative index summarizing frequency of childhood trauma (OR = 3.26; 95% CI = 1.86 to 5.72, *P* < 0.001). After controlling for comorbid anxiety disorders, severity of depressive symptoms, and age of onset of depression, we found that the association between childhood trauma index and chronicity of depression remained significant (OR = 2.06; 95% CI = 1.13 to 3.73, *P* = 0.02).

Conclusions: These results suggest that multiple childhood traumas can be seen as an independent determinant of chronicity of depression. For treatment of depressed patients, it is therefore important to detect the presence of childhood trauma.

Introduction

Approximately 20% of individuals with major depressive disorder (MDD) experience periods of depression that last for two years and often much longer (1). Chronic MDD is associated with a greater illness burden, more suicide attempts and more hospital admissions compared to those with episodic major depression (2, 3). Chronic depression is difficult to treat, and misdiagnosis and undertreatment are common (4). A better understanding of the factors underlying chronicity may improve the prevention and treatment of chronic depression and may be of prognostic importance. In a review (5) describing six putative determinants of chronic depression, the strongest support was found for the role of developmental factors, such as childhood trauma and childhood life events.

There is some evidence that a history of childhood trauma, such as emotional neglect and psychological, physical, and sexual abuse, is associated with the development of chronic depressive episodes; however, only women (6-9) or subjects diagnosed with dysthymic disorder (10-11) were being considered in these studies. Studies that examined the role of childhood life events, such as parental loss, divorce of parents, and separation, in the development of chronic depressive episodes, found little evidence for predictive value of chronicity (12-16). However, these studies lacked an exclusive focus on chronic depression (14-16) or considered only women (13). Furthermore, with a few exceptions (14-16), most of these studies used rather small samples and focused on either childhood life events or childhood trauma, but not on both concomitantly.

Since there is a lack of studies that examined the role of developmental factors in chronic depression in a large and representative sample, the purpose of the current study was to investigate how childhood trauma and childhood life events relate to chronicity of depression in a large group of adults with an MDD diagnosis. Different types of childhood trauma, such as emotional neglect, psychological abuse, physical abuse, and sexual abuse, as well as different types of childhood life events, such as parental loss, divorce of parents, and separation, were considered in the present study.

Our goals were (i) to compare the risk of chronicity of depression in depressed adults by type of childhood trauma (emotional neglect, psychological abuse, physical abuse, and sexual abuse) and childhood life events (parental loss, divorce of parents, and separation); (ii) to examine putative dose-response relationships between the frequency of childhood trauma and childhood life events and chronicity of depression; and since literature indicates that childhood trauma is associated with an earlier age at onset of depression and more comorbidity (6, 17), our final goal was (iii) to investigate whether the relationships between childhood trauma and chronicity of depression and between childhood life events and chronicity of depression could be explained by these clinical characteristics, such as

comorbidity with anxiety disorders, age at onset of first depressive episode, and severity of depressive symptoms.

Method

Sample
The data for the present study, collected during 2004 through 2007, were drawn from the Netherlands Study of Depression and Anxiety (NESDA) (18), an ongoing 8-year longitudinal cohort study aimed at examining the long-term course of depressive and anxiety disorders in different health care settings and phases of illness. A total of 2,981 respondents were recruited from the community, primary care settings, and specialized mental health care facilities and included healthy controls, respondents with subthreshold symptoms, and those with an anxiety and/or depressive disorder (18). All 2,981 respondents were administered a baseline assessment that lasted, on average, 4 hours and included assessment of psycho-pathology, demographic and personal characteristics, psychosocial functioning, and bio-markers. Further details about NESDA are provided elsewhere (18). The research protocol was approved by the Ethical Committee of participating universities and, after complete description of the study all respondents provided written informed consent. A total of 1,230 adults with a current diagnosis of MDD in the past year were selected for the present study (113 from the community, 478 from primary care, and 639 from specialized mental health care). The diagnosis of MDD in the past year was established with the Composite Interview Diagnostic Interview (CIDI) (25) (World Health Organization [WHO] version 2.1), which classifies diagnoses according to DSM-IV-TR criteria (19).

Measures
Chronicity of depression. Chronicity of depression was measured by the Life Chart Interview (20). This instrument uses a calendar method to determine life events during the past 4 years to refresh memory and then assesses presence and severity of symptoms during that period (20). For each participant, the total number of months depressed in the past 4 years was computed. Participants who were depressed for 24 months or more over the past 4 years were defined as *chronically depressed*.

Childhood life events. Childhood life events and childhood trauma were assessed retro-spectively using the Childhood Trauma Interview as used in the Netherlands Mental Health Survey and Incidence Study (21-23). All questions pertained to the respondent's first 16 years of life. The first section consisted of several questions about important life events in early life, including death of a parent, divorce of parents, being placed in a juvenile prison, being raised in a foster family, and being placed in a child home (21). Only a few participants reported being placed in a juvenile prison, raised in a foster family, or placed in a child home. We will

refer to these types of childhood life events as "separation". Thus, in total, the following 3 childhood life events were being measured: parental loss, divorce of parents, and separation. Each childhood life event was scored as 0 (did not happen) or 1 (did happen). Besides considering the 3 childhood life events separately, a cumulative index called "childhood life event index", was calculated as the sum of the experienced childhood life events for each participant (range, 0-3). Because there were only few participants who scored 3 on the childhood life event index (N=3), we recoded the maximum score on the childhood life event index to 2 or more (> 2).

Childhood trauma. The second section of the Childhood Trauma Interview consisted of 4 questions about emotional neglect, psychological abuse, physical abuse, and sexual abuse (21). Participants were asked the following questions: (i) "Were you emotionally neglected, meaning nobody ever listened to you at home, your problems and experiences were ignored, and you felt that there was no attention or support from your parents?" (ii) "Were you psycho-logically abused, meaning being yelled at, falsely punished, subordinated to your siblings, or being blackmailed?" (iii) "Were you being abused physically, meaning being hit, kicked, beaten up or other types of physical abuse?" (iv) "Were you sexually abused, meaning being touched or having to touch someone in a sexual way against your will?" Scores for each question were categorized from 0-2 (0, never happened; 1, happened once or sometimes; 2, happened regularly/[very] often). Besides considering the 4 types of childhood trauma separately, a cumulative index, called childhood trauma index, was calculated as the sum of experienced number and frequency of childhood trauma for each participant (range, 0-8).

Other clinical characteristics. Severity of depressive symptoms was measured using the 30-item Inventory of Depressive Symptomatology-Self-Report (IDS-SR) (24), which has shown high correlations with observer-rated scales and established responsiveness to change. Information on age at onset of first depressive episode and comorbidity with anxiety disorders in the past year was established with the CIDI interview to determine the history, recency, and age at onset of episodes. Persons who experienced their first depressive episode before the age of 21 years were considered to have an early illness onset, while persons who experienced their first depressive episode at or after the age of 21 years were considered to have a late illness onset. Comorbid anxiety disorders were defined as social phobia, panic disorder, agoraphobia, and generalized anxiety disorder. The CIDI is used worldwide, and WHO field research has found high interrater reliability (25), high test-retest reliability (26), and high validity for depressive and anxiety disorders (27, 28). Specially trained clinical staff conducted the CIDI.

Statistical analyses
Baseline characteristics were compared first according to MDD chronicity status using χ^2 tests for categorical variables and independent t tests for continuous variables. Second, logistic

regression analyses were used to examine the associations between childhood trauma, childhood life events, and chronicity of depression and to explore potential dose-response relationships between the childhood trauma and childhood life events indices and chronicity of depression. Logistic regression analyses were adjusted for age, sex, and education. Third, to investigate whether the relationships between the childhood indices and chronicity of depression could be explained by other psychopathology characteristics, we first examined whether the childhood indices were associated with comorbidity with anxiety disorders, age at onset of first depressive episode, and severity of depressive symptoms, using χ^2 tests for categorical variables and independent t tests for continuous variables. Subsequently, using multivariable logistic regression analysis, we examined whether the relationship between the childhood indices and chronicity of depression still existed after adjusting for comorbidity with anxiety disorders, age of illness onset, and severity of depressive symptoms.

Results

The study sample of 1,230 depressed subjects consisted of 67.3% women and 32.7% men. The mean age was 40.7 years (SD = 12.2). The mean educational level was 11.6 years (SD = 3.2). The chronicity criterion was fulfilled by 32.8% (N = 395). Table 1 summarizes the demographic characteristics of the nonchronically and chronically depressed participants in the present study. Chronically depressed participants were older (*P* < 0.001) and had less education (*P* = 0.005) than the nonchronically depressed participants. The mean number of months participants were depressed in the past 4 years was 40.7 (SD = 12.1) for the chronically depressed participants compared to 10.3 (SD= 6.2) for the nonchronically depressed participants. Besides having longer illness duration, chronically depressed participants reported more severe depressive symptoms (*P* < 0.001) and more comorbid anxiety disorders (*P* < 0.001).

Spearman correlations between the types of childhood trauma - emotional neglect, psychological abuse, physical abuse, and sexual abuse - were fairly modest in magnitude. The highest correlations were found between emotional neglect and psychological abuse (0.61, *P* < 0.001); others were below (0.55, *P* < 0.001).

To compare the risk of chronicity in depressed adults according to type of childhood trauma and childhood life events, we computed odds ratios (Table 2). Chronicity of depression was significantly associated with all 4 types of childhood trauma. No significant associations between childhood life events and chronicity of depression were found.

Table 1. Demographic characteristics of participants in the present sample with nonchronic MDD and chronicity of depression[a].

Characteristic[b]	Nonchronic MDD (n=809)	Chronicity of Depression (n=395)	P[c]
Female gender	68.5	65.1	.24
Age, mean (SD), y	39.7 (12.3)	42.4 (11.8)	<.001
Educational level, mean (SD), y	11.8 (3.2)	11.3 (3.2)	.005
No. of months depressed in past 4 years, mean (SD)	10.3 (6.2)	40.7 (12.1)	NA
IDS score, mean (SD)	28.3 (12.5)	36.5 (12.4)	<.001
Onset of depression before age 21 years	36.5	39.2	.30
Total comorbid anxiety in past year	62.2	77.7	<.001
Social phobia	31.1	45.1	<.001
Panic with agoraphobia	22.5	23.3	.77
Panic without agoraphobia	12.4	18.5	.005
Agoraphobia	8.0	8.4	.91
GAD	24.0	44.3	<.001
Emotional neglect:			<.001
No	51.7	42.5	
Once/sometimes	7.9	4.3	
Regularly/often/very often	40.2	53.2	
Psychological abuse:			.002
No	68.5	58.2	
Once/sometimes	6.3	5.8	
Regularly/often/very often	25.0	35.7	
Physical abuse:			.001
No	83.4	75.4	
Once/sometimes	8.0	8.4	
Regularly/often/very often	8.4	16.2	
Sexual abuse:			.03
No	78.9	74.2%	
Once/sometimes	16.4	17.2%	
Regularly/often/very often	4.7	8.4%	
Childhood trauma index[d]:			<.001
0	41.6	34.9	
1-2	24.6	19.3	
3-4	19.6	21.4	
5-6	11.2	15.8	
7-8	3.1	8.7	
Childhood life events:			.80
Parental loss	6.8	6.3	.34
Divorce parents	15.3	13.2	.21
Separation (prison, childhome, foster family)	6.4	7.8	
Childhood life event index[d]:			.04
0	76.0	79.7	
1	20.5	15.1	
2+	3.5	5.2	

[a] Chronicity of depression was defined as being depressed for 24 months or more in the past 4 years.
[b] Values are shown as percents except where noted otherwise.
[c] Comparison using Chi square statistics (categorical variables) and analyses of variance (continuous variables).
[d] The childhood trauma and life event indices were calculated as the sum of the number (and severity) of experienced childhood trauma and life events, respectively.
 Abbreviations: IDS-SR = Inventory of Depressive Symptomatology-Self Report, MDD = major depressive disorder.
 NA = not applicable.

To examine dose-response relationships between frequency of childhood trauma and childhood life events and chronicity of depression, we computed odds ratios for chronicity of depression on the childhood trauma index and the childhood life event index (Figure 1). Although not entirely consistent with a linear trend, a dose-response relationship was found between the childhood trauma index and chronicity of depression. The higher the score on the childhood trauma index, the stronger the association with chronicity of depression for score 7 to 8 versus score 0 (OR= 3.26; 95% CI= 1.86 to 5.72, $P < 0.001$). No associations were found for the childhood life event index and chronicity of depression for score 2 or more versus score 0 (OR= 1.30; 95% CI= 0.71 to 2.35, $P = 0.40$).

Figure 1. Odds Ratios for chronicity of depression on childhood trauma and childhood life event indices.
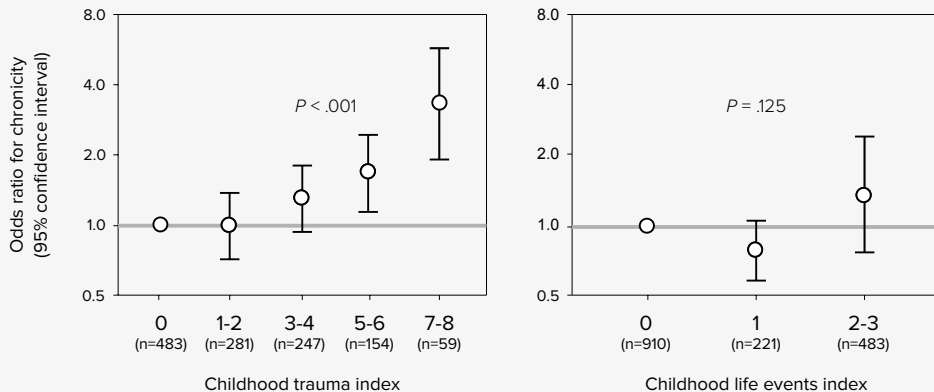
To investigate whether the relationship between the frequency of childhood trauma and chronicity of depression could be explained by other clinical characteristics, we first examined whether the childhood trauma index was associated with comorbid anxiety, onset of depression before age 21 years, and severity of depressive symptoms (Table 3).

Subjects with the highest scores on the childhood trauma index reported significantly more comorbid anxiety ($P = 0.005$), more often an early age of depression onset ($P < 0.001$), and more severe depressive symptoms (P < 0.001). Secondly, we tested these variables in multivariable models (Table 4). We found that, for the subjects with the highest scores (7-8) on the childhood trauma index, the association with chronicity of depression persisted after controlling for comorbid anxiety, age at onset of depression, and severity of depressive symptoms compared to those scoring 0 on the childhood trauma index (OR, 2.06; 95% CI, 1.13 to 3.73, $P = 0.018$).

Table 2. Adjusted[a] Odds Ratio (OR) of chronicity of depression according to childhood trauma and childhood life events variables.

Variable	OR (95% CI)	P
Childhood trauma		
Emotional neglect:		
No	1	
Once/sometimes	0.67 (0.38-1.18)	.16
Regularly/often/very often	1.55 (1.20-1.99)	.001
Psychological abuse:		
No	1	
Once/sometimes	1.10 (0.65-1.85)	.73
Regularly/often/very often	1.59 (1.22-2.09)	.001
Physical abuse:		
No	1	
Once/sometimes	1.16 (0.75-1.81)	.50
Regularly/often/very often	1.99 (1.37-2.88)	<.001
Sexual abuse:		
No	1	
Once/sometimes	1.16 (0.83-1.62)	.37
Regularly/often/very often	1.90 (1.15-3.12)	.01
Childhood life events		
Parental loss	0.90 (0.54-1.48)	.67
Divorce parents	1.10 (0.77-1.57)	.60
Separation	1.08 (0.67-1.72)	.76

[a] Adjusted for gender, age and education.

Table 3. Childhood trauma index and other depression characteristics[a].

Childhood Trauma Index Score	Comorbid Anxiety,%	Onset of Depression Before Age 21, %	IDS-SR score, mean (SD)
0	61.7	29.6	28.7 (12.8)
1-2	68.3	39.3	29.6 (13.1)
3-4	69.2	38.9	32.8 (12.7)
5-6	72.7	48.7	34.5 (12.7)
7-8	81.4	54.2	38.2 (12.8)
	P = .005	*P* < .001	*P* <.001

[a] Comparison using Chi square statistics (categorical variables) and analyses of variance (continuous variables).
Abbreviations: IDS-SR = Inventory of Depressive Symptomatology-Self-Report.

Table 4. Risk for chronicity of depression according to childhood trauma index without[a] and with[b] adjustment for clinical characteristics.

	Risk for Chronicity, OR (95% CI)	P	Risk for Chronicity, OR (95% CI)	P
Childhood trauma index (0-8):				
0	1		1	
1-2	0.94 (0.68-1.32)	74	0.86 (0.60-1.22)	.40
3-4	1.25 (0.90-1.75)	.19	1.00 (0.70-1.43)	.99
5-6	1.63 (1.11-2.40)	.01	1.20 (0.80-1.81)	.38
7-8	3.26 (1.86-5.72)	<.001	2.06 (1.13-3.73)	.02
Comorbid Anxiety:				
No				
Yes	NA	NA	1.57 (1.17-2.11)	.003
Onset of depression before age 21:				
No				
Yes	NA	NA	1.27 (0.95-1.70)	.11
Severity of depressive symptoms				
Per 1 IDS-SR score increase	NA	NA	1.05 (1.03-1.06)	<.001

[a] Adjusted for age, gender, and education.
[b] Adjusted for age, gender, education, comorbid anxiety, age at onset of depression, and severity of depressive symptoms.
Abbreviations: IDS-SR = Inventory of Depressive Symptomatology-Self-Report.

Discussion

The results of the current study demonstrate that a reported history of childhood trauma is associated with a significant increased risk of chronicity of depression in adults with an MDD diagnosis in the past year. Emotional neglect, psychological abuse, physical abuse, and sexual abuse were all significantly associated with chronicity of depression, whereas a reported history of objective childhood life events, such as parental loss, divorce of parents, and separation, were not. There was a dose-response relationship between the frequency of childhood trauma and chronicity of depression. Subjects with the highest scores on the childhood trauma index (score 7-8) had a 3-fold increase in chronicity of depression compared to those with no childhood trauma (score 0). A high score on the childhood trauma index was also associated with a significantly higher prevalence of comorbid anxiety, more severe depression, and an earlier onset of the first depressive episode. However, after controlling for these characteristics, we found that the association between a high score on the childhood trauma index and chronicity of depression persisted. Consequently, even after considering that childhood trauma was also associated with comorbid anxiety, earlier age at onset of depression, and a more severe depression, childhood trauma was an independent determinant of chronicity of depression.

Our findings that childhood trauma but not childhood life events can be seen as a potential risk factor for a chronic course of depression are in line with the findings of prior studies on the role of childhood trauma (6-11) and childhood life events (12-16) in chronicity of depression. Our results support the assumption that the most important factor is not the life event per se but, rather, the quality of the childhood home environment (29). Dose-response relationships between childhood trauma and chronic depression have also been reported by Bifulco and colleagues (9). The greater the number of childhood trauma the individual reported, the higher the probability of lifetime chronic or recurrent depression.

Although the results of the current study are compelling with respect to the strong relation between the frequency of childhood trauma and chronicity of depression, there are some limitations. The fact that chronicity of depression was not defined according to DSM-IV-TR criteria (19) can be seen as a limitation of this study. *Chronicity of depression* was defined as being depressed for 24 months or more in the past 4 years instead of being depressed for 24 consecutive months. Therefore, it could be that some of the participants in the chronically depressed group did not strictly fulfill a diagnosis of chronic MDD, but rather a diagnosis of recurrent MDD according to DSM-IV-TR criteria (19). Nonetheless, the mean number of months depressed in the past 4 years was 40.7 for the chronically depressed group (versus 10.3 months for the nonchronically depressed group), which indicates that many chronically depressed participants also would fulfill DSM-IV-TR criteria. Furthermore, some persons in the nonchronic depression group may have had a chronic depression in the past. However, this would have led to a weakening of the association between chronicity of depression and childhood trauma.

Our current findings are based on a cross-sectional survey. Hence, the specific pathways by which childhood trauma may be related to chronicity of depression are unknown. In the near future, data from NESDA will give us the opportunity to repeat this study using prospective methods. These longitudinal analyses should confirm the relationship between childhood trauma and chronicity of depression and will help us to determine factors mediating the relationship between childhood trauma and chronicity of depression. Another limitation due to the cross-sectional analysis is the possibility of reverse causation: the presence of chronic depression could lead patients to perceive and report more childhood trauma in retrospection. Since our results are based on retrospective reports of childhood trauma and childhood life events in a depressed sample, they may reflect perceptions of childhood trauma and childhood life events rather than actual events. Although studies of retrospective reports of childhood trauma conclude that there is little evidence that psychopathology is associated with less reliable or less valid recollections (30, 31), caution is still necessary (5).

Finally, comorbid personality disorder was not assessed in this study but could confound the link between childhood trauma and chronic depression (32, 33). In prior studies on chronic

depression, personality disorders, and personality, neuroticism was found to be the strongest predictor of chronicity (34, 35). Since NESDA has data on personality traits, measured by the NEO-Five Factor Inventory questionnaire (36), we included the personality trait *neuroticism* in a post hoc analysis. Although neuroticism was related to chronicity of depression and childhood trauma, inclusion of neuroticism in multivariate analyses did not change the association between childhood trauma and chronicity of depression.

Despite the limitations of this study, the use of a large, representative sample in which both childhood trauma and childhood life events were considered and for which other clinical characteristics, such as severity, comorbid anxiety, and age at onset of depression, were adjusted provides more insight into the relationship between childhood trauma and chronic depression. Given the heterogeneity of MDD, linking childhood trauma to particular expressions of depression might help to identify high-risk individuals, thus improving our ability to adequately treat depression over time. Other research has suggested that individuals with and without a history of childhood trauma may react differently to treatment (37). In a large group of chronically depressed patients (N= 681), a differential response to psychotherapy versus pharmacotherapy was found as a function of the presence of childhood trauma. Psychotherapy was superior over pharmacotherapy for patients who reported childhood trauma. This suggests that there may be important differences in the etiology and pathogenesis of depression in individuals with and without history of childhood trauma (37).

For this reason, there are several implications for clinical practice. First, clinicians in mental health care should be aware that the presence of childhood trauma, especially the presence of multiple childhood traumas, may imply a more chronic course of depression. Thus, childhood trauma provides prognostic information beyond that available from clinical information of the current depressive episode. Second, estimation of the risk of chronicity may be of importance in the subsequent management of depression. As yet, there is little attention on childhood trauma in the current evidence-based treatments of depression. Interventions that focus on childhood trauma could potentially lead to a better treatment response, especially in treating chronic depression.

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3

Chapter 4

Impact of Childhood Life Events and Trauma on the Course of Depressive and Anxiety Disorders

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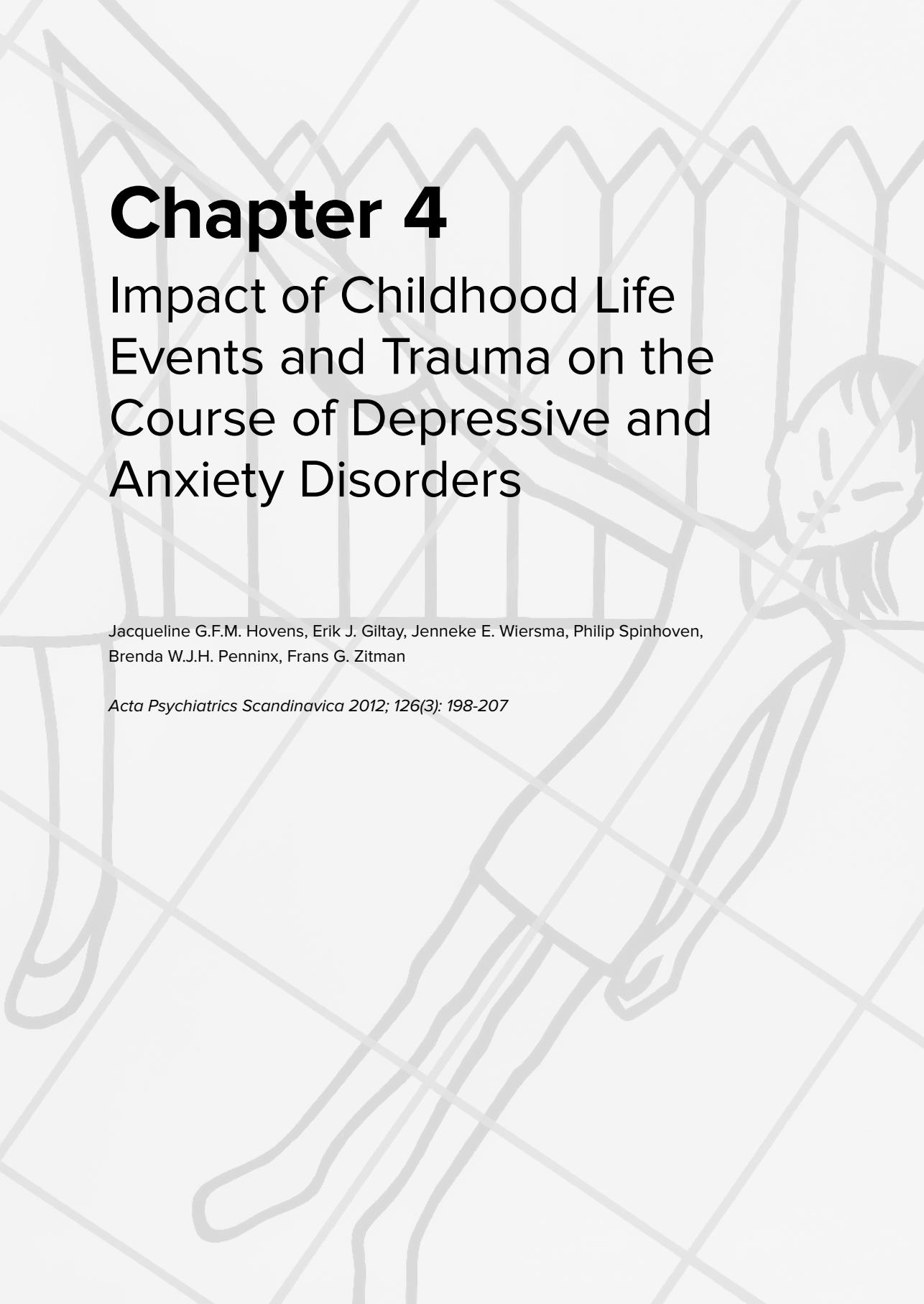
Abstract

Objective: Data on the impact of childhood life events and childhood trauma on the clinical course of depressive and anxiety disorders are limited.

Method: Longitudinal data were collected from 1,209 adult participants in the Netherlands Study of Depression and Anxiety (NESDA). Childhood life events and trauma at baseline were assessed with a semi-structured interview and the clinical course after 2 years with a DSM-IV-based diagnostic interview and Life Chart Interview.

Results: At baseline, 18.4% reported at least one childhood life event and 57.8% any childhood trauma. Childhood life events were not predictive of any measures of course trajectory. Emotional neglect, psychological and physical abuse, but not sexual abuse, were associated with persistence of both depressive and comorbid anxiety and depressive disorder at follow-up. Emotional neglect and psychological abuse were associated with a higher occurrence of a chronic course. Poor course outcomes were mediated mainly through a higher baseline severity of depressive symptoms.

Conclusion: Childhood trauma, but not childhood life events, was associated with an increased persistence of comorbidity and chronicity in adults with anxiety and/or depressive disorders. More unfavourable clinical characteristics at baseline mediate the relationship between childhood trauma and a poorer course of depressive and anxiety disorders.

Introduction

Childhood abuse and other adverse childhood experiences have been associated with an increased risk of psychopathology, in particular, the emergence of depressive and anxiety disorders in adulthood (1-6). In addition, early childhood adversities may play an important role in the maintenance of depressive and anxiety disorders. Childhood adversities have been linked to a more chronic and unfavourable course of depression later in life (5-8), while data on their role in the maintenance of anxiety disorder are lacking.

We would expect that childhood trauma is not only associated with an increased risk for depressive and anxiety disorders but also has an impact on clinical course. In a 5-year prospective study among 174 patients with an anxiety disorder and current major depression, patients with a positive trauma history were less likely to remit from depression than those without a trauma history (9). Another study of 38 female in-patients with major depression showed that depressed women without a history of abuse were nearly four times more likely to recover from their illness by 12 months (10). In a large community sample, childhood adversity (i.e. emotional neglect, physical/sexual abuse) was strongly associated with chronicity (11). These findings were replicated in a clinical sample of female patients with major depression (12). Childhood adversity also predicted a longer period of depressive or anxiety symptoms among 303 subjects with a depressive and/or anxiety disorder, followed up for 7 years (13). A population-based study among 1,405 subjects demonstrated that multiple traumatic experiences increase the likelihood of persistent depressive symptoms at 2-year follow-up (14).

Our previous cross-sectional study demonstrated a relationship between childhood trauma and chronicity of depression. Childhood trauma was associated with more unfavourable clinical characteristics, such as more comorbidity, an earlier age of depression onset and more severe depression (5). The question whether these clinical characteristics mediate the link between childhood trauma and the course of depressive and/or anxiety disorders deserves better attention than it received in previous studies (9-14). Assuming potential effects of clinical factors on illness course, the role of childhood trauma as an independent determinant of illness course has not yet been clarified. Longitudinal analyses of the predictive value of childhood adversities on the course of anxiety and depressive disorders are preferred as longitudinal analyses reduce the chance of reverse causation.

Aims of the Study

This study examines the effect of childhood trauma and childhood life events on the 2-year course of depressive and/or anxiety disorders in a large cohort of subjects with a baseline diagnosis of depressive and/or anxiety disorder, recruited from both primary care and specialized mental health care. We also determined which clinical factors (and to what extent

they) are important in mediating the relationship between childhood trauma and the course of depressive and/or anxiety disorders.

Material and methods

Sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing cohort study designed to investigate the course and consequences of depressive and anxiety disorders. Data were obtained from NESDA, an 8-year longitudinal cohort study that includes 2,981 participants, aged 18 through 65 years. Participants were recruited through different settings (general population, primary care and mental health care) and for different phases of illness (healthy controls, subjects with prior history, subjects with a current depressive and/or anxiety disorder). Subjects gave their informed consent and institutional review board approval was obtained for the study. A detailed description of the study design and sample has been previously published (15). Depressive (Major Depressive Disorder, Dysthymia) and anxiety (Panic disorder, Agoraphobia, Social phobia, Generalized Anxiety Disorder) disorders were defined according to DSM-IV criteria and diagnosed with Composite International Diagnostic Interview (CIDI; WHO version 2.1), a fully structured diagnostic interview (16, 17). The CIDI is used worldwide and WHO field research has found high interrater reliability and high validity for depressive and anxiety disorders (16, 17). The CIDI was conducted by specially trained clinical staff.

After two years, a face-to-face follow-up assessment was conducted with a response of 87.1% (N = 2,596). Non-response was significantly higher among those with younger age, lower educational level, non-North European ancestry and depressive disorder, but was not associated with gender or the presence of anxiety disorder (18). In the present study, the sample was restricted to the 1,456 subjects with a 6-month depressive or anxiety diagnosis at baseline and confirmed symptoms in the month prior to baseline at either the CIDI recency questions or the Life Chart Interview. In the 2-year follow-up, 1,209 subjects (83.0%) participated: 267 (22.1%) with a pure depressive disorder, 487 (40.2%) with a pure anxiety disorder and 455 (37.6%) with a comorbid depressive and anxiety disorder at baseline. Subjects who had a diagnosis before the first assessment and remitted during the 6-month period preceding the first wave were excluded from the analyses.

Course of depressive and anxiety disorders

The course of depressive and anxiety disorders was determined using two interviews collected during the 2-year follow-up assessment: (i) the CIDI interview and (ii) the Life Chart Interview (LCI). The CIDI interview determined the presence of depressive and anxiety disorders during the interval between baseline assessment and 2-year follow-up.

All subjects with depressive or anxiety symptoms in the CIDI interview also completed the LCI (19). For each month with reported symptoms during the 2-year follow-up, severity was assessed ranging from no or minimal severity to mild, moderate, severe or very severe. Symptoms on LCI were only considered to be present when at least of mild severity. The following course indicators were created:

Psychiatric status after two years was based on the presence of CIDI DSM-IV diagnosed anxiety and/or depressive disorders (6-month recency) at the time of 2-year follow-up. The group with 'no diagnosis' refers to subjects without any anxiety and/or depressive disorder (6-month recency) at the time of 2-year follow-up.

Clinical course trajectory after two years was defined by categorizing subjects into three categories on the basis of their depressive or anxiety symptoms over time. As done before (20), distinction was made between: (i) early sustained remission (defined as remission within six months) without recurrence of any symptoms during follow-up, (ii) late sustained remission (defined as remission after six months) without recurrence of any symptoms or remission with recurrence (defined as remission with later recurrence of symptoms) and (iii) chronic course: those without remission, but with enduring symptoms of at least mild severity during the entire follow-up period.

Determinants of 2-year course
Sociodemographics. Demographic data used in our study were gender, age and years of education attained. As gender, age and education are strongly associated with the childhood trauma score (Table 1), we included these three demographic variables as potential confounders.

Clinical characteristics. Several clinical characteristics were taken into account, because they showed an effect on the 2-year course of depressive and/or anxiety disorders in an earlier NESDA study (21). Severity of depressive symptoms was measured with the 30-item Inventory of Depressive Symptomatology (IDS) (22). Severity of anxiety symptoms was measured using the 15-item Fear Questionnaire (23). Information on duration of symptoms prior to baseline was derived from the Life Chart Interview (LCI) (23) conducted at baseline, which assessed the percentage of time the patient spent with depressive and/or anxiety symptoms in the 4 years prior to baseline. Age of onset was part of the CIDI interview, and earliest age was used for those with comorbid disorders. In 3 cases the age of onset could not be considered as a mediating variable, because the age of onset preceded the childhood adverse events. Finally, baseline psychiatric status (depression only/anxiety only/comorbid status) was included.

Trauma assessment

At baseline, childhood life events and childhood trauma were assessed retrospectively by a structured interview, used in the Netherlands Mental health Survey and Incidence Study within the age range 18-64 (21).

The childhood trauma NEMESIS Questionnaire is a comprehensive trauma interview focused on five areas of childhood interpersonal trauma: (i) childhood life events defined as separations and losses, (ii) emotional neglect, (iii) psychological, (iv) physical and (v) sexual abuse. This instrument measures trauma with a continuous scoring system rather than dichotomous ratings of trauma (i.e. present/absent), which is advantageous from a clinical perspective as well as statistical power (24). The childhood trauma NEMESIS Questionnaire shows a high similarity with the Childhood Trauma Interview, which is a reliable and valid method for brief assessment of multiple dimensions of childhood interpersonal trauma (25). The childhood trauma NEMESIS Questionnaire was administered by specially trained clinical staff and positioned half-way through the 4 h baseline assessment, at which point, the participant became more familiar and felt more comfortable with the interviewer. Interviewers and patients were not gender-matched; the majority of our subjects (91%) were interviewed by a female interviewer.

Childhood life events. Participants were asked if any of the following life events had happened before the age of 16 years: death of either biological father or mother, divorce of the parents or being placed in care (defined as children's home, juvenile prison or foster family). Each childhood life event was coded in a dichotomous format (0 absent /1 present). The childhood life events were analysed per item separately, as well as cumulative. As done before (3, 5), the childhood life event index, a cumulative index ranging from 0 to 3, reflects the number of life events experienced.

Childhood trauma. The participants were asked whether they had experienced any kind of emotional neglect, psychological, physical or sexual abuse before the age of 16. The definition of emotional neglect included lack of parental attention or support and ignorance of one's problems and experiences. Psychological abuse was defined as being verbally abused, undeserved punishment, subordinated to siblings and being blackmailed. Physical abuse was defined as being kicked or hit with hands or an object, beaten up or physical abuse in any other way. Sexual abuse was defined as being sexually approached against your will, meaning being touched or having to touch someone in a sexual way. Participants answered 'yes' or 'no' to each of the four forms of childhood trauma and were asked to give an indication about the frequency on a five-point scale (i.e, once, sometimes, regularly, often and very often). In the analyses, the frequencies were categorized into three groups (0: absent, 1: once or sometimes, 2: regularly, often and very often). As before (3, 5), a cumulative childhood trauma index, defined as the sum scores ranging from 0-8, was created with a higher score indicating more types and a higher frequency of childhood trauma.

Statistical analyses

Baseline characteristics were compared across the childhood life event and childhood trauma indices, using analysis of variance for continuous variables and chi-squared tests for categorical variables. Associations between specific childhood life events and specific childhood trauma domains with the 2-year course measures (i.e. diagnosis after two years and clinical course trajectory after two years) were examined. Subsequently, multinomial logistic regression analysis was used to calculate odds ratios for the presence of diagnostic categories and clinical course trajectory categories after 2-year follow-up, according to childhood trauma domain and the index score, adjusted for age, gender, and education. The childhood trauma index was considered a continuous variable ranging from 0 to 8. The 'no diagnosis' and 'early remission' groups were regarded as reference groups and *P*-values were derived by likelihood ratio tests.

To examine the mediation effects of baseline clinical characteristics on the relationship between childhood trauma index and 2-year course, a multiple mediation model by Preacher and Hayes (26) was used. Mediation was investigated by directly testing significance of the indirect effect of the independent variable (IV) on the dependent variable (DV) through the mediator (M) quantified as the product of the effects of the IV on M (a) and the effect of M on DV (b), partialling out the effects of the IV. Analyses were also performed with a multiple mediator model using a bootstrapping approach in which a point estimate of the indirect effect was derived from the mean of the 1000 estimates of a x b. The 95% percentile-based confidence intervals (CI) were computed using the cut-offs for the 2.5% highest and lowest scores of the empirical distribution. Mediating effects were considered as significant when the bias corrected and accelerated confidence interval did not include zero.

A two-tailed *P* < 0.05 was considered statistically significant; the statistical software used was SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Sixty-six percent of the study population was female, the mean age was 42.1 years (SD = 12.3). At baseline, 18.4% reported at least one childhood life event and 57.8% any childhood trauma. Baseline disease characteristics showed less pronounced differences between groups categorized according to the childhood life-event index (Table 1) than between groups categorized by the childhood trauma index (Table 2). However, a lower level of education and an earlier age of onset were associated with a higher childhood life events index (Table 1). A higher childhood trauma score was associated with being female, a lower level of education, earlier age of onset, longer duration of symptoms, higher severity scores for both anxiety and depressive symptoms and more comorbidity.

Table 1. Baseline characteristics according to the childhood life-event score in participants with a baseline diagnosis of depressive or anxiety disorder (N=1,209).

	Childhood life-event score			
	0	1	2 to 3	P-value*
No. of participants	987	194	28	
Age (years, ± SD)	42.5 ± 12.2	39.5 ± 13.0	42.5 ± 11.4	0.02
Female gender (n, %)	647 (65.6%)	136 (70.1%)	18 (64.3%)	0.40
Education level attained (years, ± SD)	11.9 ± 3.3	11.5 ± 3.4	10.6 ± 3.0	0.01
Age of onset (years, ± SD)	21.3 ± 12.8	19.9 ± 11.7	16.2 ± 9.8	0.02
Duration of symptoms at baseline** (%, ± SD)	54.4 ± 33.3	52.3 ± 31.8	62.2 ± 32.4	0.89
IDS-SR (score, ± SD)	30.0 ± 12.2	30.6 ± 11.5	33.0 ± 9.5	0.20
Fear Questionnaire (score, ± SD)	33.9 ± 20.5	32.2 ± 20.6	37.9 ± 18.7	0.85
Baseline diagnosis:				
Pure depression	223 (22.6%)	41 (21.1%)	3 (10.7%)	0.28
Pure anxiety	393 (39.8%)	84 (43.3%)	10 (35.7%)	
Comorbid depression-anxiety	371 (37.6%)	69 (35.6%)	15 (53.6%)	

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of mental disorders – fourth edition; IDS-SR, Inventory of Depressive Symptoms Self Report.
Data are number (percentage) or mean (± SD), when appropriate.
*: *P*-values by ANOVA linear term or Chi square tests (for linear association).
**: % of months with symptoms in the past 4 years.

Table 2. Baseline characteristics according to the childhood trauma score in participants with a baseline diagnosis of depressive or anxiety disorder (N=1,209).

	Childhood trauma score			
	0	1 to 3	4 to 8	P-value*
No. of participants	510	428	271	
Age (years, ± SD)	40.6 ± 12.7	42.6 ± 12.2	43.9 ± 11.6	< 0.001
Female gender (n, %)	303 (59.4%)	299 (69.9%)	199 (73.4%)	< 0.001
Education level attained (years, ± SD)	11.9 ± 3.2	12.0 ± 3.3	11.2 ± 3.3	0.02
Age of onset (years, ± SD)	23.4 ± 12.9	20.5 ± 12.5	17.2 ± 10.9	<0.001
Duration of symptoms at baseline** (%, ± SD)	52.2 ± 33.3	54.9 ± 33.3	57.0 ± 32.1	0.047
IDS-SR (score, ± SD)	27.1 ± 12.1	30.7 ± 11.4	34.9 ± 11.3	< 0.001
Fear Questionnaire (score, ± SD)	30.3 ± 18.8	34.1 ± 20.1	39.6 ± 22.5	< 0.001
Baseline diagnosis:				
Pure depression	115 (22.5%)	99 (23.1%)	53 (19.6%)	0.001
Pure anxiety	232 (45.5%)	167 (39.0%)	88 (32.5%)	
Comorbid depression-anxiety	163 (32.1%)	162 (37.9%)	130 (48.0%)	

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of mental disorders – fourth edition; IDS-SR, Inventory of Depressive Symptoms Self Report.
Data are number (percentage) or mean (± SD), when appropriate.
*: P-values by ANOVA linear term or Chi square tests (for linear association).
**: % of months with symptoms in the past 4 years.

The diagnostic status after 2 years of follow-up is presented in Table 3: 38.5% of the 1,209 participants had no disorder, 21.6% had a pure anxiety disorder, 14.9% had a pure depressive disorder and 25.0% had a comorbid depressive and anxiety disorder. Concerning the clinical course trajectory after 2 years, 24.2% of the 1,209 participants had an early remission, 31.4% had a late remission and 42.8% showed a chronic course. Data on the 2 year course trajectory were not available for 18 participants (1.6%).

Childhood life-events
No statistically significant associations were found between specific childhood life events and the psychiatric diagnostic status or clinical course trajectory after 2 years. Moreover, the childhood life event index did not show any statistically significant relationship with the 2-year course measures (Table 3).

Childhood trauma
Emotional neglect and psychological and physical abuse were all associated with the 2-year psychiatric diagnostic status (Table 3). The prevalence of emotional neglect, psychological and physical abuse gradually increased in the following order: from no disorder, anxiety disorder, depressive disorder to comorbid anxiety and depressive disorder. The childhood trauma index did follow the same pattern ($P < 0.001$). Looking at the clinical course trajectory after 2 years, emotional neglect and psychological abuse were increasingly prevalent from early to late remission to the highest prevalence in chronic course. In addition, a higher childhood trauma index was associated with a higher probability of a chronic course ($P < 0.001$).

Additional multivariable analyses, adjusted for age, sex and education, were conducted on the association between childhood trauma and 2-year clinical course measures (Table 4). Regular emotional neglect (OR = 2.04), psychological (OR = 2.58) and physical abuse (OR = 2.39) were associated with a higher probability of having comorbid depressive and anxiety disorders after 2 years, whereas emotional neglect (OR = 1.82) and psychological abuse (OR = 1.63) were associated with a higher probability of chronicity. No significant associations were found with sexual abuse. An additional gender-congruent analysis among female participants interviewed by females did not show significant results for sexual abuse either. The childhood trauma index was significantly related to both psychiatric diagnostic status ($P < 0.001$) and the clinical course trajectory ($P = 0.01$) after 2 years.

An increased score on the childhood trauma index corresponded with a greater chance of having a depressive disorder ($P = 0.01$) and a comorbid anxiety and depressive disorder ($P < 0.001$) after 2 years, but not for having an anxiety disorder (Figure 1). Increasing childhood trauma index was also associated with a higher probability of late remission ($P = 0.04$) and a chronic course ($P = 0.004$) after 2 years.

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Table 3. Independent contributions of childhood life events and trauma score for the 2-year psychiatric diagnosis and course trajectory outcomes, in participants with a baseline diagnosis of depressive or anxiety disorder (N=1,209).

	Diagnosis after 2 years					Clinical course trajectory after 2 years			
	No disorder	Anxiety disorder	Depressive disorder	Comorbidity	P-value*	Early remission	Late remission	Chronic course	P-value** for trend
No. of participants	465	261	180	303		293	380	518	
Childhood life events:									
Divorce parents	65 (14.0%)	33 (12.6%)	25 (13.9%)	42 (13.9%)	0.96	35 (11.9%)	52 (13.7%)	75 (14.5%)	0.32
Early parental loss	33 (7.1%)	22 (8.4%)	12 (6.7%)	24 (7.9%)	0.88	24 (8.2%)	35 (9.2%)	31 (6.0%)	0.17
Placed in care	31 (6.7%)	20 (7.7%)	11 (6.1%)	23 (7.6%)	0.89	22 (7.5%)	19 (5.0%)	41 (7.9%)	0.62
Childhood life event score									
0	376 (80.9%)	218 (83.5%)	146 (81.1%)	247 (81.5%)	0.19	240 (81.9%)	316 (83.2%)	419 (80.9%)	0.31
1	82 (17.6%)	33 (12.6%)	32 (17.8%)	47 (15.5%)		49 (16.7%)	57 (15%)	82 (15.8%)	
2 to 3	7 (1.5%)	10 (3.8%)	2 (1.1%)	9 (3.0%)		4 (1.4%)	7 (1.8%)	17 (3.3%)	
Childhood trauma:									
Emotional neglect									
Once or sometimes	88 (18.9%)	68 (26.1%)	41 (22.8%)	57 (18.8%)	< 0.001	55 (18.8%)	81 (21.2%)	113 (21.8%)	0.001
Regularly or very often	101 (21.7%)	66 (25.3%)	55 (30.6%)	106 (35.0%)		61 (20.8%)	106 (27.9%)	156 (30.1%)	
Psychological abuse									
Once or sometimes	71 (15.3%)	49 (18.8%)	36 (20.0%)	60 (19.8%)	< 0.001	43 (14.7%)	76 (20.0%)	90 (17.4%)	0.02
Regularly or very often	47 (10.1%)	31 (11.9%)	29 (16.1%)	64 (21.1%)		33 (11.3%)	51 (13.4%)	86 (16.6%)	
Physical abuse									
Once or sometimes	32 (6.9%)	26 (10.0%)	16 (8.9%)	27 (8.9%)	0.002	22 (7.5%)	34 (9.0%)	40 (7.7%)	0.65
Regularly or very often	34 (7.3%)	21 (8.0%)	18 (10.0%)	49 (16.2%)		27 (9.2%)	40 (10.5%)	54 (10.4%)	
Sexual abuse									
Once or sometimes	41 (8.8%)	18 (6.9%)	16 (8.9%)	32 (10.6%)	0.79	25 (8.5%)	37 (9.7%)	42 (8.1%)	0.08
Regularly or very often	58 (12.5%)	34 (13.0%)	27 (15.0%)	40 (13.2%)		31 (10.6%)	47 (12.4%)	79 (15.3%)	
Childhood trauma score									
0	232 (49.9%)	105 (40.2%)	71 (39.4%)	102 (33.7%)	< 0.001	150 (51.2%)	158 (41.6%)	197 (38.0%)	0.001
1 to 3	147 (31.6%)	102 (39.1%)	67 (37.2%)	112 (37.0%)		90 (30.7%)	137 (36.1%)	193 (37.3%)	
4 to 8	86 (18.5%)	54 (20.7%)	42 (23.3%)	89 (29.4%)		53 (18.1%)	85 (22.4%)	128 (24.7%)	

* P-value by chi-squared test and **linear-by-linear term.

Table 4. Odds ratios adjusted for sociodemographic covariates for the 2-year psychiatric diagnosis and course trajectory outcomes, in participants with baseline diagnoses of depressive or anxiety disorders (N=1,209) according to childhood trauma.

	Diagnosis after 2 years					Clinical course trajectory after 2 years			
	No disorder	Anxiety disorder	Depressive disorder	Comorbidity	P-value*	Early remission	Late remission	Chronic course	P-value*
Emotional neglect:									
No	1.0					1.0			
Once or sometimes	1.0	1.67 (1.14-2.45)	1.69 (1.12-2.56)	1.26 (0.85-1.87)	< 0.001	1.0	1.35 (0.91-2.02)	1.46 (1.00-2.13)	0.01
Regularly or very often	1.0	1.42 (0.97-2.07)	1.49 (0.95-2.33)	2.04 (1.45-2.88)		1.0	1.62 (1.11-2.36)	1.82 (1.27-2.60)	
Psychological abuse:									
No	1.0					1.0			
Once or sometimes	1.0	1.31 (0.87-1.97)	1.47 (0.93-2.32)	1.60 (1.09-2.37)	< 0.001	1.0	1.51 (0.99-2.30)	1.31 (0.88-1.96)	0.08
Regularly or very often	1.0	1.25 (0.76-2.03)	1.79 (1.07-2.98)	2.58 (1.69-3.93)		1.0	1.32 (0.82-2.12)	1.63 (1.05-2.52)	
Physical abuse:									
No	1.0					1.0			
Once or sometimes	1.0	1.50 (0.87-2.58)	1.36 (0.72-2.55)	1.48 (0.87-2.55)	0.009	1.0	1.21 (0.69-2.12)	1.04 (0.60-1.80)	0.94
Regularly or very often	1.0	1.13 (0.64-1.99)	1.39 (0.76-2.55)	2.39 (1.49-3.83)		1.0	1.16 (0.69-1.95)	1.10 (0.67-1.80)	
Sexual abuse:									
No	1.0					1.0			
Once or sometimes	1.0	0.75 (0.42-1.34)	1.07 (0.58-1.99)	1.26 (0.76-2.07)	0.75	1.0	1.13 (0.66-1.94)	1.02 (0.60-1.72)	0.40
Regularly or very often	1.0	0.98 (0.61-1.56)	1.22 (0.73-2.03)	1.05 (0.67-1.64)		1.0	1.15 (0.70-1.88)	1.50 (0.95-2.37)	
Childhood trauma score:**	1.0	1.06 (0.98-1.14)	1.12 (1.03-1.21)	1.18 (1.10-1.26)	< 0.001	1.0	1.08 (1.00-1.17)	1.11 (1.03-1.19)	0.01

* P-value and odds ratios (with 95% confidence intervals) by multinomial logistic regression analysis, adjusted for gender, age, and education.
** The childhood trauma score was considered a continuous variable ranging from 0 to 8.

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Figure 1. Odds ratios for the two-year diagnosis and course trajectory outcomes in participants with baseline diagnoses of depressive or anxiety disorders (N=1,209) according to the level of childhood trauma (versus no childhood trauma as the reference category), adjusted for gender, age, and education. The size of each square is proportional to the number of participants; vertical lines indicate 95% confidence intervals. *P*-values by multinomial logistic regression analysis.

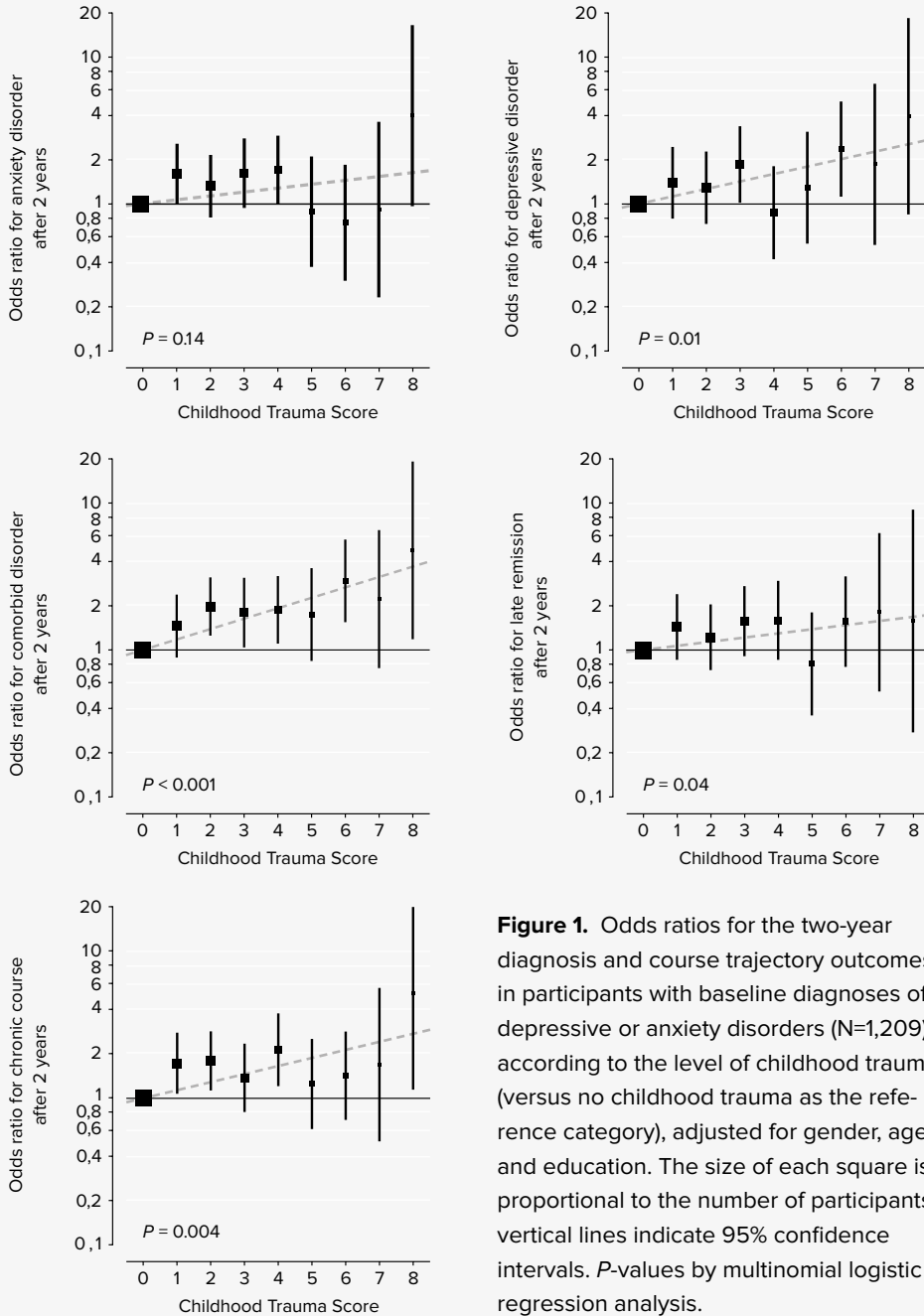**Table 5.** Explained variance of baseline disease characteristics on the relationship between the childhood trauma index (IV) and 2-year diagnosis and course trajectory outcomes (DV) in participants with baseline diagnoses of depressive or anxiety disorders.

Mediating variable (M)	No. DV / reference	Effect of trauma on M (a)	Effect of M on DV (b)	Direct effect of trauma on DV (c')	Mediating effect (a x b; 95% CI)	Total effect (c)
Depressive disorder (DV)						
Age of onset	180 / 465	−1.458	−0.001	0.104	0.001 (−0.020; 0.024)	0.110
Duration of symptoms	180 / 465	0.484	0.002	0.097	0.001 (−0.006; 0.003)	0.106
DSM IV comorbidity diagn	180 / 465	0.016	0.629	0.096	0.010 (−0.001; 0.027)	0.112
IDS-SR score	180 / 465	1.262	0.049	0.043	0.062 (0.038; 0.098)	0.107
Fear Questionnaire	180 / 465	1.175	−0.003	0.108	0.003 (−0.017; 0.008)	0.112
Comorbid disorder (DV)						
Age of onset	303 / 465	−1.046	−0.031	0.129	0.033 (0.017; 0.057)	0.164
Duration of symptoms	303 / 465	1.392	0.017	0.148	0.023 (0.005; 0.047)	0.161
DSM IV comorbidity diagn	303 / 465	0.040	1.418	0.120	0.057 (0.032; 0.086)	0.165
IDS-SR score	303 / 465	1.525	0.080	0.073	0.123 (0.088; 0.170)	0.167
Fear Questionnaire	303 / 465	1.631	0.036	0.129	0.059 (0.030; 0.090)	0.165
Late remission (DV)						
Age of onset	380 / 293	−1.206	−0.008	0.065	0.010 (−0.008; 0.030)	0.079
Duration of symptoms	380 / 293	0.899	0.006	0.076	0.005 (−0.006; 0.018)	0.081
DSM IV comorbidity diagn	380 / 293	0.021	0.612	0.069	0.013 (0.002; 0.050)	0.082
IDS-SR score	380 / 293	1.430	0.038	0.027	0.055 (0.033; 0.086)	0.080
Fear Questionnaire	380 / 293	1.967	0.020	0.048	0.039 (0.021; 0.065)	0.082
Chronic course (DV)						
Age of onset	518 / 293	−1.188	−0.029	0.067	0.034 (0.018; 0.056)	0.105
Duration of symptoms	518 / 293	1.436	0.019	0.093	0.027 (0.008; 0.051)	0.107
DSM IV comorbidity diagn	518 / 293	0.039	1.186	0.068	0.046 (0.026; 0073)	0.106
IDS-SR score	518 / 293	1.420	0.050	0.039	0.071 (0.046; 0.100)	0.106
Fear Questionnaire	518 / 293	1.619	0.033	0.071	0.054 (0.028; 0.082)	0.106

IV denotes Independent variable, M denotes mediating variable, DV denotes dependent variable, a denotes effect of IV on M, b denotes effect of M on DV, c' denotes direct effect, a x b denotes indirect effect, c denotes total effect. Diagn = diagnosis.

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We investigated whether the relationship between the childhood trauma index (IV) and the 2-year diagnosis and course trajectory outcomes (DV) could be explained by the clinical baseline characteristics as mediating variables (M). Table 5 presents the results from mediation analyses. In the comorbid and chronic course groups, all clinical baseline characteristics significantly mediated the relation between childhood trauma and 2-year course. Moreover, the IDS-SR score, reflecting the severity of depressive symptoms at baseline, emerged as a significant mediator of the relation between childhood trauma and 2-year course in all groups. After adjustment of all potential mediating baseline characteristics, the effect of the childhood trauma index on psychiatric diagnostic status and clinical course trajectory after 2 years was no longer statistically significant (all P's > 0.3), indicating the major mediating contribution of clinical baseline characteristics to these relationships.

Discussion

The present study examined the effect of childhood trauma and childhood life events on the 2-year course of depressive and/or anxiety disorders in a large cohort of subjects with a baseline diagnosis of depressive and/or anxiety disorders from both primary care and specialized mental health care. The results demonstrate that a reported history of childhood trauma, but not childhood life events, was associated with a poorer course outcome in adults with baseline anxiety and/or depressive disorders. A prominent finding was that emotional neglect, psychological abuse and physical abuse were associated with comorbidity, whereas emotional neglect and psychological abuse were also associated with chronicity. Remarkably, no significant associations were found between sexual abuse and the 2-year course of anxiety and depressive disorders. The childhood trauma index was predictive of both a depressive or comorbid disorder and a chronic course after 2 years of follow-up. These associations appeared to be mediated through more unfavourable baseline clinical characteristics, of which the severity of depressive symptoms contributed most.

Many of the previous studies investigating the association of childhood adversities with illness course were using cross-sectional designs and showed inconsistent results (1, 6-8). In our cross-sectional study (5), we found a strong dose-response relationship between childhood trauma and chronicity of depression, which was confirmed in this prospective study.

Several prospective studies (9-14) have linked childhood adversity to an unfavourable course of depressive illness, characterized by less recovery, longer duration of symptoms and chronicity. However, prospective studies among patients with anxiety and/or depressive disorders are scarce and report only on small patient groups (N < 200 patients) (9, 10, 12) or focus on specific types of abuse (i.e. childhood sexual abuse). Rhebergen et al. (13) recently described the 7-year course of depression and anxiety among 303 patients and

studied childhood adversity only as a covariate in their multivariate models. Childhood adversity was identified as a risk factor for both the occurrence and persistence of depressive and anxiety symptoms.

Our results are generally consistent with earlier studies reporting a relationship between a history of childhood trauma and a more chronic and unfavorable course of psychopathology in adulthood. The effect of childhood trauma on outcome diagnosis at 2-year follow up was larger for depressive and comorbid disorders than for anxiety. We also provide new evidence that emotional neglect, psychological and physical abuse are all consistently and strongly associated with persistent comorbid depressive and anxiety disorders at 2 year follow-up. In contradiction with previous studies (8, 12, 27), sexual abuse was not associated with the course of depressive and anxiety disorders. Previous research demonstrates that patients are biased to underreport sexual abuse histories rather than overreport them (28). However, we had the impression that we arranged the interview conditions to be safe and confidential, so the participants would feel familiar and comfortable with the interviewers. This notion is supported by the high response rates at 2- and 4-year follow-ups.

Among our subjects, a positive sexual abuse history was prevalent in 22.0%, whereas emotional neglect and psychological abuse were reported in 48.1% and 32.0%, respectively. Thus, the lack of an association with sexual abuse could partially be attributed to a somewhat lower statistical power. The sexual abuse section inquired about contact experiences, specifically being touched or having to touch someone in a sexual way. Therefore we could not differentiate between the effects of touching in a sexual way and the more severe forms of sexual abuse, i.e. rape and/or penetration. We could therefore not explore whether the latter component of the most insidious trauma was associated with the course of depressive and anxiety disorders.

Analogous to our previous cross-sectional studies (3, 5), childhood life events were not pivotal and were not associated with 2-year course indicators. In the replicated US National Comorbidity Study (27) parental death, parental divorce or other parental loss was not associated with persistence of psychopathology. Parental loss in childhood was only associated with an increased likelihood of a depressive disorder in adulthood if the quality of the surviving family relationship was poor (29). Our findings support the hypothesis that the quality of the childhood holding environment is more important than life events per se.

We found that baseline clinical characteristics were important in determining the relationship between childhood trauma and the course of depressive and/or anxiety disorders. In our previous cross-sectional study (5), childhood trauma was an independent determinant of chronicity of depression, even after adjustment for comorbid anxiety, age of onset and severity of depression. In this longitudinal analysis, we found further evidence that more

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unfavorable clinical disease characteristics at baseline, such as severity, duration, age of onset and comorbidity, mediated the differences in course measures between patients with and without a history of childhood trauma. The severity of depressive symptoms played a predominant role. This study is unique because previous prospective studies have not investigated potential mediators (9-14).

The strength of the current study consists of a large, representative sample of participants with a baseline diagnosis of depressive and/or anxiety disorder, longitudinally examined for 2 years, in which childhood trauma and childhood life events were considered. Furthermore, outcome measures were based on both a diagnostic and a symptom trajectory approach and important baseline clinical characteristics were taken into account as potential media- tors. Also, some limitations have to be acknowledged. The trauma assessment at baseline was assessed retrospectively, which may incur the possibility of reverse causation: patients with baseline anxiety and/or depressive disorders might perceive and report more childhood trauma in retrospection, which may be secondary to their mental problems. Although studies of retrospective reports of childhood trauma conclude that there is little evidence that psychopathology is associated with less reliable or less valid recollections (30, 31), caution is still necessary. Therefore, our findings cannot be extrapolated to psychiatric disorders that were not assessed in this study.

For clinical practice, raising awareness of childhood trauma, especially multiple childhood traumas, is crucial as these may contribute to a more complex and chronic course of anxiety and depressive disorders. Unfavourable clinical characteristics are strongly linked to childhood trauma and may provide important prognostic information about the course of depressive and anxiety disorders.

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Chapter 5

Impact of Childhood Life Events and Childhood Trauma on the Onset and Recurrence of Depressive and Anxiety disorders

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Abstract

Objective: To investigate the effect of childhood life events and childhood trauma on the onset and recurrence of depressive and/or anxiety disorders over a 2-year period in participants without current psychopathology at baseline.

Method: Longitudinal data in a large sample of participants without baseline DSM-IV depressive or anxiety disorders (N = 1,167, aged 18 to 65 years; assessed between 2004 and 2007) were collected in the Netherlands Study of Depression and Anxiety (NESDA). Childhood life events and childhood trauma were assessed at baseline with a semi-structured interview. The Composite International Diagnostic Interview, based on DSM-IV criteria, was used to diagnose first onset or recurrent depressive and/or anxiety disorders over a 2-year period.

Results: At baseline, 172 participants (14.7%) reported at least 1 childhood life event, and 412 (35.3%) reported any childhood trauma. During 2 years of follow-up, 226 participants (19.4%) developed a new (N = 58) or recurrent (N = 168) episode of a depressive and/or anxiety disorder. Childhood life events did not predict the onset and recurrence of depressive or anxiety disorders. Emotional neglect and psychological, physical, and sexual abuse were all associated with an increased risk of first onset and recurrence of either depressive or comorbid disorders ($P < 0.001$), but not of anxiety disorders. In multivariate models, emotional neglect was the only significant independent predictor of first onset and recurrence of any depressive or comorbid disorder ($P = 0.02$). These effects were primarily mediated by the severity of (subclinical) depressive symptoms at baseline and, to a lesser extent, by a prior lifetime diagnosis of a depressive and/or anxiety disorder.

Conclusion: Childhood maltreatment is a key environmental risk factor, inducing vulnerability to develop new and recurrent depressive and comorbid anxiety and depressive episodes.

Introduction

Childhood abuse and other adverse childhood experiences have been linked to an increased risk of psychopathology, in particular the emergence of depressive and anxiety disorders in later life (1-6). Although previous research has documented long-term associations, these studies have largely focused on the prevalence of disorders rather than on first onset. Most studies investigating the association between childhood adversities and psycho-pathology in adulthood used cross-sectional designs (1-6) and were limited to specific trauma domains (7-11). Prospective evidence for childhood adversity predicting incident psychopathology in adulthood is rather limited. Several prospective studies that assessed the risk of depression and anxiety disorders included children exposed to childhood maltreatment and followed them up until (young) adulthood (12-15). Studies on anxiety disorders have been conducted much less often than studies on depressive disorders and have mainly focused on generalized anxiety disorders (14, 15).

In the US National Comorbidity Study, Kessler et al showed that childhood adversities were consistently associated with a higher risk of first onset of depressive episodes (1), and this was confirmed in a replication study (16). This finding, although retrospective, is important to advance our understanding of the chain of events and dynamic relationships between childhood trauma and adult-onset psychopathology. Longitudinal research offers excellent opportunities to predict the development of psychopathology after exposure to childhood trauma and to study its potential mediators.

In this prospective study, the impact of childhood trauma and childhood life events on the occurrence of adult psychopathology is studied in more detail and approached from different points of view to identify: (1) the differential effects on anxiety, depressive and comorbid disorders, (2) the specific effect of various childhood life events and all domains of child-hood trauma, (3) whether relationships differed in subjects with and without lifetime psycho-pathology, and (4) whether clinical factors such as severity of baseline anxiety and depressive symptoms and a prior lifetime diagnosis, are important in mediating the relationship between childhood trauma and the occurrence of depressive and anxiety disorders. To address these topics, a large cohort of subjects without any current depressive and/or anxiety disorder at baseline was followed over a 2-year time period.

Method

Sample
Baseline data were collected between 2004 and 2007 from a longitudinal cohort study including 2,981 participants aged 18 to 65 years from the Netherlands Study of Depression

and Anxiety (NESDA). To represent various settings and stages of psychopathology, NESDA recruited from three different settings: the general population (N = 564), primary care (N = 1,610) and mental health organizations (N = 807), in which persons with depressive and/or anxiety disorders were overrecruited. Since we utilized a sample without current psycho-pathology in this study, participants came from the general population (N = 380) and primary care settings (N = 787) only, where they were largely recruited through a 3-step screening approach. A detailed description of the study design, its rationale, and methods have been reported elsewhere (17). At baseline, lifetime presence of depressive and anxiety disorders was defined according to DSM-IV criteria and diagnosed with the Composite International Diagnostic Interview, WHO version 2.1 (CIDI), a fully structured diagnostic interview (18, 19). The present study reports on data from baseline and 2-year follow-up assessments.

Of the 2,981 participants in NESDA, we included 1,280 participants (42.9%) without a current depressive and/or anxiety disorder (defined as no disorder within the 6 months preceding baseline), of whom 1,167 (91.2%) participated in the 2-year follow-up interview. The effect of childhood trauma on illness course, in participants with a current depressive and/or anxiety disorder has been described in a previous article (20). Non-response was associated with fewer years of education (P = 0.001) and with reported childhood trauma (P = 0.002). The sample analyzed in this study constituted a mixture of individuals in remission after a previous episode of anxiety and/or depressive disorders (N = 569) and individuals free of any lifetime anxiety and/or depressive disorders (N = 598).

Trauma assessment
At baseline, childhood life events and childhood trauma were assessed retrospectively by a structured interview, used in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) within the age range 18-64 years (5, 21).

NEMESIS Childhood Trauma Interview (CTI) is a comprehensive trauma interview focused on five areas of childhood interpersonal trauma prior to the age of 16 years: (1) childhood life events defined as separations and losses, (2) emotional neglect, (3) psychological abuse, (4) physical abuse, and (5) sexual abuse. This instrument measures trauma with a continuous scoring system, which is advantageous from a clinical and statistical perspective, rather than dichotomous ratings of trauma (22).

Childhood life events. Participants were asked if any of the following life events had happened before the age of 16 years: death of either biological father or mother, divorce of the parents or being placed in care (defined as children's home, juvenile prison or foster family). Each childhood life event was coded in a dichotomous format (0 absent / 1 present). The childhood life events were analyzed for each separate item, as well as cumulative. The childhood life event score, a cumulative index ranging from 0 to 3, reflects the number of life events experienced (5, 21).

Childhood trauma. The definition of *emotional neglect* included lack of parental attention or support and parental ignorance of the child's problems and experiences. *Psychological abuse* was defined as being verbally abused, being given undeserved punishment, being subordinated to siblings, and being blackmailed. *Physical abuse* was defined as being kicked or hit with hands or an object, being beaten up or subjected to physical abuse in any other way. *Sexual abuse* was defined as being sexually approached against their will, meaning being touched or having to touch someone in a sexual way. Participants were asked to give an indication about the frequency on a five-point scale (i.e. once, sometimes, regularly, often and very often). In the analyses, the frequencies were categorized into three groups (0: absent, 1: once or sometimes, 2: regularly, often and very often). A *cumulative childhood trauma score*, defined as the sum of the frequency scores ranging from 0 to 8, was created, with a higher score indicating more types and a higher frequency of childhood trauma (5, 21).

Two-year occurrence of depressive and anxiety disorders
At the 2-year follow-up assessment, the CIDI was repeated to assess the occurrence of depressive and/or anxiety disorders since the baseline interview. Occurrence of a disorder was defined as either first onset or recurrence of the disorder anytime between baseline and 2-year follow-up assessment. Various disorder groups were identified: no occurrence, occurrence of depressive disorder, occurrence of anxiety disorder, and occurrence of comorbid depressive and anxiety disorder, defined as both disorders occurring at any time within the 2-year of follow-up.

Determinants of 2-year course
Sociodemographics. Demographic data used in our study were gender, age and years of education attained. Since gender, age and education were significantly associated with the childhood life-event or trauma score (Table 1), we included these demographic variables as covariates. The presence of lifetime alcohol abuse and/or dependence was diagnosed with the CIDI and used as a covariate (18, 19). The number of participants who abused substances other than alcohol was almost negligible and therefore not tested for.

Clinical characteristics. Previous NESDA studies showed that a psychiatric history and subthreshold depression and anxiety independently predict the subsequent occurrence of depressive or anxiety disorders (23) and that childhood trauma is associated with higher severity of depressive and anxiety symptoms (20). Therefore, subthreshold symptoms of depression and anxiety and a lifetime history were used to assess their potential role as mediators. Severity of depressive symptoms was measured with the 30-item Inventory of Depressive Symptomatology-Self Rated (IDS-SR) (24). Severity of anxiety symptoms was measured using the 15-item Fear Questionnaire (25) and the 21-item Beck Anxiety Inventory (26). Lifetime diagnosis was defined as the presence of an earlier episode of a depressive and/or anxiety disorder at any time during the individual's lifespan, with the exception of the 6 month period preceding baseline.

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Table 1. Baseline characteristics according to the childhood life-event score and the childhood trauma score in participants without a baseline diagnosis of depressive or anxiety disorder (N=1,167).

	Childhood life-event score			
	0	1	2 to 3	P-value[a]
No. of participants	996	156	15	
Age (years, ± SD)	42.9 ± 13.9	40.5 ± 14.0	45.0 ± 11.8	0.17
Female gender	66.3%	64.1%	46.7%	0.20
Education level attained (years, ± SD)	12.9 ± 3.2	12.3 ± 3.4	10.1 ± 2.7	0.001
IDS-SR (score, ± SD)	10.8 ± 8.3	12.2 ± 8.8	17.6 ± 11.8	0.002
BAI (score, ± SD)	5.4 ± 5.8	5.7 ± 5.2	8.2 ± 7.8	0.15
FQ (score, ± SD)	0.9 ± 0.9	1.0 ± 0.9	1.3 ± 1.6	0.02
Lifetime diagnosis:				
No lifetime psychopathology	51.6%	48.7%	53.3%	0.63
Depressive disorder	21.3%	21.2%	20.0%	0.91
Anxiety disorder	8%	9.0%	6.7%	0.93
Comorbid depressive and anxiety disorder	18.3%	21.2%	20.0%	0.42

	Childhood trauma score			
	0	1 to 3	4 to 8	P-value[a]
No. of participants	755	303	109	
Age (years, ± SD)	40.9 ± 14.4	44.4 ± 12.9	49.4 ± 9.7	< 0.001
Female gender	61.6%	75.2%	67.9%	0.002
Education level attained (years, ± SD)	12.7 ± 3.2	12.9 ± 3.2	12.2 ± 3.5	0.5
IDS-SR (score, ± SD)	9.4 ± 7.8	13.4 ± 8.5	16.5 ± 9.5	<0.001
BAI (score, ± SD)	4.5 ± 5.1	6.8 ± 5.9	8.4 ± 7.4	<0.001
FQ (score, ± SD)	0.8 ± 0.8	1.1 ± 1.0.	1.1 ± 1.0	<0.001
Lifetime diagnosis:				
No lifetime psychopathology	60.5%	36.6%	27.5%	<0.001
Depressive disorder	19.7%	23.4%	25.7%	0.08
Anxiety disorder	8.1%	10.9%	8.3%	0.43
Comorbid depressive and anxiety disorder	11.7%	29.0%	38.5%	<0.001

[a] P values by analysis of variance (ANOVA) linear term or X^2 tests (for linear association).
Abbreviations: BAI=Beck Anxiety Inventory; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FQ=Fear Questionnaire; IDS-SR, Inventory of Depressive Symptoms Self Report.
Data are numbers, percentages or mean (± SD).

Statistical analyses

Baseline characteristics were compared across the childhood life event and childhood trauma indices, using analysis of variance for continuous variables and chi-square tests (for linear by linear association) for categorical variables. Multinomial logistic regression analysis was used to calculate odds ratios (ORs with 95% confidence intervals [CIs]) for the 2-year occurrence rates of depressive and/or anxiety disorders, according to childhood trauma domains and childhood trauma score, adjusted for age, gender, and education (Model 1).

In an extra multivariable model (Model 2), all childhood trauma domains were included in 1 model to determine the independent predictors for 2-year occurrence of anxiety and depressive disorders. Next, the childhood trauma score was considered a continuous variable ranging from 0 to 8, in which the "no diagnosis" group was regarded as reference group. Post-hoc analyses were done in subgroups of separate anxiety disorders. *P*-values were derived from likelihood ratio tests.

The interaction term of a lifetime diagnosis x trauma (based on childhood trauma score) was added to the analyses to assess potential moderators. To examine the mediation effects of baseline clinical characteristics on the relationship between childhood trauma score and 2-year occurrence rates, a multiple mediation model by Preacher and Hayes (27) was used. Mediation was investigated by directly testing significance of the indirect effect of the independent variable (IV) on the dependent variable (DV) through the mediator (M) quantified as the product of the effects of the IV on M (a) and the effect of M on DV (b), partialling out the effects of the IV. The indirect effect is the product a x b, and this is about equivalent to c minus c' (ie, the difference between the total effect and the direct effect). The 95% percentile-based CIs were computed using the cut-off values for the 2.5% highest and lowest scores of the empirical distribution. A 2-tailed $P < 0.05$ was considered statistically significant; the statistical software used was SPSS 18.0 (SPSS Inc., Chicago, Illinois).

Results

Sixty-six percent of the study population was female, the mean age was 42.6 years (standard deviation [SD] = 13.9). At baseline, 14.7% reported at least 1 childhood life event and 35.3% any childhood trauma. A lifetime diagnosis of a depressive and/or anxiety disorder was present in 569 of the participants (48.8%). Sample characteristics at baseline are shown in Table 1. A higher childhood life-event score was associated with a lower level of education and higher severity scores for both anxiety and depressive symptoms. A higher childhood trauma score was associated with being older, being female, higher severity scores for both anxiety and depressive symptoms, and a positive lifetime history of a depressive and/or anxiety disorder.

The 2-year occurrence rates of depressive and/or anxiety disorders are presented in Table 2: 941 (80.6%) of the 1,167 participants remained without a disorder, 66 (5.7%) had a pure anxiety disorder, 97 (8.3%) had a pure depressive disorder, and 63 (5.4%) had a comorbid disorder. Of the 569 participants with a baseline lifetime diagnosis of a depressive and/or anxiety disorder, 168 (29.5%) reported any disorder since baseline, compared to 58 (9.7%) of the 598 participants without a lifetime diagnosis at baseline (P < 0.001). Thus, within the 2-year follow-up period, 25.7% experienced first episodes and 74.3% recurrent episodes.

Table 2. Contributions of childhood life events and trauma score to the occurrence of depressive and/or anxiety disorders, in participants without a baseline diagnosis of depressive or anxiety disorder (N=1,167).

	Diagnosis between baseline and 2-year follow-up[a]				
	No disorder	Anxiety disorder	Depressive disorder	Comorbidity	P value[b]
	N=941	N=66	N=97	**N=63**	
Childhood life events:					
Divorce parents	99 (10.5%)	6 (9.1%)	11 (11.3%)	10 (15.9%)	0.36
Early parental loss	61 (6.5%)	7 (10.6%)	7 (7.2%)	3 (4.8%)	0.77
Placed in care	45 (4.8%)	3 (4.5%)	7 (7.2%)	5 (7.9%)	0.29
Childhood life event score:					
0	808 (85.9%)	58 (87.9%)	80 (82.5%)	50 (79.4%)	0.20
1	122 (13.0%)	7 (10.6%)	16 (16.5%)	11 (17.5%)	
2 to 3	11 (1.2%)	1 (1.5%)	1 (1.0%)	2 (3.2%)	
Childhood trauma:					
Emotional neglect:					
Once or sometimes	107 (11.4%)	14 (21.2%)	20 (20.6%)	15 (23.8%)	
Regularly or very often	101 (10.7%)	10 (15.2%)	18 (18.6%)	15 (23.8%)	<0.001
Psychological abuse:					
Once or sometimes	80 (8.5%)	6 (9.1%)	11 (11.3%)	10 (15.9%)	
Regularly or very often	48 (5.1%)	4 (6.1%)	7 (7.2%)	13 (20.6%)	<0.001
Physical abuse:					
Once or sometimes	46 (4.9%)	3 (4.5%)	7 (7.2%)	3 (4.8%)	
Regularly or very often	20 (2.1%)	2 (3.0%)	6 (6.2%)	8 (12.7%)	<0.001
Sexual abuse:					
Once or sometimes	61 (6.5%)	4 (6.1%)	7 (7.2%)	2 (3.2%)	
Regularly or very often	56 (6.0%)	4 (6.1%)	12 (12.4%)	12 (19.0%)	0.003
Childhood trauma score:					
0	640 (68.0%)	38 (57.6%)	53 (54,6%)	24 (38.1%)	<0.001
1 to 3	227 (24.1%)	21 (31.8%)	30 (30.9%)	25 (39.7%)	
4 to 8	74 (7.9%)	7 (10.6%)	14 (14.4%)	14 (22.2%)	

[a] Values are N (%)
[b] P value by X^2 test

Childhood life-events and incidence of depressive and anxiety disorders
Neither specific childhood life events nor the childhood life event score showed statistically significant associations with the occurrence of psychopathology within a 2-year follow-up period (Table 2).

Childhood trauma and incidence of depressive and anxiety disorders
Emotional neglect and psychological, physical, and sexual abuse were all associated with the 2-year occurrence rates of depressive, anxiety and comorbid disorders (Table 2).

The presence of all childhood abuse domains (regularly or very often) gradually increased in the following order: from no disorder, anxiety disorder, depressive disorder, to a comorbid disorder. The cumulative childhood trauma score followed the same pattern (P <0.001).

Odds ratios for the 2-year occurrence of any depressive and/or anxiety disorder are listed in Table 3. Multivariate regression analyses, adjusted for age, gender, and education (Model 1), showed that the occurrence of any disorder was predicted by all trauma domains. The effect of childhood trauma on the occurrence of anxiety, depressive or comorbid disorders was investigated (Model 1). Regularly or frequent emotional neglect, physical abuse, and sexual abuse were associated with an increased risk of occurrence of depressive disorders. An even stronger association was found between emotional neglect and psychological, physical, and sexual abuse and the occurrence rate of comorbid disorders within a 2-year period. None of the childhood trauma domains were significantly associated with the risk of anxiety disorders, except for the relationship with emotional neglect (but only for the "once or sometimes" category). In addition, multivariate analyses were done, in which all separate childhood trauma domains were entered simultaneously to investigate which trauma domains were independent predictors (Model 2). Emotional neglect was the only significant independent predictor of 2-year occurrence rates for depressive and comorbid disorder (P = 0.002). Severe psychological and sexual abuse did independently predict the occurrence of comorbid disorders. The effect of childhood trauma on incident anxiety and depressive disorders did not change when we added baseline alcohol abuse or dependence as a covariate in the model (Table 3). The number of participants who abused substances other than alcohol was almost negligible and therefore not tested for.

Figure 1 graphically displays the childhood trauma score with OR's for occurrence of disorders. An increased score for childhood trauma corresponded in a dose-response manner with a higher likelihood of having a depressive (P < 0.001) and a comorbid disorder (P < 0.001) within 2 years, but not for having an anxiety disorder.

Finally, to determine the possible moderating effect of a lifetime diagnosis at baseline, the interaction term of a lifetime diagnosis x trauma was added to the analyses. In all trauma domains, no significant moderating effect of lifetime psychopathology at baseline was found in predicting the occurrence of any depressive and/or anxiety disorder in the 2-year follow-up period. This finding suggests that the predictive effects of childhood trauma were of similar strength among subjects with and without lifetime psychopathology.

We further analyzed whether the relationship between childhood trauma score (IV) and 2-year occurrence rates of depressive and anxiety disorders (DV) could be explained by baseline clinical characteristics as mediating variables (M). Table 4 presents the results of mediation analyses: all clinical characteristics demonstrated significant indirect effects (a x b effects) in

Table 3. Odds ratios adjusted for sociodemographic covariates for the occurrence of depressive and/or anxiety disorders, in participants without a baseline diagnosis of depressive or anxiety disorder (N=1,167).

		Model [b]	Any disorder	Anxiety disorder	Depressive disorder	Comorbid disorder
Childhood trauma scorea score[a]		Model 1	1.25 (1.15-1.36)**	1.09 (0.93-1.27)	1.25 (1.11-1.40)**	1.41 (1.25-1.60)**
Emotional neglect:	Once or sometimes	Model 1	2.66 (1.79-3.95)**	2.26 (1.18-4.33)**	2.64 (1.51-4.61)**	3.23 (1.67-6.24)**
		Model 2	2.71 (1.75-4.21)**	2.76 (1.37-5.57)**	2.76 (1.50-5.10)*	2.44 (1.13-5.28)*
	Regularly or very often	Model 1	2.47 (1.64-3.73)**	1.72 (0.83-3.57)	2.51 (1.40-4.49)**	3.42 (1.77-6.63)**
		Model 2	2.06 (1.23-3.44)**	2.21 (0.94-5.21)	2.48 (1.22-5.04)*	1.39 (0.56-3.46)
Psychological abuse:	Once or sometimes	Model 1	1.63 (1.01-2.62)*	1.06 (0.44-2.56)	1.55 (0.78-3.07)	2.63 (1.25-5.55)*
		Model 2	0.82 (0.47-1.45)	0.61 (0.22-1.68)	0.63 (0.28-1.42)	1.61 (0.65-4.01)
	Regularly or very often	Model 1	2.42 (1.43-4.11)*	1.21 (0.42-3.53)	1.59 (0.69-3.68)	5.96 (2.91-12.20)*
		Model 2	1.20 (0.59-2.44)	0.73 (0.20-2.72)	0.56 (0.19-1.69)	4.36(1.55-12.28)*
Physical abuse:	Once or sometimes	Model 1	1.33 (0.70-2.53)	0.97 (0.29-3.22)	1.72 (0.75-3.97)	1.16 (0.35-3.89)
		Model 2	0.79 (0.39-1.60)	0.77 (0.21-2.86)	1.23 (0.48-3.13)	0.38 (0.10-1.44)
	Regularly or very often	Model 1	3.48 (1.76-6.87)*	1.39 (0.32-6.10)	3.14 (1.22-8.09)*	6.50 (2.70-15.62)*
		Model 2	1.81 (0.79-4.13)	1.15 (0.21-6.19)	2.35 (0.73-7.60)	1.60 (0.52-4.87)
Sexual abuse:	Once or sometimes	Model 1	0.96 (0.51-1.80)	0.87 (0.30-2.50)	1.35 (0.59-3.07)	0.53 (0.13-2.26)
		Model 2	0.89 (0.47-1.70)	0.84 (0.29-2.43)	1.27 (0.55-2.93)	0.43 (0.10-1.89)
	Regularly or very often	Model 1	2.15 (1.32-3.51)*	0.91 (0.32-2.61)	2.42 (1.23-4.75)*	3.29 (1.63-6.61)*
		Model 2	1.60 (0.94-2.70)	0.76 (0.26-2.26)	1.75 (0.86-3.59)	2.27 (1.05-4.90)*

[a] The childhood trauma score was considered a continuous variable ranging from 0 to 8.
[b] Model 1: odds ratios (with 95% confidence intervals) by multinomial logistic regression analysis, adjusted for gender, age, and education. Model 2: additionally adjusted for all other childhood trauma domains.
P-value by X^2 test (*: P <0.05, **: P <0.001)

univariate regression analyses. In multivariate regression analyses, the indirect effects of the IDS-SR score and an earlier diagnosis before baseline remained significant, suggesting that they are important in mediating the association between childhood trauma and 2-year occurrence of depressive and/or anxiety disorders. When all the mediating variables were added into the model, the direct effect (c') between trauma and 2-year occurrence of depressive and/or anxiety disorders was no longer statistically significant (0.078 of total effect, approximately 36%).
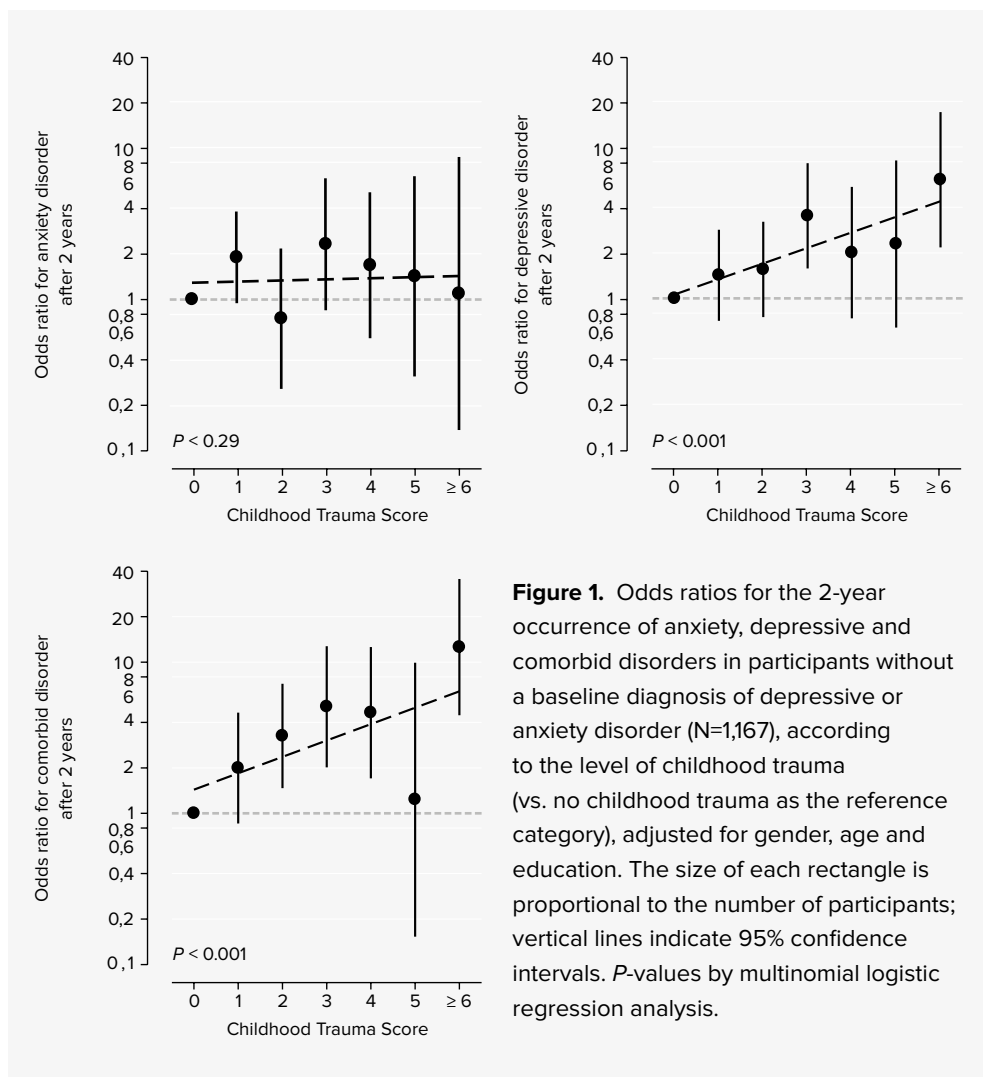

Figure 1. Odds ratios for the 2-year occurrence of anxiety, depressive and comorbid disorders in participants without a baseline diagnosis of depressive or anxiety disorder (N=1,167), according to the level of childhood trauma (vs. no childhood trauma as the reference category), adjusted for gender, age and education. The size of each rectangle is proportional to the number of participants; vertical lines indicate 95% confidence intervals. *P*-values by multinomial logistic regression analysis.

Table 4. Mediation analysis of baseline disease characteristics on the relationship between the childhood trauma index (IV) and occurrence of a diagnosis within 2 years (DV) in participants without a baseline diagnosis of depressive or anxiety disorder (N=1,167).

Mediating variable (M)	No. DV / reference	Effect of trauma on M (a)	Effect of M on DV (b)	Mediating effect[a] (a x b; 95% CI)	Direct effect of trauma on DV (c')	Total effect (c)
IDS-SR	226 / 941	1.528	0.102	**0.156 (0.114; 0.202)**	0.116	0.217
BAI	226 / 941	0.825	0.113	**0.094 (0.061; 0.135)**	0.163	0.217
Fear Questionnaire	226 / 941	0.082	0.422	**0.035 (0.016; 0.060)**	0.198	0.217
Earlier diagnosis before baseline	226 / 941	0.075	1.288	**0.097 (0.063; 0.134)**	0.161	0.217
All mediating variables combined:	226 /941					
– IDS-SR		1.528	0.077	**0.117 (0.077; 0.173)**	0.078	0.217
– BAI		0.825	0.029	0.024 (-0.005; 0.063)		
– Fear Questionnaire		0.082	0.061	0.005 (-0.009; 0.022)		
– Lifetime diagnosis before baseline		0.075	0.961	**0.072 (0.042; 0.108)**		

[a] Mediating effects were considered as significant when the bias corrected and accelerated confidence interval did not include zero (indicated in bold).
Abbreviations: a=effect of IV on M, a x b = indirect effect, b = effect of M on DV, BAI = Beck Anxiety Inventory, c = total effect, c' = direct effect, DV = dependent variable, IDS-SR = Inventory of Depressive Symptoms Self Report, IV = independent variable, M = mediating variable.

Discussion

In our present study, we examined whether childhood trauma and childhood life events were predictive for the occurrence of depressive and/or anxiety disorders over a 2-year period in a large cohort of subjects without any current depressive and/or anxiety disorder at baseline. We demonstrated that childhood life events did not predict the occurrence of depressive or anxiety disorders, whereas a history of childhood trauma did predict the occurrence of depressive disorders and comorbid disorders. In particular, of all trauma domains emotional neglect was the main independent predictor. These associations were mediated through a higher severity of depressive symptoms at baseline and the presence of a prior history of a disorder at baseline, indicating that the increased onset of (comorbid) depressive disorders among individuals with childhood trauma is partially due to their already mildly elevated depressive symptom levels at baseline and earlier episodes of anxiety and/or depression.

Our findings are consistent with the results of previous prospective studies of children, exposed to maltreatment, who were followed until (young) adulthood. Childhood neglect and physical abuse were associated with an increased risk of lifetime major depression (13). A 45-year prospective study of a large British birth cohort (N = 9,337), showed that

cumulative adversity and physical and sexual abuse were significantly associated with mid-life psychopathology (ICD-10 depressive and anxiety disorders) (15). In the Dunedin birth cohort (N = 1,037) (14), the group that developed comorbid major depression *plus* generalized anxiety disorder reported significantly higher levels of childhood adversities. Both studies support our finding of a dose-response relationship between childhood trauma score and likelihood of developing a depressive and a comorbid disorder within a 2-year period. The lack of a significant association between childhood trauma and anxiety disorders in adulthood suggests that causal pathways to the development of anxiety disorders are less vulnerable to the impact of childhood trauma.

Among the specific effects of childhood trauma, emotional neglect was the most important predictor of the occurrence of psychopathology in adulthood at 2-year follow-up, suggesting that the relationship between childhood trauma and psychopathology is predominantly driven by emotional neglect. In a recent systematic review assessing the association between child maltreatment and mental health outcome, a 3-fold higher risk of developing a depressive disorder was found among emotionally abused individuals than non-abused individuals (28). Although emotional neglect is a major public health problem, its serious lifelong consequences and impact on adult psychopathology have not been recognized for a long time. Previous prospective studies were usually conducted in non-representative samples. Childhood abuse data were often drawn from official court records and/or behavioral observations and most likely represent the most extreme cases processed in the system and were skewed towards the lower end of the socio-economic spectrum. *Childhood neglect* was defined as lack of child care and emotional abuse was often not specifically asked for, and thus, underreported. In 2 prospective studies, physical and sexual abuse was added later, based on retrospective reports during adulthood (14, 15).

We provide new evidence that in all trauma domains, no significant moderating effect of lifetime psychopathology at baseline was found in the occurrence of any depressive and/or anxiety disorder in the 2-year follow-up. The relative effects of childhood trauma were of similar strength in patients with and without lifetime psychopathology, which demonstrates that childhood trauma is associated with both onset and recurrence of psychopathology.

We found that more unfavorable clinical disease characteristics at baseline, such as severity of subsyndromal depressive symptoms and presence of lifetime psychopathology, mediated the differences such that the direct relationship between childhood trauma and psycho-pathology became non-significant. Patients with a history of childhood trauma had a higher severity of anxiety and depressive symptoms at baseline, in the absence of a depressive or anxiety disorder. We speculate that these subsyndromal symptoms increase vulnerability for additional exposure to stressful life events, which subsequently predispose to disorder onset (29). Clark et al. (15) found that psychopathology at 23 years, but not at 16 years, partially

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mediated the associations of physical and sexual abuse and cumulative adversity with mid-life disorder. This finding is congruent with the importance of our finding of lifetime psycho-pathology as a potential mediator. These mediation analyses are demonstrating the lifelong influence and mechanisms through which childhood trauma may affect psychopathology throughout the lifespan. Our results feed into the enduring effect model, which assumes that early experiences continue to influence the outcome over time as recently described by Fraley et al. (30). This model is represented by a remaining direct path (about 36%) after the mediating factors have been taken into account. In other words, childhood trauma is a key environmental risk factor triggering a chain of risks, such as recurrent depressive episodes that may enhance the vulnerability to develop further depressive disorders.

Our findings are in agreement with the hypothesis that patients with childhood trauma represent a vulnerable group with long-term psychopathology, characterized by a course of chronic waxing and waning of the mental disorder. On the other hand, the association between childhood adversity and occurrence of adulthood psychopathology may also refer to the "kindling hypothesis", assuming that with each previous episode, less stressful life events are needed to elicit a subsequent episode (31, 32).

The findings of this study have implications for clinical practice. Information about a history of childhood maltreatment helps to identify individuals who are at high risk of developing recurrent and chronic subtypes of depression. The ability to predict which traumatized individuals will develop a depressive and/or anxiety disorder in the near future will provide more insight into the mechanisms of psychopathology related to childhood trauma. Clinicians should, therefore, routinely inquire about childhood trauma, which can add important prognostic information to update risk assessment and provide opportunities for preventive interventions.

The strength of this study is the prospective design and large sample of midlife participants without a baseline diagnosis of depressive and/or anxiety disorder. All childhood trauma domains and childhood life events were considered. Furthermore, outcome measures were based on structured diagnostic interviews, and important baseline clinical characteristics were taken into account as potential mediators. Methodological limitations include the retrospective trauma assessment at baseline, although participants were not suffering from any anxiety and/or depressive disorder at the time of the interview. Our findings cannot be extrapolated to psychiatric disorders that were not assessed in this study, which may be of particular importance to post-traumatic stress disorder. Given the long time elapsed between childhood trauma and adult psychopathology, we were not able to consider the multifaceted mediating mechanisms that have largely occurred before the NESDA baseline wave.

We could test only a crude mediation model, while a more complex interplay between the family context and psychosocial resources and vulnerabilities should be the perspective of further research. The chain of events linking childhood adversities to psychopathology in adulthood involves a highly complex interplay of multiple psychological vulnerabilities and environmental factors (33, 34). Our 2-year follow-up period is a very short period considering the length of time elapsed between the exposure of childhood trauma and baseline assessments of adult participants and all the additional events that may have occurred since childhood, which we could not grasp with our current design. Nevertheless, significant effects of childhood trauma on incident adult psychopathology were found within this relative short follow-up period.

In conclusion, we found that all childhood trauma domains predicted the occurrence of either depressive or comorbid disorders within 2 years in adults without current psychopathology at baseline. Part of the impact of childhood trauma on the occurrence of depressive and comorbid disorder after 2 years of follow-up was found to be mediated through the severity of subsyndromal depressive symptoms and a prior history of psychopathology. Childhood maltreatment is a key environmental risk factor, which contributes to a course of chronic waxing and waning of depressive and comorbid disorders.

Clinical points

- A history of childhood trauma predicts the development of new and recurrent depressive and comorbid disorders in patients without a current depressive/anxiety disorder.
- Emotional neglect in childhood is the main independent predictor of all trauma domains.
- Higher severity of depressive symptoms and the presence of an earlier history of a disorder at baseline are important mediators between childhood trauma and the onset/recurrence of depressive and comorbid disorders.

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Chapter 6

Childhood Maltreatment and
the Course of Depressive
and Anxiety Disorders:
the Contribution of Personality
Characteristics

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Abstract

Background: We investigated the effect of childhood maltreatment on predicting the 4-year course of depressive and anxiety disorders and the possible mediating role of personality characteristics in the association between childhood maltreatment and illness course.

Methods: Longitudinal data in a large sample of participants with baseline depressive and/or anxiety disorders (N = 1,474, 18–65 years) were collected in the Netherlands Study of Depression and Anxiety (NESDA). At baseline, childhood maltreatment was assessed with a semi-structured interview. Personality trait questionnaires (NEO-FFI, Mastery Scale and LEIDS), recent stressful life events (LTE-Q), and psychosocial variables were administered. The Life Chart Interview (LCI) was used to determine the time to remission of depressive and/or anxiety disorders.

Results: At baseline, 846 participants (57.4%) reported any childhood maltreatment. Childhood maltreatment had a negative impact on psychosocial functioning and was predictive of more unfavorable personality characteristics and cognitive reactivity styles ($P<0.001$). Childhood maltreatment was a significant predictor of lower likelihood of remission of depressive and/or anxiety disorders (HR=0.94, $P<0.001$). High levels of neuroticism, hopelessness, and external locus of control, and low levels of extraversion were mediating the relationship between childhood maltreatment and 4-year remission of depressive and anxiety disorders.

Conclusions: Certain personality characteristics are key players in the mechanism linking childhood maltreatment to an adverse illness course of depressive and anxiety disorders. Early interventions - reducing neuroticism and hopelessness, and enhancing extraversion and locus of control - might contribute to a better prognosis in a 'high risk' group of depressive and anxiety disorders.

Introduction

Previous research has shown that childhood maltreatment predicts an adverse course of depressive and anxiety disorders in adulthood, i.e., increased comorbidity and chronicity of depressive and anxiety disorders (1-3). In addition, childhood maltreatment can result in adverse psychosocial circumstances and unfavorable personality and coping styles.

The effects of childhood maltreatment may continue as adult impairment in psychosocial functioning. Individuals with reported histories of maltreatment lead more disadvantaged lives in general, with less capacity to make and maintain personal and social relationships (4, 5) and lower levels of education, employment, and earnings (6-8). Childhood maltreatment is associated with an increased vulnerability to stressful life events in adulthood, especially in the interpersonal domain (9-12). Prior studies on personality characteristics have demonstrated a positive association between childhood maltreatment and high neuroticism (12-16). Neuroticism is one of the major temperamental personality dimensions, attributing to an increased risk of onset and persistence of affective disorders (17). Higher openness and lower extraversion scores were found in a recent general population-based study of adults exposed to childhood emotional abuse (16). High openness, indicative of curiosity and impulsive sensation seeking, has been linked to an increased risk for revictimization (15). Low extraversion scores, reflecting the lack of enjoyment of close interpersonal bonds, leadership roles, and assertiveness, have been related to vulnerability and persistence of depression (18). The cognitive vulnerability theory postulates that childhood maltreatment contributes to vulnerability to depression through a general negative attributional style (19, 20).

The mechanism through which childhood maltreatment attributes to an adverse course of depressive and anxiety disorders in adulthood is still in need of comprehensive studies. This prospective study describes a large sample of adults with depressive and/or anxiety disorders, followed over a 4-year time period. We simultaneously investigated personality domains, cognitive reactivity styles, and psychosocial factors in relation to childhood maltreatment. The purpose of this study was to increase our understanding of the complex interplay between childhood maltreatment and personality characteristics in determining the chance of remission of depressive and anxiety disorders.

The following research questions were addressed: a) do maltreated individuals differ on baseline personality domains, cognitive reactivity styles, and psychosocial factors from non-maltreated individuals who did not experience maltreatment, and b) are personality characteristics important factors in mediating the unfavourable 4-year course of depressive and anxiety disorders, in patients with a history of childhood maltreatment?

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Materials and methods

Sample

Data were derived from a longitudinal cohort study including 2,981 participants, aged 18-65 years: the Netherlands Study of Depression and Anxiety (NESDA). Participants were recruited through different settings (general population, primary care, and mental health care) and in different phases of illness. The sample consisted of 1,701 persons with a current diagnosis of depression and/or anxiety disorder, 907 persons with life-time diagnoses or at risk because of a family history or subthreshold depressive or anxiety symptoms, and 373 healthy controls. At baseline, lifetime presence of depressive (i.e., major depressive disorder, dysthymia) and anxiety disorders (i.e., panic disorder, agoraphobia, social phobia, generalized anxiety disorder) were diagnosed using the Composite International Diagnostic Interview (CIDI; version 2.1), a fully structured diagnostic interview (21). Study design, rationale, and methods have been reported elsewhere (22).

The present study reports data from the baseline, 2-year and 4-year follow-up assessments of 1,474 (49.4%) participants of the NESDA study, who had a depressive and/or anxiety disorder within the 6 months preceding the study and participated in the 2 or 4 year follow-up. The participants were recruited from the general population (9.3%), primary care (43.8%), and specialised mental care (46.9%). The response rate at 2 and 4 year follow-up was 83.4% and 75.9%, respectively. Non-response was associated with significantly fewer years of education ($P<0.001$), more adverse life events ($P=0.002$), and smaller social network size ($P=0.003$), but not with age, gender or reported childhood maltreatment.

Assessment of childhood maltreatment

At baseline, childhood maltreatment was assessed retrospectively with the NEMESIS Childhood Trauma Interview (CTI), focusing on four domains of childhood maltreatment prior to the age of 16 years (1, 23). Emotional neglect included lack of parental attention or support and ignorance of one's problems and experiences. Psychological abuse was defined as verbal abuse, undeserved punishment, and blackmail. Physical abuse was defined as being kicked or hit with hands or an object, beaten up or any other physical abuse. Sexual abuse was defined as being sexually approached against their will, meaning being touched or having to touch someone in a sexual way. Participants were asked to score the frequency on a five-point scale (i.e., once, sometimes, regularly, often and very often). The frequencies were divided into three groups: no childhood maltreatment, mild childhood maltreatment defined as once or sometimes (in at least one domain), and severe childhood maltreatment defined as regularly, often and very often (in at least one domain). A cumulative childhood maltreatment score, defined as the sum scores ranging from 0-8, was created with a higher score indicating more types and a higher frequency of childhood maltreatment (Figure 1) (1).

Figure 1. Distribution of the cumulative childhood maltreatment score.
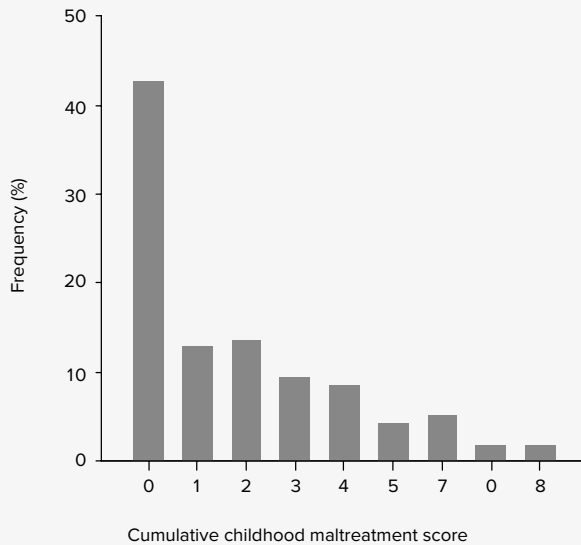
The CTI is a reliable and valid method for assessment of multiple dimensions of childhood maltreatment (1). The CTI was conducted by specially trained clinical staff and positioned half-way through the 4-hour baseline assessment.

Adult psychosocial and personality characteristics
Socioeconomic context. Adverse life events, at any time in the preceding 12 months before baseline, were assessed as a sum of 12 possible events measured by the List of Threatening Experiences (LTE) (24). The presence of a partner at baseline and up to two close friends (first and second confident) at baseline was assessed using the Close Person Inventory (25). Social network size was measured by the total number of important relatives, friends and others with whom the participants had regular contact (from 1 to >20) (25). Feelings of lone-liness were assessed by using the Loneliness Scale, an 11-item questionnaire consisting of the emotional loneliness subscale and the social loneliness subscale (26). The score ranges from 0 to 11 points, with higher scores being indicative of higher loneliness levels. Participants with a paid job of >8 h per week were considered to be employed versus participants being unemployed (<8 h per week or without a job). The household income was determined with 24 categories, from < 500 up to 5000 Euro's per month. A continuous variable was created, based on the mean of the applicable income category.

Personality was operationalized using the Neuroticism–Extroversion–Openness Five Factor Inventory (NEO-FFI), a 60-item self-report questionnaire measuring the 'big 5' personality domains: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience (27). Each domain consists of 12 items. Scoring for each item ranged from 1 (totally disagree) to 5 (totally agree). External locus of control reflects the extent to which individuals feel they are not able to control or influence outcomes, and assessed by the 5-item Mastery Scale (28). Scoring for each item ranged from 1 (strongly disagree) to 5 (strongly agree), resulting in an overall score of 5 to 25, with higher scores indicating greater external locus of control.

Cognitive vulnerability. The Leiden Index of Depression Sensitivity-Revised (LEIDS-R) is a 34-item self-report questionnaire that measures cognitive reactivity in response to low mood (29). Participants were asked to indicate the degree to which a list of statements would reflect their cognitions and behaviors in response to sad mood – for example, "When I feel sad, I feel more hopeless about everything" (hopelessness); When I feel sad, I spend sad, I spend more time thinking about the possible causes of my moods" (rumination). Scoring for each question ranged from 1 (not applicable) to 5 (very strongly applicable). For this study, we only used the subscales hopelessness and rumination.

4-year chronicity of depressive and/or anxiety disorders
At the 2-year and 4-year follow-up assessment, the CIDI and life chart were repeated to determine the course of depressive and anxiety disorders (30). Using a calendar method, life events were recalled to refresh memory, after which the presence and severity of symptoms of depression and anxiety were determined. We have LCI information on the years between baseline and 4-year follow-up. For each month with reported symptoms during the 4-year follow up, severity of symptoms was assessed ranging from none or minimal severity to mild, moderate, and severe or very severe. Symptoms on the LCI were only considered to be present when at least of mild severity. Remission of depressive and anxiety disorders was defined as absence of both depressive and anxiety symptoms during 3 consecutive months, based on the LCI. We calculated the 'time to remission' of depressive disorders and 'time to remission' of anxiety disorders in months (minimum of 4 and maximum of 64 months), from baseline until the 4-year follow-up. 'Time to remission' of participants, not reaching the remission status during the 4-year follow-up (35.3%) or who did not participate between 2 and 4 years follow-up, was censored at the latest available assessment time. Subsequently, we also analyzed the 'time to remission' of depressive disorders or 'time to remission' of anxiety disorders separately, to explore whether the impact of childhood maltreatment differed for the remission of depressive versus anxiety disorders.

Statistical Analyses

We used descriptive statistics to describe socioeconomic, psychosocial, and personality characteristics. Linear regression analysis was used to test whether all of the above characteristics were associated with specific domains of childhood maltreatment. Demographic data were gender, age, and years of education attained. Since gender, age, and years of education were significantly associated with childhood maltreatment, we included these demographic variables as covariates. Univariate and multivariate Cox regression analyses were used to examine the associations between the childhood maltreatment domains and 'time to remission' of a depressive and/or anxiety disorder. After adjusting for age, gender, and education (Model 1), all childhood maltreatment domains were included in one model (Model 2) to yield the independent predictors for 4-year remission of anxiety and depressive disorders. In addition, Cox regression analysis was performed with the cumulative childhood maltreatment score, adjusted for age, gender, and education (Model 1). Cox regression analyses yielded hazard ratios with 95% confidence intervals and accompanying P-values. To determine whether personality characteristics mediated the associations found between childhood maltreatment and the 4-year remission of depressive and anxiety disorders, we used the indirect method by Preacher and Hayes (31). The indirect method estimates the total, direct, and indirect unstandardized effects of the independent variable on the dependent variable through the mediator variable, controlling for covariates. The 95% percentile-based confidence intervals (CI) were computed using the cut-offs for the 2.5% highest and lowest scores of the empirical distribution. A two-tailed $P < 0.05$ was considered statistically significant. The statistical software used was SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Socioeconomic, psychosocial, and personality characteristics and childhood maltreatment

Sample characteristics at baseline are listed in Table 1. Sixty-seven percent of the participants were female, mean age was 41.6 years, and mean level of education was 11.9 years. At baseline, 57.4% (n=846) of the participants reported childhood maltreatment, of which 20.2% (n=298) classified as mild and 37.2% (n=548) as severe. All sociodemographic and psychosocial variables (except for having friends) were significantly associated with the severity of the childhood maltreatment status. All personality characteristics were strongly associated with the severity of the childhood maltreatment status ($P < 0.001$).

Table 1. Socioeconomic, psychosocial and personality characteristics in 1,474 participants with depressive and/or anxiety disorders according to childhood maltreatment status.

	Mean (SD) or %	No childhood maltreatment (n=628)	Mild childhood maltreatment (n=298)	Severe childhood maltreatment (n=548)	*P*-value
Socioeconomic characteristics:					
Age (years)	41.6 ± 12.3	39.9 ± 12.6	41.6 ± 11.9	43.4 ± 11.8	<0.001
Female gender	67.0%	61.0%	68.5%	73.0%	<0.001
Education level attained (years)	11.9 ± 3.3	12.0 ± 3.2	12.2 ± 3.4	11.6 ± 3.3	0.02
Household income (×1,000 euro)	2.2 ± 1.5	2.2 ± 1.5	2.2 ± 1.6	2.0 ± 1.5	0.05
Unemployed	46.7%	42.2%	44.6%	53.1%	<0.001
Psychosocial characteristics:					
Social network size	2.6 ± 1.0	7.4 ± 6.0	6.2 ± 5.2	5.2 ± 4.2	<0.001
Partner present	63.8%	68.2%	62.7%	61.4%	0.02
Friend(s) present	75.5%	79.1%	72.2%	75.2%	0.10
Loneliness	4.8 ± 4.4	4.2 ± 4.2	4.8 ± 4.4	5.6 ± 4.5	<0.001
No. of adverse life events	1.0 ± 1.2	0.9 ± 1.1	1.0 ± 1.2	1.1 ± 1.2	0.008
Personality characteristics (NEO–FFI):					
Neuroticism	41.0 ± 7.1.	39.2 ± 6.8	41.6 ± 7.4	42.8 ± 6.8	<0.001
Extraversion	34.3 ± 6.8	35.7 ± 6.6	33.7 ± 6.4	32.9 ± 7.0	<0.001
Openness	38.3 ± 6.2	37.7 ± 6.2	38.4 ± 6.2	38.9 ± 6.1	<0.001
Agreeableness	43.1 ± 5.4	43.7 ± 5.2	43.1 ± 5.3	42.4 ± 5.5	<0.001
Conscientiousness	39.9 ± 6.6	40.9 ± 6.5	39.2 ± 6.8	39.0 ± 6.3	<0.001
LEIDS Rumination	4.8 ± 4.7	4.8 ± 4.7	5.8 ± 4.8	6.8 ± 5.7	<0.001
LEIDS Hopelessness/suicidality	9.2 ± 5.7	9.2 ± 5.7	9.8 ± 5.8	10.8 ± 6.1	<0.001
External locus of control	13.2 ± 6.7	12.0. ± 6.6	13.7 ± 6.6	14.0 ± 6.7	<0.001

Plus–minus values are means ± SD

Table 2 summarizes the socioeconomic, psychosocial, and personality characteristics of the study sample, according to specific domains of childhood maltreatment and cumulative childhood maltreatment score. Linear regression analysis showed a significant association of emotional neglect and psychological abuse with all socioeconomic and psychosocial variables, except for unemployment (*P* <0.05). Sexual abuse was the domain the least strongly associated (only for social network size and loneliness). The cumulative childhood maltreatment score was associated with all socioeconomic and psychosocial variables: a higher childhood maltreatment score was associated with being older, being female, having a lower level of education, having a lower household income, being unemployed, having a smaller social network size, not having a partner/friends, experiencing increased loneliness, and having a higher number of adverse life events. Emotional neglect and psychological abuse were associated with all personality characteristics in detrimental directions (*P* values <0.05), whereas physical and sexual abuse only predicted for neuroticism, openness, rumination, hopelessness and external locus of control (*P* values <0.05). The childhood

maltreatment score corresponded with more unfavorable personality characteristics and cognitive reactivity styles. In other words, lower levels of extraversion, agreeableness, conscientiousness and higher levels of neuroticism, openness, hopelessness, rumination and external locus of control were highly associated with the level of reported childhood maltreatment (P <0.001).

Table 2. Socioeconomic, psychosocial and personality characteristics in 1,474 participants with depressive and/or anxiety disorders according to childhood maltreatment domains and childhood maltreatment score.

	Emotional neglect	Psychological abuse	Physical abuse	Sexual abuse	Childhood maltreatment score
Socioeconomic characteristics:					
Age (years)	0.145**	0.097**	0.057*	0.046	0.124**
Female gender	0.070*	0.077*	0.046	0.205**	0.135**
Education level attained (years)	0.004	-0.063*	-0.091**	-0.106*	-0.082*
Household income (×1,000 euro)	-0.072*	-0.061*	-0.057*	-0.020	-0.074*
Unemployed	0.069	0.048	0.068	0.045	0.080*
Psychosocial characteristics:					
Social network size	-0.194**	-0.141**	-0.085*	-0.083*	-0.180**
Partner present	-0.101**	-0.082*	-0.001	-0.004	-0.071*
Friend(s) present	-0.068*	-0.050*	-0.007	-0.004	-0.048*
Loneliness	0.133**	0.124**	0.078*	0.069*	0.143**
No. of adverse life events	0.071*	0.077*	0.100**	0.025	0.093**
Personality characteristics (NEO−FFI):					
Neuroticism	0.239**	0.195**	0.134**	0.082*	0.231**
Extraversion	-0.197**	-0.128**	-0.055*	-0.041	-0.153**
Openness	0.116**	0.071*	0.065*	0.099**	0.111**
Agreeableness	-0.154**	-0.162**	-0.135**	-0.023	-0.131**
Conscientiousness	-0.154**	-0.055*	-0.050	-0.059*	-0.114**
LEIDS Rumination	0.112**	0.101**	0.083*	0.079*	0.129**
LEIDS Hopelessness/suicidality	0.181**	0.180**	0.120**	0.097**	0.205**
External locus of control	0.157**	0.135**	0.122**	0.052*	0.163**

Linear regression analysis yielded beta-coefficients adjusted for age, gender, and education.
*: P <0.05, **: P <0.001

Impact of childhood maltreatment on remission of depression and anxiety
Table 3 shows the association between the domains of childhood maltreatment and remission of depressive and anxiety disorders during the 4-year follow-up. Multivariate regression analyses, adjusted for age, gender, and education (Model 1), showed that emotional neglect and psychological abuse were negatively associated with the 4-year remission of depressive and anxiety disorders. In addition, multivariate analyses were conducted, in which emotional neglect and psychological, physical, and sexual abuse were

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entered simultaneously to investigate which domains were independent predictors (Model 2). Emotional neglect was the only significant independent predictor of the 4-year remission for depressive and/or anxiety disorder (P =0.001).

The cumulative childhood maltreatment score, adjusted for age, gender, and education score predicted the 4-year remission for depressive and/or anxiety disorder as well (P <0.001). To determine the impact of childhood maltreatment on the course of either depressive or anxiety disorders, we performed the analyses for the 4-year remission of depressive and 4-year remission of anxiety disorders separately. The childhood maltreatment score, adjusted for age, gender, and education was similarly predictive of the 4-year remission of depressive disorders (HR=0.94, 95% CI [0.91-0.97], P <0.001) and anxiety disorders (HR=0.96, 95% CI [0.92-0.99], P =0.02).

Table 3. Chance of remission of depressive and anxiety disorders according to childhood maltreatment during 4 years of follow-up.

Emotional neglect:	No	Mild	Severe	*P*-value for trend
No. of patients	766	316	392	
Crude	1.0 (Ref.)	0.87 (0.74-1.03)	0.66 (0.56-0.78)	< 0.001
Model 1	1.0 (Ref.)	0.88 (0.74-1.04)	0.69 (0.58-0.81)	< 0.001
Model 2	1.0 (Ref.)	0.90 (0.75-1.08)	0.71 (0.57-0.88)	0.001
Psychological abuse:	**No**	**Mild**	**Severe**	***P*-value for trend**
No. of patients	1011	257	206	
Crude	1.0 (Ref.)	0.80 (0.67-0.96)	0.73 (0.59-0.91)	0.001
Model 1	1.0 (Ref.)	0.82 (0.69-0.99)	0.76 (0.61-0.94)	0.003
Model 2	1.0 (Ref.)	0.93 (0.75-1.16)	0.92 (0.69-1.21)	0.42
Physical abuse:	**No**	**Mild**	**Severe**	***P*-value for trend**
No. of patients	1217	115	142	
Crude	1.0 (Ref.)	0.78 (0.61-1.02)	0.88 (0.70-1.11)	0.10
Model 1	1.0 (Ref.)	0.78 (0.60-1.02)	0.92 (0.73-1.17)	0.26
Model 2	1.0 (Ref.)	0.95 (0.71-1.26)	1.18 (0.89-1.58)	0.34
Sexual abuse:	**No**	**Mild**	**Severe**	***P*-value for trend**
No. of patients	1156	126	192	
Crude	1.0 (Ref.)	1.07 (0.85-1.36)	0.82 (0.67-1.01)	0.12
Model 1	1.0 (Ref.)	1.05 (0.83-1.32)	0.83 (0.67-1.03)	0.14
Model 2	1.0 (Ref.)	1.08 (0.85-1.36)	0.91 (0.73-1.13)	0.52
Childhood maltreatment score (continuous):				
Crude		0.93 (0.90-0.96)		< 0.001
Model 1		0.94 (0.91-0.97)		< 0.001

Data are hazard ratio's (95% confidence intervals).
Model 1: adjusted for age, gender, level of education.
Model 2: adjusted for age, gender, level of education and emotional neglect, psychological abuse, physical abuse and sexual abuse.

Potential mediating factors between childhood maltreatment and remission of depression and anxiety

We analyzed whether the relationship between childhood maltreatment score (IV) and 4-year remission of depressive and anxiety disorders (DV) could be explained by personality characteristics as mediating variables (M). Table 4 presents the results of mediation analyses, which confirmed that the childhood maltreatment score is associated with all personality characteristics (a) and that most of these personality characteristics are associated with 4-year remission of depressive and anxiety disorders (b). All personality variables, except openness and agreeableness, showed significant indirect effects (a * b effects) in univariate regression analyses. In multivariate regression analyses, the indirect effects (a * b effects) remained significant for neuroticism, extraversion, hopelessness, and external locus of control. In the multivariate model, the direct effect (c') between childhood maltreatment and 4-year remission of depressive and/or anxiety disorders was no longer statistically significant (0.044 of total effect, approximately 40%). Nevertheless, this mediation model suggests that there is an overall effect of childhood maltreatment on the 4-year remission of depressive and/or anxiety disorders, with neuroticism, extraversion, hopelessness, and external locus of control mediating the associations.

Table 4. Mediation analysis of personality characteristics on the relationship between childhood maltreatment score (IV) and remission of anxiety and/or depression within 4-years (DV) in participants with a baseline diagnosis of depressive or anxiety disorder (N=1,474).

Mediating variable (M)	Effect of maltreatment on M	Effect of M on DV (b)	Indirect effect[a] (a x b; 95% CI)	Direct effect of trauma on DV (c')	Total effect (c)
Neuroticism	0.698**	-0.060**	**-0.042 (-0.061; -0.028)**	-0.064*	-0.111**
Extraversion	-0.497**	-0.060**	**-0.030 (-0.044; -0.018)**	-0.077*	-0.111**
Openness	0.259*	0.005	0.001 (-0.004; 0.007)	-0.105*	-0.111**
Agreeableness	-0.355**	0.004	-0.001 (-0.009; 0.007)	-0.100*	-0.111**
Conscientiousness	-0.249*	0.033*	**-0.008 (-0.017; -0.003)**	-0.093*	-0.111**
LEIDS hopelessness	0.457**	-0.057**	**-0.026 (-0.040; -0.015)**	-0.082*	-0.111**
LEIDS rumination	0.336**	-0.030*	**-0.010 (-0.021; -0.003)**	-0.096*	-0.111**
Mastery scale	-0.465**	0.032*	**-0.015 (-0.026; -0.006)**	-0.091*	-0.111**
All mediating variables combined					
Neuroticism	0.694**	-0.026*	**-0.018 (-0.035; -0.002)**	-0.044	-0.111**
Extraversion	-0.496**	0.035**	**-0.017 (-0.032; -0.007)**		
Conscientiousness	-0.249*	0.001	0.000 (-0.007; 0.005)		
LEIDS hopelessness	0.457**	-0.033*	**-0.015 (-0.033; -0.001)**		
LEIDS rumination	0.335**	0.001	0.001 (-0.012; 0.012)		
External locus of control	0.469**	0.024*	**-0.011 (-0.023; -0.001)**		

[a] Indirect effects were considered to be significant when the bias-corrected and accelerated confidence interval did not include zero (indicated in bold).
Abbreviations: a =effect of IV on M, b = effect of M on DV, a x b = indirect effect, c = total effect, c' = direct effect, DV = dependent variable, IV = independent variable, M = mediating variable.
*: P <0.05, **: P <0.001

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Discussion

Our results demonstrated that, in a large sample of adults with depressive and/or anxiety disorders, childhood maltreatment has a negative impact on socioeconomic and psychosocial factors in adulthood. Childhood maltreatment is associated with lower levels of extraversion, agreeableness, and conscientiousness, and higher levels of neuroticism, openness, hopelessness, rumination, and external locus of control. Childhood maltreatment, i.e. emotional neglect, was a strong independent predictor of poor remission of depressive and/or anxiety disorders during the 4-year follow-up. Personality characteristics, such as higher levels of neuroticism, hopelessness, and external locus of control and lower levels of extraversion, appear to have a strong mediating effect on the relationship between childhood maltreatment and 4-year remission of depressive and/or anxiety disorders.

Adult psychosocial and personality characteristics in relation to childhood maltreatment
Our socioeconomic results concur with prior findings associating childhood maltreatment with lower levels of education, substantial income loss, and significant loss of adult economic productivity (6-8). Childhood maltreatment has been frequently correlated with difficulties in the interpersonal domain (4, 5, 32). We extend these data by documenting the specific effect of the four domains of maltreatment. Analyzing the differential effects, we found emotional neglect and psychological abuse to have the largest impact on social network size, loneliness, and presence of a partner and friends. Furthermore, we found that physical abuse and sexual abuse in childhood have enduring psychosocial effects in adulthood. In agreement with the 'stress generation model' (9, 10), childhood maltreatment is associated with a higher number of adverse life events in adulthood. Childhood maltreatment increases the likelihood of experiencing adult life events (e.g. divorce, separation of long-term friendships, violence) and contribute to the ongoing cycle of revictimization.

Childhood maltreatment has been postulated as an important determinant of neuroticism (33) and has consistently been associated with high levels of neuroticism (12-16). In line with previous studies, emotional neglect and psychological abuse were the most pervasively related to the 'big 5' personality domains, whereas physical and sexual abuse were only associated with neuroticism and openness (13, 15, 16). In addition, we found that all domains of childhood maltreatment were associated with increased cognitive vulnerability and increased external locus of control. We therefore speculate that neuroticism, a negative cognitive style and an external locus of control might act as distal vulnerability factors, in patients with childhood maltreatment.

Mediation model between childhood maltreatment and remission of depression and anxiety
Several prospective studies have linked childhood maltreatment to an unfavourable illness course characterized by less recovery, longer duration of symptoms, and chronicity (1, 2). We found that the childhood maltreatment score was also a significant predictor of remission of depressive disorders and, separately, of remission of anxiety disorders. This finding justified our decision to perform mediation analyses on the remission of both depression and anxiety symptoms.

This study investigates the possible mediating role of personality characteristics in the association between childhood maltreatment and the course of depressive and anxiety disorders in adults. After all potential mediating variables were added into the model, we provided new evidence that high levels of neuroticism, hopelessness and external locus of control, and low levels of extraversion significantly mediate the association between childhood maltreatment and remission of depressive and anxiety disorders. This mediation model assumes a causal chain in which: (a) exposure to childhood maltreatment influences personality characteristics and (b) personality characteristics influence the chances of remission of depressive and/or anxiety disorders. Since personality characteristics reflect relatively enduring characteristics of the individual, our findings might be consistent with the hypothesis that personality characteristics mediate the association between childhood maltreatment and remission of depressive and anxiety disorders. We speculate that our results are suggestive of prevailing strong mediating effects of personality characteristics on the association between childhood maltreatment and remission rates.

The strength of this study is the prospective design; the large sample of midlife participants with a baseline diagnosis of depressive and/or anxiety disorder; the use of both structured interviews and standardized self-report questionnaires; simultaneous consideration of all domains of childhood maltreatment, key psychosocial measures, and personality dimensions; and the use of a mediation model to investigate the predictive value of personality variables on illness course. Methodological limitations include the retrospective assessment of childhood maltreatment at baseline, although recall of childhood maltreatment does not seem to be critically affected by current mood state (34). Common source bias may have been a potential problem, as both personality and childhood maltreatment were measured at the same time and retrospectively. Measures of personality, based on limited self-reports, cannot portray a wide enough range of all traits to cover the potential consequences of the complexities of upbringing. Moreover, as our participants were having current depressive and/or anxiety disorders, personality measurements may be contaminated with 'state' effects. However, traits such as neuroticism are stable, pervasive, and influential and consistently emerge in many analyses (35). Remission of depressive and anxiety disorders during the 4-year follow-up was based on the LCI, determining the presence and severity of symptoms of depression and anxiety, instead of a CIDI diagnosis.

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In conclusion, we found that childhood maltreatment, especially emotional neglect and psychological abuse, was associated with more psychosocial impairment in adulthood. Childhood maltreatment was associated with more unfavorable personality characteristics and coping styles. Personality characteristics, such as high levels of neuroticism, hopelessness and external locus of control, and low levels of extraversion are important independent predictors on the relationship between childhood maltreatment and 4-year remission of depressive and anxiety disorders. A maladaptive personality profile may be one mechanism linking childhood maltreatment to an adverse illness course of depressive and anxiety disorders. Emphasis on specific interventions, focused on neuroticism, extraversion, and locus of control, can contribute to a better prognosis in a 'high risk' group of depressive and anxiety disorders.

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Chapter 7

Summary, General Discussion, Clinical Implications, and Future Research
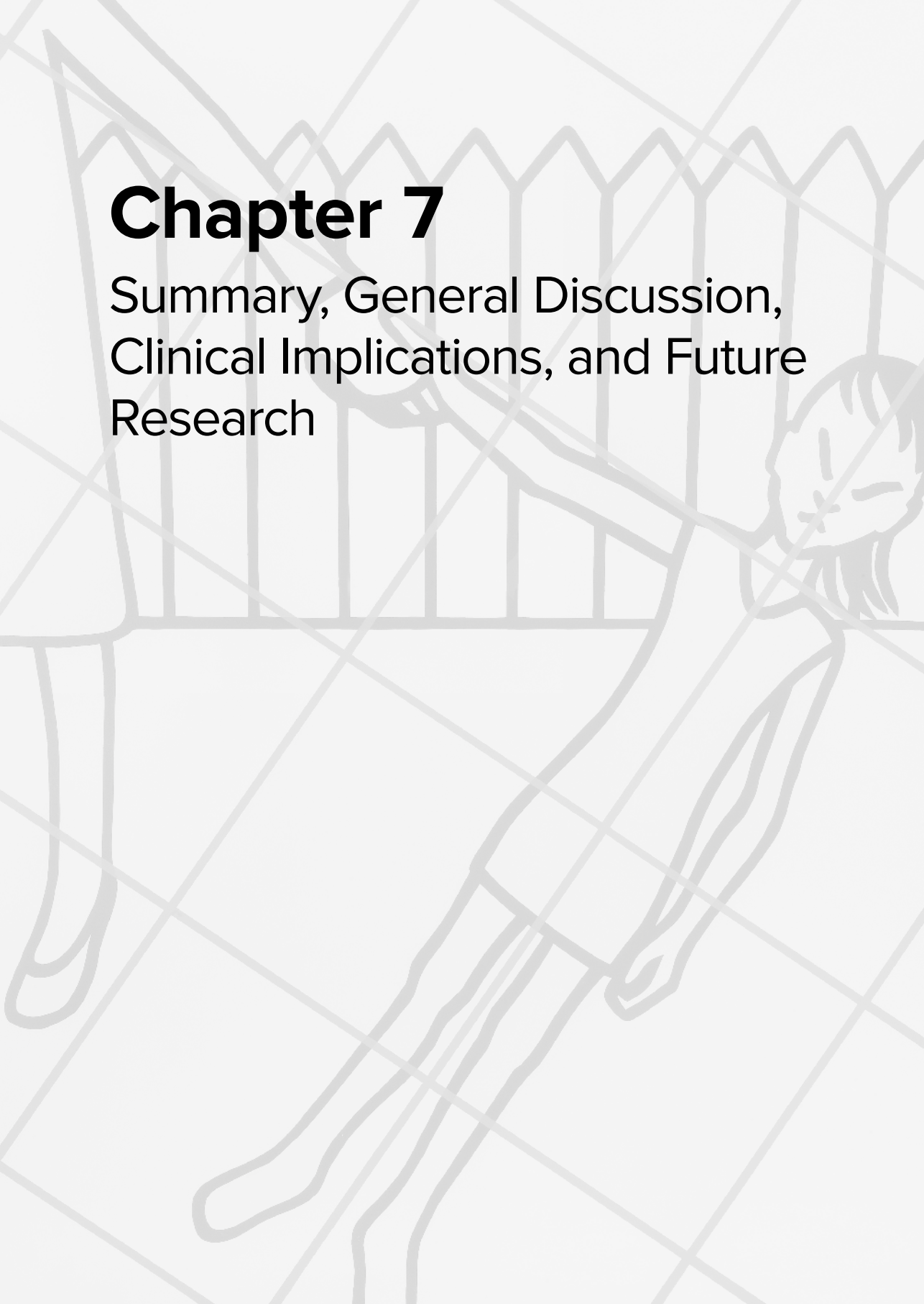
Summary and general discussion

The aim of this thesis was threefold: (1) to gain insight into the associations between childhood trauma, childhood life events and depressive and anxiety disorders in adulthood; (2) to better understand the longitudinal associations between childhood trauma, childhood life events and the course, onset, and recurrence of depressive and anxiety disorders, and (3) to examine the association of childhood trauma on psychosocial characteristics and personality dimensions and their potential mediating role in the relationship between childhood trauma and adult psychopathology. This thesis was based on the Netherlands Study of Depression and Anxiety (NESDA), which recruited 2,981 individuals at the age of 18 to 65 years.

Here, the main findings of this thesis will be summarized and discussed in the context of current research. Subsequently, our main findings will be reviewed in an attempt to contribute to a more comprehensive theory of the interrelatedness of childhood trauma and depressive and anxiety disorders. In addition, methodological considerations relevant for this thesis and the possible implications for clinical practice will be outlined, followed by suggestions for future research.

Childhood trauma, childhood life events and depressive and anxiety disorders in adulthood

In *Chapters 2* and *3*, cross-sectional associations between childhood trauma and childhood life events and depressive and anxiety disorder in adulthood were examined.
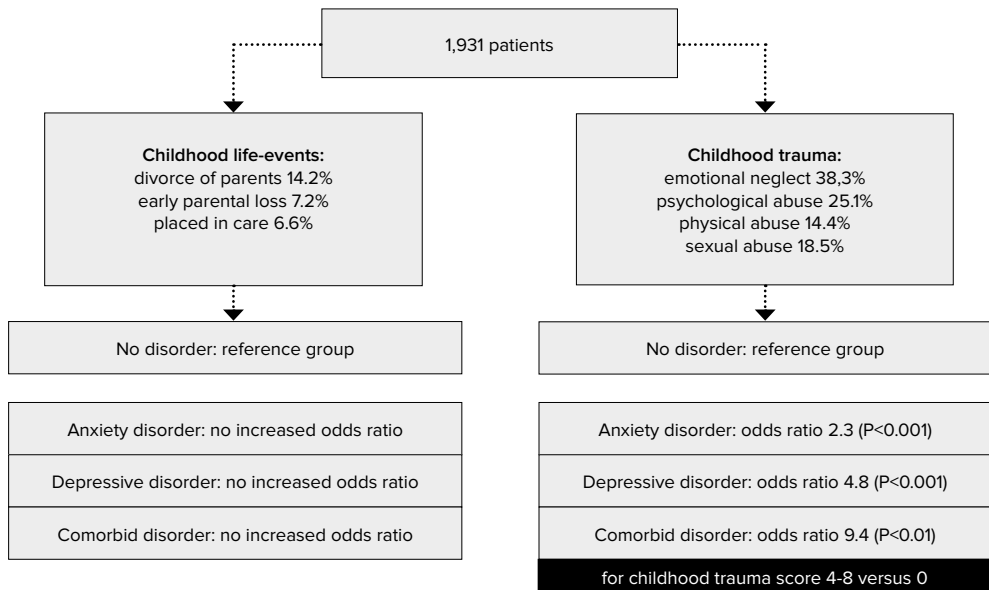

Figure 1. Study design of chapter 2.

Our goal in *Chapter 2* was to estimate to what extent childhood trauma and childhood life events were associated with depressive and anxiety disorders in adulthood. Many previous studies that reported a relationship between childhood trauma and childhood life events and depressive and anxiety disorders in adulthood have focused on lifetime psychopathology (1, 2) and on the more obvious forms of maltreatment, such as physical and sexual abuse (3-5). Our emphasis was on multiple childhood trauma domains (e.g., emotional neglect, psychological, physical, and sexual abuse), and we examined the specificity of associations with psychopathology by comparing impact on depressive versus anxiety disorders.

We demonstrated that a reported history of childhood trauma was associated with a higher risk of (current) anxiety and depressive disorders in increasing strength from (current) anxiety to (current) depressive to (current) comorbid depressive and anxiety disorders. Emotional neglect and psychological, physical and sexual abuse in childhood were all consistently and strongly associated with the presence of (current) anxiety and depressive disorders in adulthood. Our findings concur with a recent meta-analysis (6), and showed robust evidence of an effect of emotional neglect, psychological and physical abuse on the presence of depressive and anxiety disorders in adulthood according to a strong dose-response gradient (Figure 1).
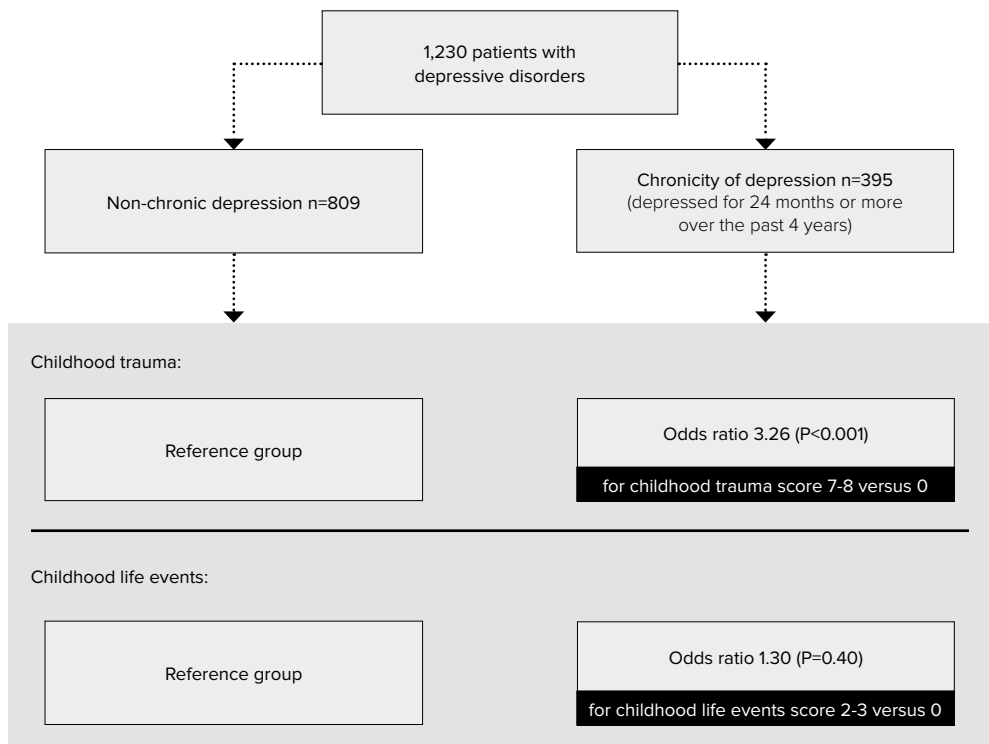

Figure 2. Study design of chapter 3.

In all trauma domains, the strongest associations were found in the comorbid group. Since co-morbidity is associated with increased number and severity of symptoms, our results suggest that childhood trauma contributes to the severity of psychopathology. The different domains of childhood trauma have frequently been identified as non-specific risk factors for adult psychiatric disorders (1, 7, 8).

A few studies, however, have analyzed associations of childhood psychological, physical, and sexual abuse (9, 10) and emotional neglect (10) separately in relation to various depressive and anxiety disorders and found that different trauma types were related to different diag-noses. Emotional neglect and psychological abuse appeared to be particularly associated with dysthymia, depression, and social phobia (9, 10), while sexual abuse was associated with dysthymia only (10). Physical abuse did not independently increase the risk of depressive or anxiety disorders (9, 10). Although we did not find unique predictive relationships between the specific domains of childhood trauma and depressive and/or anxiety disorders, we found support for the expectation that emotional neglect and psychological abuse had a stronger link with (current) depression than (current) anxiety. In line with the above mentioned studies (9, 10), physical and sexual abuse were not discriminative for depression or anxiety.

Chapter 3 focused on the importance of childhood trauma and childhood life events for chronicity of depression (cross-sectional associations). We found that a reported history of childhood trauma was associated with a significant increased risk of chronicity of depression in adults with a major depressive disorder in the past year. Emotional neglect, psychological abuse, physical abuse, and sexual abuse were all significantly associated with chronicity of depression. A dose-response relationship between the frequency of childhood trauma and chronicity of depression was found (Figure 2). Individuals with the highest scores on the childhood trauma index (score 7-8) had a 3-fold increased risk for chronicity of depression compared to those with no childhood trauma score (score 0). As in *Chapter 2*, a high score on the childhood trauma index was associated with a significantly higher prevalence of comorbid anxiety, more severe depression, and an earlier onset of the first depressive episode. The association between a high score on the childhood trauma index and chronicity of depression persisted, after controlling for clinical characteristics (anxiety comorbidity, number and severity of depressive symptoms and age of onset). In these cross-sectional analyses childhood trauma seems to be a potential risk factor for a chronic course of depression, independent of the above disease characteristics. Similar evidence that the risk for (chronic) depression increases in a graded, dose-dependent fashion with the number of childhood adversities has been found in the Adverse Childhood Experience study (11).

The specific childhood life events addressed in *Chapter 2* and *Chapter 3* were parental loss, parental divorce, and 'placed in care'. Our findings that childhood life events were not associated with either depressive and/or anxiety disorders (*Chapter 2*) or subsequent

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chronicity of depression (*Chapter 3*) in adulthood, support the assumption that life events per se are not the most important factors, but rather the quality of childhood holding environment and the presence of a healthy and caring parent or substitute caretaker.

Table 1. Correlations between childhood trauma domains.

	Psychological abuse	Physical abuse	Sexual Abuse
Emotional neglect	0.62 (*P<0.001*)	0.43 (*P<0.001*)	0.27 (*P<0.001*)
Psychological abuse		0.56 (*P<0.001*)	0.23 (*P<0.001*)
Physical abuse			0.27 (*P<0.001*)

Data are Spearman's correlation coefficients.

Table 2: Correlations between childhood trauma domains and childhood life events.

	Early parental loss	Divorce parents	Placed in care
Emotional neglect	0.04 (*P=0.04*)	0.15 (*P<0.001*)	0.19 (*P<0.001*)
Psychological abuse	0.03 (*P=0.17*)	0.15 (*P<0.001*)	0.22 (*P<0.001*)
Physical abuse	0.03 (*P=0.17*)	0.09 (*P<0.001*)	0.19 (*P<0.001*)
Sexual Abuse	0.03 (*P=0.17*)	0.07 (*P<0.001*)	0.13 (*P<0.001*)

Data are Spearman's correlation coefficients.

Although the correlations between emotional neglect, psychological abuse, physical abuse and sexual abuse were modest to large in magnitude (Table 1), the correlation between childhood trauma domains and childhood life-events was weak (Table 2). This finding implicates that the experience of parental loss or parental divorce does not necessarily result in emotional neglect. Research on the impact of parental loss (parental death, divorce or other loss of contact with parents) has given inconsistent results (12), which might be due to parental loss not being a good indicator of the level of conflict within a family. For example, the negative impact of a divorce in case of significant post-separation conflict, or a positive effect, if divorce leads to the cessation of chronic family conflict or the removal of an abusive parent. Recent large adult population-based studies in the Netherlands, the US, and Mexico (13-15) agree with our findings that parental loss or parental divorce before the age of 16 was not associated with an increase in depressive and or anxiety disorders. These studies, however, also suggest that family dysfunction or high levels of parental conflict do have a negative impact on psychopathology.

Childhood trauma and childhood life events as course predictors of depressive and anxiety disorders

Childhood trauma and childhood life events as predictors of longitudinal course of depressive and anxiety disorders were addressed in *Chapters 4, 5* and *6*.
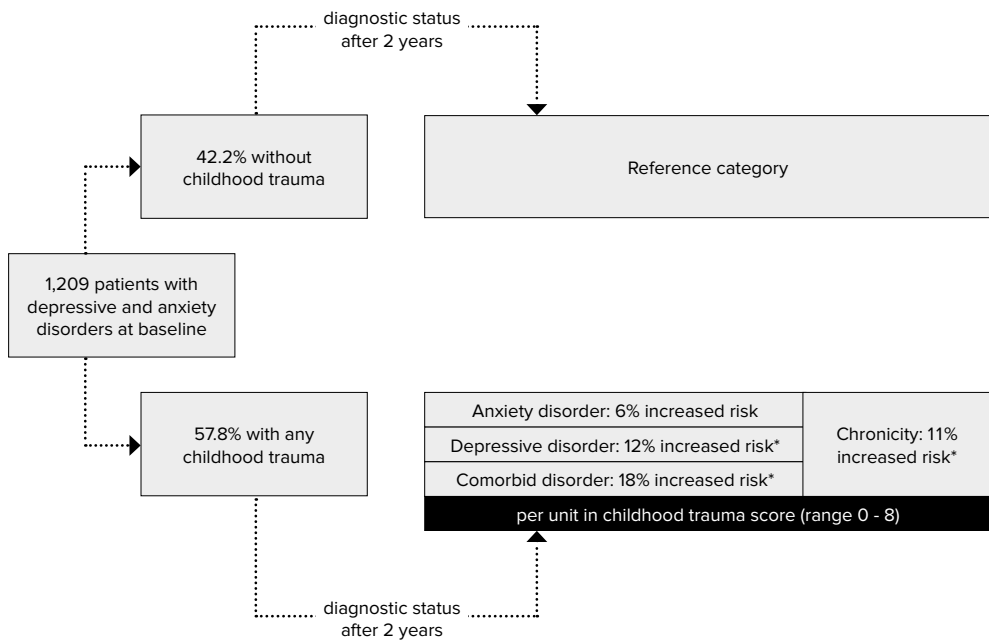
Figure 3. Study design of chapter 4. *: *P* <0.001.

In *Chapter 4* the effect of childhood trauma and childhood life events as predictors of the 2-year course of depressive and/or anxiety disorders was studied in a follow-up cohort of adults with baseline diagnosis of depressive and/or anxiety disorders. Our results confirmed that a reported history of childhood trauma was associated with a poor outcome, characterized by more comorbidity and chronicity, in adults with baseline anxiety and ⁄or depressive disorders (Figure 3). Our prospective study was different from the handful of previous prospective studies in regard to a considerably larger sample size and the inclusion of a range of trauma domains. We found that childhood emotional neglect, psychological abuse and physical abuse were all (consistently and strongly) associated with persistence of both depressive and comorbid depressive and anxiety disorders. Emotional neglect and psychological 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 a surprising and counter-intuitive finding. This could partially be attributed to a somewhat lower statistical power of sexual abuse when compared to emotional neglect and psychological abuse. The childhood trauma score was predictive of both a depressive or comorbid disorder and a chronic course after 2 years of follow-up. Our data show that the impact of childhood trauma on outcome diagnosis (diagnostic status and course) at 2-year follow-up is not as strong for anxiety disorders.

Baseline disease characteristics of participants with reported childhood trauma (versus no childhood trauma) showed an earlier age of onset, longer duration of symptoms, more and more severe symptoms of anxiety and/or depressive symptoms and, more comorbidity. To explore potential mediation effects of those baseline disease characteristics on illness course (16-18) we conducted mediation analysis. We found that baseline disease characteristics were important factors in mediating the relationship between childhood trauma and the course of illness. These associations appear to be mediated through more unfavorable baseline disease characteristics, among which the number and severity of depressive symptoms predominated. These findings suggest that childhood trauma does not add predictive validity - over and above - baseline clinical characteristics when it would be solely used in a prediction model. In a causal model, childhood trauma would be at the root of the causal pathway leading to an increased risk of more and more severe symptoms and subsequently a poor outcome.
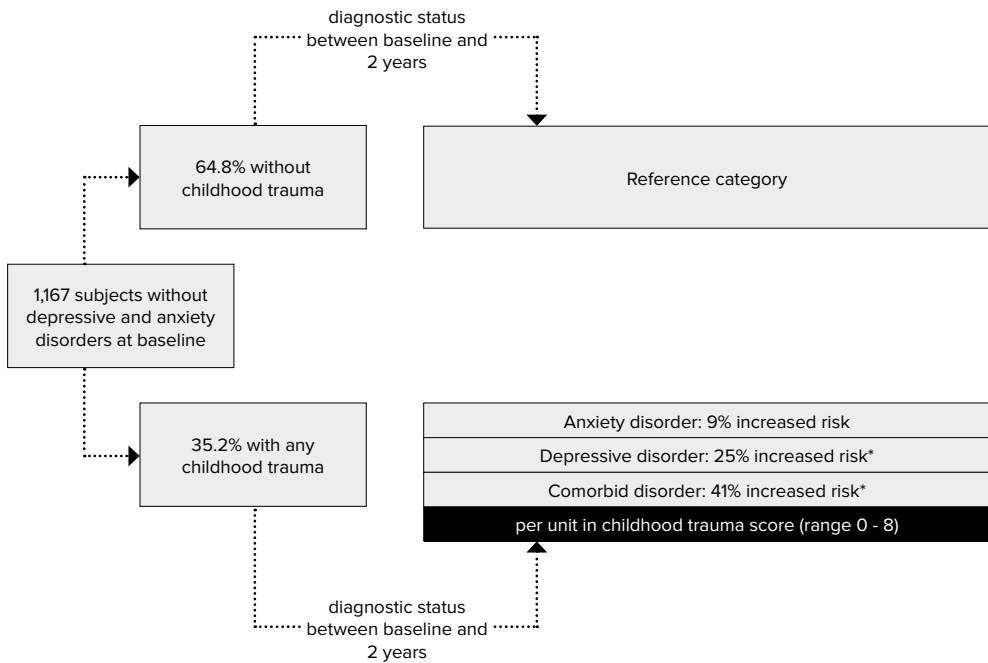

Figure 4. Study design of chapter 5. *: *P* <0.001.

In *Chapter 5*, we explored (1) the differential effects of childhood trauma and childhood life events on the onset or recurrence of anxiety, depressive and comorbid disorders, (2) the specific effect of various childhood life events and all domains of childhood trauma, (3) whether relationships differed in subjects with and without lifetime depressive and/or anxiety disorders, and (4) whether clinical factors such as severity of baseline anxiety and depressive

symptoms and a prior lifetime diagnosis, are important in mediating the relationship between childhood trauma and the occurrence of depressive and anxiety disorders. To address these topics, a cohort of 1,167 adults without current depressive and/or anxiety disorder at baseline was followed over a 2-year time period. Prospective evidence of childhood trauma predicting onset and recurrence of adult mood disorders is scarce and limited to children exposed to childhood maltreatment, who were followed until (young) adulthood (19-21). We found that a history of childhood trauma predicted the first onset and recurrence of depressive or comorbid disorders in adults without a baseline depressive and/or anxiety disorder (Figure 4). Our findings support the idea that childhood trauma only weakly increases the risk of anxiety disorders. Among the specific effects of childhood trauma, 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 childhood trauma and psychopathology is predominantly driven by emotional neglect. We found that in all trauma domains, there was no significant moderating effect of lifetime psychopathology at baseline on the occurrence of depressive and/or anxiety disorder in the 2-year follow-up. The relative effects of childhood trauma were of similar strength in patients with and without lifetime psychopathology, which demonstrates that childhood trauma is associated with both onset and recurrence of psychopathology. Severity of subsyndromal depressive symptoms and a prior lifetime diagnosis were the most important mediating risk factors between childhood trauma and outcome (new and recurrent depressive and anxiety disorders). The effect was mediated in such a way that the direct relationship between childhood trauma and outcome data became non-significant. The possible mechanisms through which childhood trauma may affect psychopathology in adulthood will be discussed in the *theoretical models* section.

In line with our previous cross-sectional studies, childhood life events were once again not found to be associated with the 2-year course indicators of onset and recurrence of depressive and/or anxiety disorders. Our findings on the course of depression in adults with reported childhood trauma, were confirmed in a recent meta-analysis based on 16 (9 population and 7 clinical) epidemiological studies (22). This meta-analysis suggests that maltreated individuals were twice as likely as those without a history of maltreatment to develop both recurrent (*Chapter 5*) and persistent (*Chapter 4*) depressive episodes. Overall, the longitudinal results in *Chapters 4 and 5* provide further support for our previously described cross-sectional findings (*Chapters 2 and 3*).

Childhood trauma and course of depressive and anxiety disorders: association with psychosocial characteristics, personality dimensions and cognitive reactivity styles
Although childhood trauma has been associated with adult impairment in psychosocial functioning, more stressful life events in adulthood and a maladaptive personality style, previous research has focused on a limited range of childhood adversities and only assessed specific psychosocial and psychological variables in heterogeneous populations (e.g. population based, community and clinical samples).
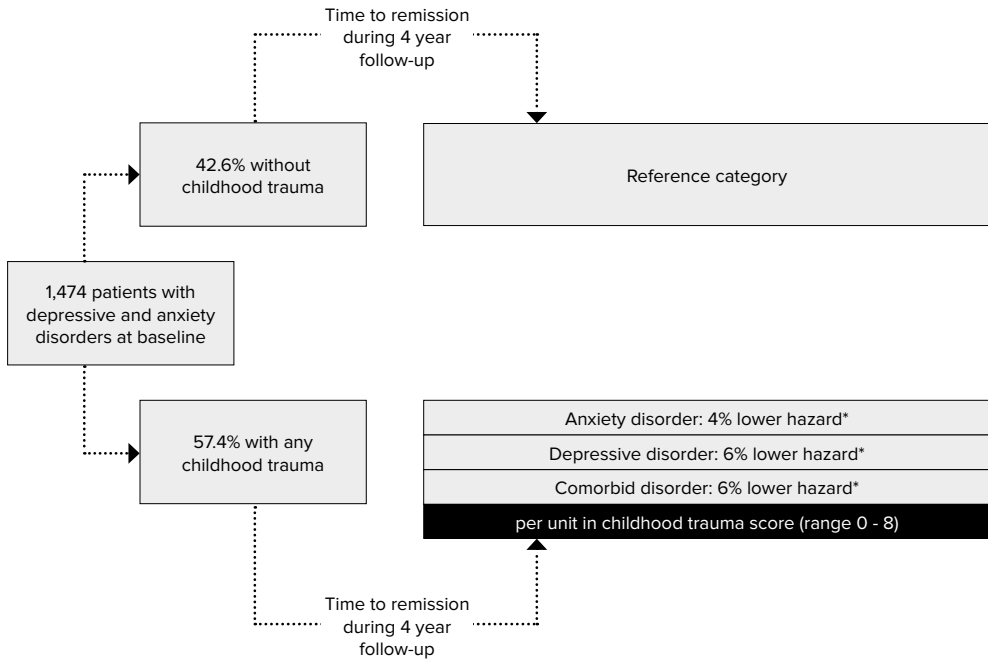
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Figure 5. Study design of chapter 6. *: *P* <0.001.

The purpose of *Chapter 6* was to simultaneously investigate psychosocial characteristics, personality dimensions, and adult life events in relation to a broad spectrum of childhood trauma domains, among adults with depressive and/or anxiety disorders during 4 year follow-up. We addressed the following research questions: (1) do individuals, traumatized as children, differ on baseline sociodemographic and psychosocial characteristics, personality dimensions, and cognitive reactivity styles from non-traumatized individuals, and (2) are these characteristics important factors in mediating the unfavourable 4-year course of depressive and anxiety disorders in patients with a history of childhood maltreatment? Our results show that childhood trauma, in particular emotional neglect and psychological abuse, has a negative impact on (interpersonal) psychosocial functioning in adulthood and increases the likelihood of being exposed to adverse life events in adulthood (Figure 5). We found that childhood trauma was associated with an unfavourable personality profile in all dimensions: lower levels of extraversion, agreeableness, conscientiousness, and higher levels of neuroticism, openness, hopelessness, rumination and external locus of control. These effects of childhood trauma on personality dimensions and cognitive reactivity styles contribute to previous findings on personality traits, which predominantly focused on neuroticism (23, 24). Two major dimensions of personality, neuroticism and extraversion are (to some degree) inherited traits (25). Neuroticism is characterized by anxiety proneness,

emotional instability, and self-consciousness; extraversion by energy dominance, and positive emotionality (26). In agreement with our findings in the 2-year course (*Chapter 4*), we found that a high childhood trauma score significantly predicts more chronicity of anxiety and (even better for) depressive disorders in the 4-year course. We provide new evidence that, in particular, certain personality dimensions (e.g. high levels of neuroticism, hopelessness and external locus of control, and low levels of extraversion) were independent mediators of the association between childhood trauma and remission of depressive and anxiety disorders. In contrast, none of the socio-demographic and psychosocial characteristics or adult adverse life events were significantly mediating risk factors and had any substantial effect on the course of depressive and anxiety disorders. To conclude, this mediation model suggests an overall effect of childhood trauma on the 4-year remission of depressive and/or anxiety disorders, with neuroticism, extraversion, hopelessness, and external locus of control mediating the associations.

Theoretical models and possible causal pathways

The mechanism through which childhood trauma leads to and influences depressive and anxiety disorders in adulthood is still an area of debate and many opinions. In this section, our findings of the interrelatedness of childhood trauma, depressive and anxiety disorders will be integrated into a schematic overview. Our results will be discussed in light of the most prevailing models of trauma-related psychopathology. Our longitudinal findings contribute to our understanding of the chain of events and dynamic relationships between childhood trauma and depressive and anxiety disorders in adulthood. In an attempt to describe the sequences in a complex interplay of multiple psychological/cognitive vulnerabilities and environmental factors, we will suggest a possible causal pathway that best fits our data.

Sensitization model
The 'scarring hypothesis of depression' is based on the assumption that some long-lasting changes ('scars') may occur during a depressive episode and persist after remission and recovery and sensitize the subject for future episodes (27). Scarring refers to a range of possible changes in cognition, emotion, behavior or biology that develop during or in the aftermath of a depressive mood state (28). Based on the scarring hypothesis, Post described 2 types of sensitization mechanisms: one related to the experience of an affective episode (episode sensitization) and one related to triggers that actually caused the depression (stressor sensitization) (29). Both stressors and negative mood states may be able to produce 'scars' that are relevant to the vulnerability and increased sensitivity for the development of psychopathology in later life. In line with the 'scarring hypothesis of depression', our findings agree with the idea that childhood trauma leads to scarring in psychosocial, cognitive or emotional functioning, and persists into adulthood. In Chapter 6 we found that childhood trauma was associated with enduring psychosocial impairment and a negative impact on

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cognitive reactivity style and personality profile in adulthood. These long-term consequences can be perceived as scars of childhood trauma and as potential risk factors for the development of subsequent anxiety and depressive disorders. For example, childhood trauma may induce increased sensitivity to interpersonal conflict, negative cognitive schemes, and low self-esteem ('scars' due to stressor), all of which are more readily activated each time they are challenged (i.e., at the time of experiencing stressors or mild dysphoric states) and subsequently lead to depressive and/or anxiety disorders.

Stress generation model

The 'stress generation model' focuses on the role of individuals as active contributors to their environment, instead of passively responding to stressful events in their lives (30). Individuals vulnerable to depression are likely to report a higher rate of stressful life events, particularly within interpersonal domains, which can be influenced by maladaptive characteristics (e.g., cognitive styles, traits, attachment styles, values, and expectations) and behaviors of the individual (30). Consistent with the stress generation perspective, chronic stress and childhood maltreatment have been postulated to contribute to the subsequent occurrence of future stressors (31, 32). Our finding in Chapter 6 that childhood trauma was associated with a higher number of adverse life events in adulthood, is in agreement with the 'stress generation model' (31, 33). One possible explanation for this association is that stress sensitization resulting from childhood trauma may cause individuals to experience external stimuli in such a way that they subsequently elicit and trigger stressful life events in adulthood (31). As shown in Chapter 6, childhood adversity is related to personality development and coping styles, which may attribute to the increased occurrence of life stressors, especially in the interpersonal domain (i.e. unstable relationships) (30).

Causal pathway of childhood trauma and depressive and anxiety disorders in adulthood

Our findings provide more insight into factors mediating the relationship between childhood trauma and depressive and anxiety disorders in adulthood, which will be discussed in more detail.

The lack of specific interrelationships between childhood trauma and psychopathology support the hypothesis of a general vulnerability for depressive and anxiety disorders among adults exposed to early childhood trauma. Much of the perceived impact of childhood trauma is likely to stem from a 'context of abuse', referring to the frequent co-occurrence of various types of childhood abuse (32). Our assumption is that in case of reports of childhood trauma, emotional neglect is (almost always) highly likely, and acts as the predominant driving force in the relationship between childhood trauma and psychopathology. Emotional neglect is a core issue in the attachment theory, which provides a useful framework for understanding lifespan linkages between childhood trauma and later psychopathology (34). Early interactions between parent and child, characterized by instability, threats or

experiences of abandonment or violence, may result in potential scars in personality and coping styles. In line with our mediation analyses, high levels of neuroticism, hopelessness and external locus of control and low levels of extraversion can be interpreted as 'scars' and subsequent factors in a causal pathway to the occurrence and persistence of depressive and anxiety disorders.

Childhood trauma predisposes to an early age of onset of depressive and/or anxiety disorder, increases number and severity of depressive and/or anxiety symptoms, and increases the likelihood of a comorbid disorder. In addition, childhood trauma acts as a course predictor of increased depressive or comorbid disorders and increased chronicity, and as a predictor of both onset and recurrence of depressive or comorbid disorders. Our mediation analyses have taught us that number and severity of depressive symptoms, and a prior lifetime history of anxiety and/or depressive disorders (in case of recurrence) are crucial in the final pathway leading to the onset, recurrence, and chronicity of full syndromal depressive and/or anxiety disorders. Overall, the impact of childhood trauma on onset, recurrence, and chronicity of anxiety disorders was not as strong as the impact on depressive and comorbid disorders. This may suggest that 'pure' anxiety disorders are more resilient to the detrimental effects of childhood trauma.

Neuroticism and extraversion are related to vulnerability and persistence of affective disorders (35, 36). A strong correlation of high neuroticism with more severe depressive symptoms has been reported (37, 38), but high extraversion has been associated with lower levels of depressive symptoms (23). We assume that the more severe depressive symptoms can be a direct result of high neuroticism or low extraversion, the so called "trait effect" (37), which may originate from experiences during childhood.

Our findings are summarized in the flowchart in Figure 6. Our data fit into a model where childhood trauma affects personality development and coping styles through a scarring mechanism. This may induce an unfavorable personality profile, characterized by high levels of neuroticism, low levels of extraversion, a negative cognitive style and external locus of control. High levels of neuroticism and maladaptive depressogenic schemata may eventually lead to depressive symptoms, and ultimately to full syndromal depressive and comorbid disorders with a chronic course.

Our model emphasizes cognitive vulnerability due to childhood trauma as the possible cause of depressive and anxiety disorders in adulthood, but this model should be regarded with the necessary caution and in the context of neurobiological vulnerability. Over the past decade, clinical studies have provided evidence that early life stress induces neurobiological changes that are similar to those in animal models (39). The hypothalamic-pituitary-adrenal (HPA)-axis is a central neuroendocrine system that serves to maintain homeostasis during
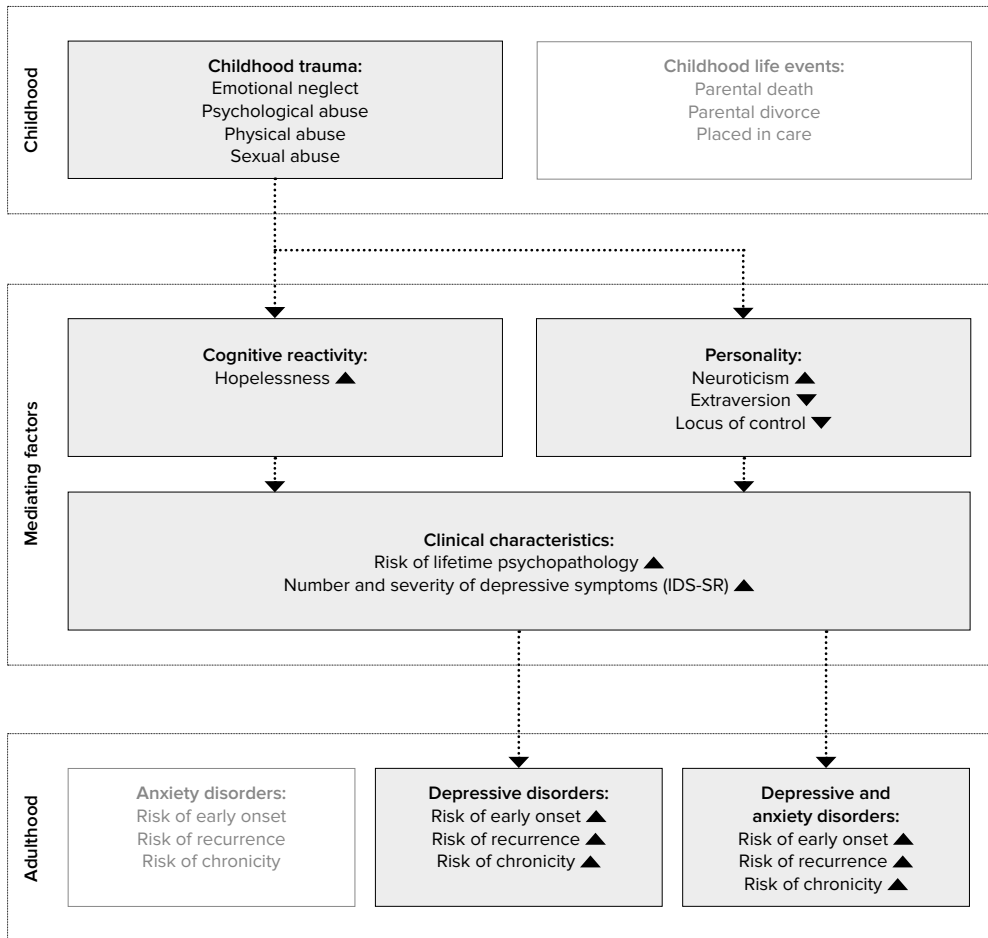
Figure 6. Flowchart summarizing our findings.

stress exposure. Childhood abuse is associated with a persistent sensitization of the HPA-axis to stress in depressed patients (40, 41) and with enhanced cortisol reactivity to psychosocial stress in patients with anxiety disorders (42). Compared to controls, depressed adults with childhood maltreatment twice as likely had elevated inflammation markers in blood samples (i.e. high-sensitivity C-reactive protein), whereas depressed-only individuals only had a non-significant increase for hsCRP levels (43). Other differences reported include decreased levels of oxytocin, a neuropeptide mediating attachment and social support and protecting against stress and anxiety, in cerebrospinal fluid in maltreated women (44).

In addition, there has been a growing body of literature linking childhood trauma with structural and functional brain differences. The most consistent neuro-imaging finding in patients with depressive and anxiety disorders consists of a reduction in hippocampal and

amygdala volume in maltreated individuals compared to non-maltreated individuals (45). A previous NESDA study shows that childhood emotional maltreatment is associated with profound reduction of medial prefrontal cortex (mPFC) volume, suggesting that sustained growth inhibition or structural damage can occur after exposure to childhood emotional maltreatment (46).

Important areas of current research include (a) gene–environment interactions investigating the differential role of certain genotypes in modifying the effects of early trauma, (b) the identification of developmentally sensitive periods of brain maturation for the effects of early trauma, and (c) epigenetic processes (47).

It is important to realize that above mentioned pathophysiological variables, which are beyond the scope of this thesis, can present as mediators or modifiers as they are able to affect both childhood trauma and psychopathology. An example is parental mental illness, which can increase the risk of depressive and anxiety disorders in its offspring through both a direct genetic pathway and through the effects of childhood adversities (emotional neglect by a depressive parent). These potential mediating pathways cannot be separated in the NESDA study. Genetically informative designs (e.g., twin-family studies) are needed to disentangle these potential mechanisms.

Methodological considerations

In this section, we will address the most important limitations that play a role in the studies reported in this thesis, i.e. sample and design, assessment of childhood trauma, measurement of psychopathology, and statistical methods.

Sample and design

This thesis was based on the Netherlands Study of Depression and Anxiety (NESDA), a large cohort study of men and women, aged 18 to 65 years, predominantly of Caucasian origin. Participants were all outpatients and recruited from the general population, primary care and mental health organizations. Due to this sample selection, the findings of this thesis are not generalizable to ethnic minorities, the elderly, and (in)patients with the most severe depressive and anxiety disorders. Detailed analyses of non-response and attrition have been provided in previous chapters.

Although part of the studies in this thesis focused on longitudinal prediction of childhood trauma in relation to psychopathology, the observational design of NESDA precludes definitive interpretations. Our 2- and 4-year follow-up data cover a sufficiently long period to evaluate the relation of trauma with time to remission and other course variables in patients with a current episode of anxiety and depression.

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Assessment of childhood trauma

In all our studies, we assessed childhood trauma using the NEMESIS interview, described in more detail in the previous chapters. The NEMESIS trauma interview has not yet been formally validated. In a previous study, the association of a history of childhood trauma, measured by this interview, with the incidence and prevalence of psychiatric disorders, was considered evidence for good construct validity (48). In agreement with our findings (*Chapters 2* through *6*), childhood trauma was consistently related to depressive and comorbid disorders, which supports the validity of this NEMESIS trauma interview.

The Childhood Trauma Questionnaire (CTQ-SF), a well-validated and reliable questionnaire that measures dimensional aspects (i.e., severity) of childhood abuse, is often considered as a gold standard in trauma research. In a recent study among the NESDA population, the CTQ-SF at T4 was compared with the NEMESIS trauma interview at T0 (49). The CTQ-SF (T4) was moderately associated with the NEMESIS trauma interview (T0), and the association was not attenuated by psychiatric disorder status. The concordance between the two trauma instruments is remarkable, given the 4-year time lag between the administration of the two instruments that differ in assessment mode and questioning format. The CTQ-SF was more sensitive in detecting emotional neglect and emotional abuse than the NEMESIS trauma interview, probably as a result of the multiple specific questions asked on emotional neglect/abuse in the CTQ-SF. The NEMESIS trauma interview, however, provides additional information on the frequency of abuse and on the relationship (type and number) with the perpetrator.

Another important pitfall might be that the assessment of childhood trauma was based on retrospective recall. Retrospective assessment of childhood trauma may be limited by several factors such as lapses in memory due to the passage of time, intentional false responding and the possible inaccessibility of memories for traumatic events. It has frequently been shown that a history of childhood trauma is more likely to be under- than over-reported. This may have resulted in selective identification of the more severe cases of childhood abuse, over-looking mild or moderate abuse. Importantly, it has been found that recall of childhood trauma did not seem to be critically affected by the psychiatric state of the respondent (10, 50, 51).

The association of negative life events in adulthood with depressive and anxiety disorders has not been explored in this thesis, but has been addressed in a previous NESDA study (10). The association of childhood trauma with affective disorders appears to be stronger than the association of adult negative life events with affective disorders, which may be due to chronicity and timing of childhood trauma. Childhood trauma and adult life events may be intertwined in complex ways. We have studied the possibility that childhood trauma affects current psychopathology through its effects on adult negative life events (*Chapter 6*). Although traumatized subjects were more prone to report negative life events in adulthood, these had no substantial effect on the course of depressive and anxiety disorders.

Measurement of psychopathology

Our findings cannot be extrapolated to psychiatric disorders that were not taken into account in the NESDA sample at baseline, for example posttraumatic stress disorder (PTSD). In a recent NESDA study, PTSD was measured with a standardized interview at T4. The prevalence of PTSD among anxiety and depressive disorders was 9.2%, and comorbidity, especially in patients with major depression, was high (84.4%) (52). The association between childhood trauma and anxiety disorders might have been stronger if more patients with PTSD would have been included at baseline. Moreover, when PTSD would also have been measured at baseline, we would expect to find stronger associations between this subgroup of anxiety patients and, in particular, in participants who reported childhood sexual and physical abuse. Previous studies reported that childhood sexual and physical abuse increases the likelihood of PTSD in adulthood (53).

Statistical issues

As shown in Table 1, the various domains of childhood trauma overlap substantially. Emotional neglect is considered a core component of childhood trauma and is almost always present, in case of other domains of abuse. This may explain why the associations with emotional neglect predominate in all analyses. The associations between emotional neglect and psychopathology might be somewhat overestimated, due to substantial collinearity, which precluded the inclusion of all co-occurring childhood trauma domains in the multivariate analyses. Especially emotional neglect and psychological abuse are strongly interrelated and have been combined into a domain called 'emotional maltreatment' in previous NESDA studies (46).

The relative narrow range of the childhood life event score (0-3) in comparison with the childhood trauma score (0-8) may have reduced the power somewhat to detect positive associations between childhood life events and psychopathology. Because the effect estimates for childhood life events in relation to outcomes were consistently insignificant and in sharp contrast with the findings of childhood trauma, we think that our conclusions are robust: childhood trauma but not childhood life events impact on psychopathology in adulthood.

The effect sizes in our studies may be underestimated because of attrition in NESDA during follow-up. Although NESDA had a relatively low attrition rate, comorbid depressive and anxiety disorders and higher symptom severity were associated with higher attrition (54). Therefore, the estimates of childhood trauma effects may have been underestimated. Individuals with the highest risk of depressive and anxiety disorders tended to leave the study, thereby diluting the associations with childhood trauma.

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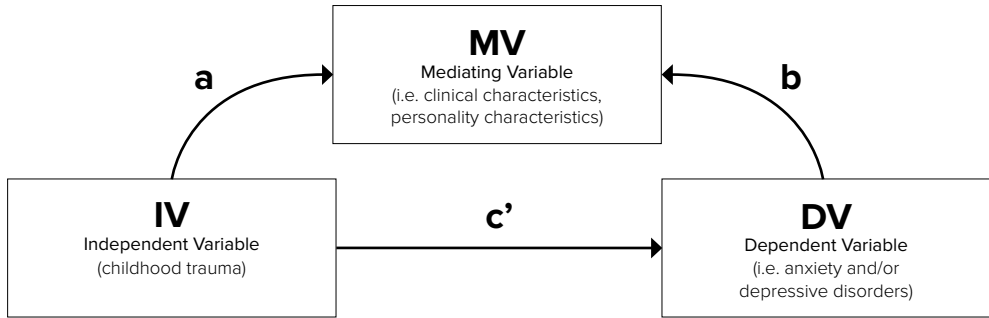
We used mediation models to investigate the association between childhood trauma and depressive and anxiety disorders when taken possible mediators into account. A mediator (M) is an intervening variable that may account (statistically) for the relationship between the independent (IV) and the dependent variable (DV) (55). A critical starting point for mediation analysis is the presence of associations between the independent childhood trauma variable and the mediating variables and between the mediating variables and the outcome variables (depressive and anxiety disorders), a requirement that we were able to test and meet. For a correlation to be interpreted as causation, the independent childhood trauma variable should at least precede the mediator variable in time. Our independent childhood trauma variable and mediating variables (i.e., age of onset, depressive and anxiety symptom severity, baseline diagnosis, lifetime diagnosis, personality characteristics) were assessed cross-sectionally, which makes it difficult to establish the exact timing. However, we tried to pinpoint the 'age of onset' retrospectively and excluded those subjects with an age of onset (for depressive and/or anxiety disorders) prior to age 16, which may have preceded the childhood adversities. In all mediation analyses, the outcome variables were assessed prospectively.

Clinical implications

What are the potential implications of our findings for clinical practice? The findings of this thesis suggest that childhood trauma has serious lifelong consequences. We demonstrate that childhood trauma can be identified as an important risk factor for the development of depressive and/or anxiety disorders and predicts a poorer clinical course of illness. A history of childhood trauma, especially the presence of multiple childhood traumata, contributes to more comorbidity, greater severity of symptoms, and more chronicity of anxiety and depressive disorders. Emotional neglect, as the core component of childhood trauma, is of particular interest. Although emotional neglect is a major public health problem, its detrimental effect on adult psychopathology has not been recognized for a long time and is considerably under-estimated (6, 8).

Clinical practice

Our study underscores the importance of heightened awareness of the possible presence of childhood trauma, especially in a subgroup of adult patients with comorbid depressive and anxiety disorders and/or those with a chronic course. Many clinicians are hesitant to ask questions or start a conversation about the possibility of childhood adversities because those are considered too sensitive and personal matters. Clinicians should be aware that routine inquiry about childhood adversities is not harmful and can add important prognostic information to update their risk assessment (56). A history of childhood trauma helps to identify individuals who are at high risk of developing recurrent and chronic depressive and anxiety disorders and those who will respond poorly to treatment. A meta-analysis of 10 clinical trials, investigating childhood trauma and treatment outcome of depression, has shown that depressed individuals with reported childhood trauma appear to benefit less from treatment (especially treatment with both structured cognitive behavioral therapy and antidepressant medications) than those without childhood trauma (22). Thus, standard treatment modalities for anxiety and depressive disorders may not be sufficient for these traumatized individuals. In agreement with studies on (complex) posttraumatic stress disorder and borderline personality disorder, more intensive and alternative treatment options have been suggested that focus on the presence of insecure attachment styles and poor emotional regulation skills in adults with histories of childhood trauma (57).

The findings in *Chapter 6* suggest that certain personality characteristics are key factors linking childhood trauma to a poor course of depressive and anxiety disorders. Psychological treatment with a greater emphasis on tackling emotional instability, hopelessness, helplessness, and poor sociability patterns may improve treatment outcome. Treatment may be most effective if it not only addresses historical traumatic events, but expands its focus onto developmental and relational life issues (58). Therapeutic interventions, such as improving emotional regulation skills and attachment styles, increasing problem solving and personal control, and empowerment, are recommended (58). In addition, a treatment approach that begins with safety, education, stabilization, skill building, and development of the therapeutic relationship with a therapist, is essential for patients who have experienced childhood trauma (45). It is important to explore new treatments that target the psychological and biological vulnerabilities described in this subgroup, and implement these in future clinical guidelines for depressive and anxiety disorders.

In analogy to other medical specialties, clinical staging and profiling is also emerging in the field of psychiatry. Clinical staging and profiling may provide a helpful framework geared towards the continuous nature of most psychiatric disorders and is sensitive to etiologic and prognostic risk factors (59). In this thesis, we have shown that childhood trauma can be considered as an important 'profiler', i.e. a specific characteristic of a patient's (history) that is related to the onset, course and prognosis of their disorder. In clinical practice, inclusion of

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a detailed trauma assessment in the diagnostic evaluation of a patient, can serve as a basis for profiling. Doing so will contribute to diagnosis and prognosis on the level of an individual patient, which contributes to 'personalized medicine' (59).

Public health

Childhood adversity has an enormous impact on mental and physical health in adulthood and should receive high priority among public health interventions (60). Interventions aimed at reducing childhood trauma can help prevent the large health and economic burden linked to poor illness course. Early preventive and therapeutic interventions may be more effective (and cost-effective) in preventing a poor longitudinal course of illness than interventions at later ages (secondary prevention), when harmful developmental trajectories have already been established. For example, prevention would require increased recognition of the occurrence of childhood trauma, in particularly emotional neglect and abuse, and the assumption that childhood adversities in many cases lead to coping and regulation strategies that often have a negative impact on health outcomes. Increased recognition is a first step towards taking preventive measures (11). If screening for psychological problems or health issues would include screening for the occurrence of childhood trauma, this could be detected at an earlier stage and treatment could have a more integrative approach towards symptoms as well as the causes of these symptoms (60). Evidence-based systematic interventions that improve parenting strategies and family functioning may be more effective and economical than attempting to treat the wide-ranging negative health outcomes in adulthood.

Future research

This thesis has contributed to our knowledge of the longitudinal association between childhood trauma and depressive and anxiety disorders and has shed light on potential risk factors and mechanisms through which childhood trauma may affect psychopathology in adulthood.

Childhood trauma is a complex phenomenon, which often occurs in the context of a variety of negative social, psychological and biological factors. The chain of events that links childhood adversities to psychopathology in adulthood involves a complex, interdependent, and sometimes interactive cascade of multiple psychological vulnerabilities and environmental factors. In this thesis, we have specifically tried to clarify the role of psychological mechanism and clinical disease characteristics in the development and course of depressive and anxiety disorders. Given the long time elapsed between childhood trauma and adult psychopathology, we were not able to consider the multifaceted mediating mechanisms that occurred largely before the NESDA baseline wave. Long-term longitudinal studies are needed

to address the complex interplay between the family context, psychosocial resources, psychological and biological vulnerabilities that interact with childhood trauma throughout the transition to adulthood. The quality of the parent-child interaction should be studied in more detail, using parental bonding and attachment instruments (61-63). Adult survivors of childhood trauma continue to develop and experience beyond childhood and have an increased likelihood to be revictimized as adults. Therefore, longitudinal research on childhood trauma could benefit from taking adult life-events into account and exploring whether the effects of early adverse experiences are independent of continuing adversity proximal to the onset of psychopathology.

Long-term outcomes of exposure to childhood trauma depend on timing, type, and severity of exposure, plus a host of genetic factors that influence susceptibility and resilience. In a recent review, Teicher et al. proposed the term *ecophenotypes*: phenotypic expression of psychopathology (especially depressive and anxiety disorders) strongly influenced by exposure to childhood trauma (45). While these *ecophenotypes* fit within conventional diagnostic boundaries, they represent clinical and neurobiological distinct subtypes. For future research, the specifier "with childhood trauma" or "with maltreatment history" to depressive and anxiety disorders is recommended, so that these populations can be studied separately or stratified within samples (45). This will lead to a better understanding of differences in clinical presentation, course, treatment response, and outcomes. Our findings that childhood trauma is strongly associated with onset and course of depressive and anxiety disorders suggests that future studies should include randomized controlled trials that examine integrated treatment modalities to optimize treatment for this subtype of depressive and anxiety disorders.

General conclusion

The aim of this thesis was to investigate the effect of childhood trauma and childhood life-events on the development and course of depressive and anxiety disorders, and to identify risk factors contributing to these associations. In brief, our findings indicate that childhood trauma is an important risk factor for the development of depressive and/or anxiety disorders, especially depressive and comorbid disorders, and predicts a more chronic course of illness. Emotional neglect, as core component of childhood trauma, is of particular relevance and has a predominant and strong negative impact on onset and course of depressive and anxiety disorders. Our mediation analyses demonstrate the lifelong scarring through which childhood trauma may affect cognitive style, personality traits and ultimately psychopathology in adulthood. The findings of this thesis are keys to increased awareness of the negative impact of childhood trauma on psychosocial functioning, personality profile, and psychopathology. Based on our findings, recommendations for

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clinical practice and future research have been formulated. Beth Finkestein, former Executive Director of the New York Center for Children, recently summarized how we and the public can help raise awareness of everyday traumas and help minimize their long-term impact:
"It's so easy to feel hopeless in the face of tragedy, especially when children are concerned. Abuse, poverty, and violence can feel like insurmountable obstacles in our communities. Focusing our attention on the professionals on the front lines can increase their capacity to help the children affected by trauma. It can help our society as a whole to raise healthy, productive citizens who are not branded for the rest of their lives as victims. It can help us al." (Daily Beast of June 10, 2013).

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Nederlandse
samenvatting

Inleiding

"Traumatische gebeurtenissen uit de jeugd zijn niet verloren maar, als de voetafdrukken van het kind in natte cement, vaak levenslang bewaard. De tijd heelt geen wonden uit de kindertijd, tijd verbergt ze. Ze zijn niet verloren, ze zijn geïncorporeerd." - Vincent Felitti, 2010*

Jeugdtrauma

Volgens de Wereldgezondheidsorganisatie (WHO) wordt jeugdtrauma als volgt gedefinieerd: 'Elke vorm van verwaarlozing en/of bedreigende of gewelddadige interactie van emotionele, lichamelijke of seksuele aard die mogelijk lichamelijke of psychische schade veroorzaakt bij het kind en plaatsvindt in de context van een relatie gekenmerkt door afhankelijkheid, ver- trouwen en macht'. Jeugdtrauma wordt vaak onderverdeeld in vier domeinen: (1) emotioneel/ psychologisch misbruik, i.e. verbale agressie, chantage of het minderwaardig laten voelen van het kind; (2) lichamelijk misbruik, i.e. slaan, schoppen, vastbinden, opsluiten en/of ander lichamelijk geweld tegen een kind; (3) seksueel misbruik, oftewel elke handeling van seksuele aard tussen een minderjarige en een gezagdragende persoon tegen de wil van de minderjarige; en (4) verwaarlozing (emotioneel of lichamelijk), gekenmerkt door afwe- zigheid van aandacht, betrokkenheid, empathie en/of zorg voor basale levensbehoeften. Emotionele verwaarlozing en emotioneel misbruik zijn de meest voorkomende vormen van jeugdtrauma (23%), gevolgd door lichamelijk misbruik (tussen 5 en 16%) en seksueel misbruik (tussen 5 en 10%). Emotioneel en lichamelijk misbruik/verwaarlozing in de jeugd vindt vooral plaats binnen het gezin (in ongeveer 80% door de ouders), bij seksueel misbruik is vaker een dader buiten het gezin betrokken. Er bestaat een grote samenhang tussen de verschillende vormen van jeugdtrauma, waarbij emotionele verwaarlozing/misbruik ook wel beschouwd wordt als het kernelement van een negatieve gezinscontext, waarbinnen andere vormen van jeugdtrauma kunnen plaatsvinden. Tot op heden hebben de meeste studies zich gericht op de effecten van lichamelijk en seksueel misbruik, terwijl emotionele verwaarlozing en emotioneel misbruik de meest verborgen, ondergerapporteerde en minst bestudeerde vormen van jeugdtrauma zijn.

In alle studies in dit proefschrift wordt jeugdtrauma gemeten aan de hand van een interview afgenomen bij volwassenen (NEMESIS Trauma Interview). Daarnaast worden ook negatieve levensgebeurtenissen in de kindertijd (<16 jaar) uitgevraagd, zoals het overlijden van een ouder, echtscheiding van ouders of uithuisplaatsing. Het retrospectief, op volwassen leeftijd, vragen naar jeugdtrauma kan resulteren in een onderrapportage, omdat mensen bepaalde

* Voorwoord in: The Impact of Early Life Trauma on Health and Disease: The Hidden Epidemic. Lanius RA, Vermetten E, Pain C, eds. Cambridge University Press, 2010.

gebeurtenissen zijn vergeten (recall bias oftewel herinneringsvertekening) of omdat zij deze niet willen rapporteren (report bias). Een andere mogelijke vorm van bias is dat het geheugen van mensen beïnvloed wordt door hun emotionele toestand op het moment van de retrospectieve rapportage. Patiënten met een psychiatrische stoornis op het moment van rapportage, zouden eerder geneigd kunnen zijn ervaringen uit het verleden te bestempelen als jeugdtrauma om (onbewust) zo hun psychische toestand te verklaren. Voor deze selectieve rapportage is echter weinig bewijs gevonden.

Verwaarlozing en misbruik leidt, naast soms ernstig lichamelijk letsel, tot een breed scala aan psychosociale-, gedrags- en emotionele problemen en tot negatieve leerprestaties bij kinderen van alle leeftijden. Volwassenen met traumatische jeugdervaringen hebben een verhoogde kans op alle onderzochte psychiatrische stoornissen zoals stemmingsstoornissen, angststoornissen, verslavingsproblematiek, eetstoornissen, persoonlijkheidsstoornissen, dissociatieve stoornissen en psychose. Daarnaast is er ook enige evidentie dat jeugdtrauma gerelateerd is aan een ongezonde leefstijl, lichamelijke ziekten (hart en vaatziekten, obesitas en type 2 diabetes) en een kortere levensverwachting. Dit proefschrift beperkt zich tot de invloed van jeugdtrauma op depressieve en angststoornissen.

Depressieve en angststoornissen

Depressieve en angststoornissen zijn veel voorkomende ziektebeelden met een grote impact op het leven van patiënten en op de samenleving als geheel. De Wereldgezondheidsorganisatie (WHO) verwacht dat in 2030 depressie op de eerste plaats staat van ziekten met de hoogste ziektelast. In Nederland krijgt 20% van de bevolking in zijn of haar leven te maken met een depressieve en/of angststoornis. Deze aandoeningen komen in bijna de helft van de gevallen samen voor (dat wordt comorbiditeit genoemd). Comorbide depressieve en angststoornissen zijn ernstiger, leiden tot meer invaliditeit en een slechtere behandelrespons, en zijn geassocieerd met een hogere medische consumptie.

Sinds 1980 wordt in de psychiatrie wereldwijd gebruik gemaakt van het 'Diagnostic and Statistical Manual' (DSM), een classificatiesysteem om psychiatrische ziektebeelden te ordenen. Een depressieve stoornis wordt gekenmerkt door een sombere stemming en/of interesseverlies die langer dan twee weken aanhoudt. Daarnaast kan er sprake zijn van veranderingen in het slaap- en/of eetpatroon, geremde of juist opgejaagde bewegingen of gedachten, vermoeidheid, moeite met concentreren, besluiteloosheid, gevoelens van schuld en waardeloosheid en terugkerende gedachten aan de dood. Veel voorkomende angststoornissen zijn sociale fobie, paniekstoornis met of zonder agorafobie en de gegeneraliseerde angststoornis. Bij sociale fobie is iemand angstig om zich in sociale situaties op genante wijze te gedragen. Een paniekstoornis betekent het optreden van herhaalde en

onverwachte paniekaanvallen. Uit angst voor paniekaanvallen gaat een deel van deze mensen situaties vermijden die daartoe kunnen leiden (agorafobie oftewel 'pleinvrees'). De gegeneraliseerde angststoornis wordt gekenmerkt door het zich gedurende langere tijd buitensporig zorgen maken over allerlei alledaagse situaties.

Een diagnose van een depressieve of angststoornis is enkel gericht op het al dan niet voldoen aan een bepaald aantal criteria. Aangezien symptomen van depressie en angst bij iedereen in min of meerdere mate kunnen voorkomen, bieden diagnoses een beperkt inzicht in subtiele individuele verschillen. Een manier om deze verschillen in kaart te brengen is het registreren van de ernst (aantal en mate) van de depressieve of angstsymptomen aan de hand van ernst-vragenlijsten.

Relatie tussen jeugdtrauma en depresieve en angststoornissen

Het is bekend dat jeugdtrauma en/of negatieve levensgebeurtenissen in de kindertijd risicofactoren zijn voor het ontwikkelen en blijven voortbestaan van depressieve en angst-stoornissen (weliswaar minder onderzocht) op volwassen leeftijd. De meeste onderzoeken tot nu toe waren beperkt van omvang en vaak gericht op een bepaalde stoornis (bijv. een depressie) in relatie tot een beperkt aantal traumatische levensgebeurtenissen. Resultaten kunnen hierdoor vertekend zijn, aangezien depressie en angst vaak samen voorkomen en de verschillende trauma domeinen aanzienlijke overlap tonen (zoals emotionele verwaarlozing en lichamelijk misbruik). Bovendien maken de meeste studies gebruik van een cross-sectioneel design, waardoor er geen goede uitspraak gedaan kan worden over oorzakelijke verbanden. Het aantal prospectieve studies die inzicht geven in de relatie tussen jeugd-trauma en psychopathologie is beperkt, vaak uitgevoerd in niet-representatieve groepen (lage socio-economische status) en vaak zonder een controle groep (niet-getraumatiseerden). De samenhang tussen enerzijds traumatische gebeurtenissen in de jeugd en anderzijds psychopathologie op volwassen leeftijd is een complexe en dynamische wisselwerking tussen omgevingsfactoren en biologische - en psychologische karakteristieken van individuen in de tijd. In het verlengde hiervan ligt de vraagstelling "hoe jeugdtrauma leidt tot depressieve en angststoornissen op latere leeftijd". Tot op heden zijn de psychologische en biologische mechanismen die jeugdtrauma in verband brengen met de verhoogde kans op depressieve en angststoornissen complex en nog maar ten dele bekend.

Doel van dit proefschrift

Samenvattend waren de doelen van de studies opgenomen in dit proefschrift drieledig: (1) inzicht verkrijgen in de associaties tussen jeugdtrauma, ingrijpende gebeurtenissen in de jeugd en depressieve en angststoornissen op volwassen leeftijd, (2) in kaart brengen van de longitudinale associaties tussen jeugdtrauma en het beloop van depressieve en angst-stoornissen, en (3) bestuderen van de associaties tussen jeugdtrauma enerzijds en latere psychosociale kenmerken en persoonlijkheidsfactoren anderzijds en de potentiële invloed hiervan op de relatie tussen jeugdtrauma en het beloop van depressieve en angststoornissen. Onze onderzoeksresultaten zijn gebaseerd op gegevens uit de Nederlandse Studie naar Depressie en Angst (NESDA). Voor NESDA werden 2981 deelnemers (leeftijd tussen de 18 en 65 jaar), afkomstig uit de algemene bevolking, de 1e lijn en de geestelijke gezondheidszorg onderzocht. NESDA is een langlopende studie met als doel het beloop van depressieve en angststoornissen te onderzoeken en factoren die daaraan gerelateerd zijn beter in beeld te krijgen.

Belangrijkste bevindingen

In de eerste studie beschreven in dit proefschrift (**hoofdstuk 2**) bestudeerden wij *welke* vorm van jeugdtrauma en *welke* negatieve levensgebeurtenissen in de kindertijd samenhangen met *welke* psychiatrische stoornis (depressie of angst, of de combinatie) op volwassen leeftijd. We hebben dit onderzocht op basis van de eerste NESDA meting ('baseline') van 1931 deelnemers: 252 met een huidige angststoornis, 314 met een huidige depressieve stoornis en 845 met beiden (zowel een huidige angststoornis en een depressieve stoornis). Daarnaast was er een gezonde controle groep van 520 personen zonder voorgeschiedenis van een angst en/of depressieve stoornis. In deze studie vonden wij dat alle vormen van jeugdtrauma een risicofactor vormen voor het optreden van angst en/of depressieve stoornissen op volwassen leeftijd; het sterkste verband werd gevonden voor de mensen met zowel een angst *en* depressieve stoornis (comorbiditeit). Aangezien comorbiditeit is geassocieerd met meer en ernstiger symptomen, lijkt een jeugdtrauma vooral bij te dragen aan meer en ernstiger psychopathologie. Het verband met jeugdtrauma lijkt sterker voor depressie dan voor angst, in het bijzonder geldt dit voor emotionele verwaarlozing en emotioneel misbruik. Hoe vaker verwaarlozing en misbruik samen voorkwamen, des te sterker was het verband met het voorkomen van psychopathologie. Opvallend was dat, in tegenstelling tot jeugdtrauma, negatieve levensgebeurtenissen in de kindertijd geen rol speelden. De resultaten suggereren dat jeugdtrauma gekenmerkt door emotionele ver-waarlozing en/of psychologisch, lichamelijk en seksueel misbruik, de kwetsbaarheid voor het ontwikkelen van angst en depressieve stoornissen kunnen vergroten. Vooral bij mensen die lijden aan een combinatie van angst en depressie, is het belangrijk om na te gaan of er

sprake is van een jeugdtrauma in het verleden. Hierbij is met name emotionele verwaarlozing en psychologisch misbruik een aandachtspunt. Adequate interventies gericht op jeugdtrauma kunnen dan bijdragen tot een effectieve behandeling voor een subgroep van patiënten met angst en depressie.

De resultaten uit deze studie nuanceren bestaande (specificiteits) hypotheses die angststoornissen vooral relateren aan bedreigende ervaringen zoals lichamelijk en seksueel misbruik, en depressie vooral in verband brengen met emotionele verwaarlozing.

In **hoofdstuk 3** werd het belang van jeugdtrauma en negatieve levensgebeurtenissen in de kindertijd onderzocht in het kader van de chronische depressie. De resultaten uit deze studie zijn ook gebaseerd op de eerste NESDA meting. In deze studie werden 1230 patiënten met een depressieve stoornis onderzocht. Binnen deze groep werden chronisch depressieve patiënten met niet-chronisch depressieve patiënten vergeleken. Hieruit kwam naar voren dat chronisch depressieve patiënten vaker jeugdtrauma, zoals emotionele verwaarlozing en/of psychologisch, lichamelijk en seksueel misbruik, rapporteerden dan niet-chronisch depressieve patiënten. Verder bleek het aantal jeugdtraumata en de frequentie van de meegemaakte traumata van belang. Depressieve patiënten met meerdere en/of meer frequente jeugdtraumata, lijken een hoger risico op het ontwikkelen van een chronische depressie te hebben dan patiënten die geen of minder jeugdtraumata hebben meegemaakt. Dit verband bleef bestaan, ook nadat rekening gehouden werd met de klinische kenmerken van de chronische depressie (leeftijd waarop de depressie zich voor het eerst manifesteert, ernst, comorbiditeit met angst). Ook in deze studie hadden negatieve levensgebeurtenissen in de kindertijd, zoals het overlijden van ouders, het scheiden van ouders of uithuisplaatsing, geen effect op het optreden van chronische depressie op latere leeftijd. Deze bevindingen steunen de hypothese dat de kwaliteit van de ouder-kind relatie, de aan/afwezigheid van een betrokken en empathische (plaatsvervangende) ouder en de mate van conflict in het gezin, een belangrijker rol spelen dan de feitelijke negatieve levensgebeurtenissen in de kindertijd. Recente bevolkingsstudies in Nederland en de Verenigde Staten bevestigen dat het verlies van een ouder of echtscheiding van de ouders voor de leeftijd van 16 jaar niet geassocieerd is met een verhoogd risico op depressieve en/of angststoornissen.

In het volgende gedeelte van het proefschrift gebruikten wij naast de baseline meting ook de vervolgmetingen van NESDA. Hierdoor was het mogelijk om voorspellers van het ziektebeloop te onderzoeken. In **hoofdstuk 4** beschreven we het effect van jeugdtrauma en negatieve levensgebeurtenissen in de kindertijd op het beloop van depressieve en angststoornissen bij volwassenen. Hiervoor gebruikten we de data van 1209 patiënten met een angststoornis en/of depressieve stoornis bij de eerste meting. In een vervolgmeting na 2 jaar werd de aanwezigheid van een angst en/of depressieve stoornis opnieuw nagegaan met behulp van een gestandaardiseerd interview. Tevens werd gedurende deze periode van

2 jaar het beloop van hun stoornis onderzocht. Van deze patiënten had 18.4% tenminste één negatieve levensgebeurtenis in de kindertijd en had 57.8% één of meer van boven-genoemde jeugdtraumata meegemaakt. Negatieve levensgebeurtenissen in de kindertijd bleken niet het beloop van angst en depressie te voorspellen. Daarentegen waren emotionele verwaarlozing, psychologisch misbruik en lichamelijk misbruik geassocieerd met een verhoogde kans dat een depressieve stoornis of een angst en depressieve stoornis na 2 jaar nog steeds aanwezig was. Emotionele verwaarlozing en psychologisch misbruik waren ook geassocieerd met een meer chronisch beloop en recidiveren van klachten van angst en depressie na aanvankelijk herstel. De depressieve en angststoornissen van patiënten die jeugdtrauma rapporteerden werden vergeleken met die van patiënten zonder jeugdtrauma. Bij de groep met een jeugdtrauma werd bij de eerste ('baseline') meting vastgesteld dat de klachten op vroegere leeftijd waren ontstaan, langer duurden, en dat er sprake was van meer en ernstiger angst en/of depressieve symptomen en meer comorbiditeit. Deze klinische factoren bleken een sterke invloed te hebben op de relatie tussen jeugdtrauma en het ziektebeloop van de depressieve en angststoornissen. Deze bevindingen suggereren een oorzakelijk model, waarbij jeugdtrauma aan de basis van het ziekteproces staat en via meer en ernstiger symptomen uiteindelijk leidt tot een slechter ziektebeloop.
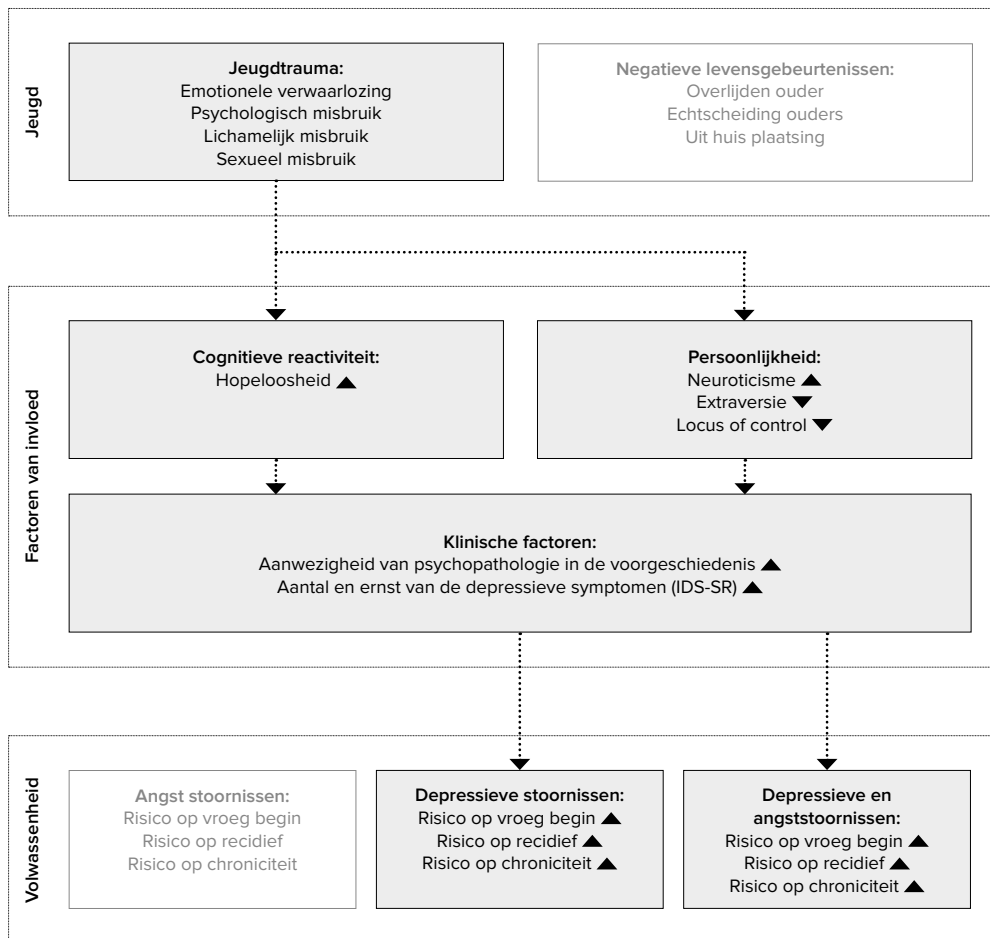
In **hoofdstuk 5** bestudeerden we ook het effect van jeugdtrauma en negatieve levens-gebeurtenissen in de kindertijd op het beloop van depressieve en angststoornissen bij volwassenen, maar dan vanuit een andere invalshoek. In deze studie beschreven we 1167 deelnemers, die bij de baseline meting geen depressieve en/of angststoornis hadden en gedurende een periode van 2 jaar gevolgd werden. Van hen had 48.7% ooit eerder in hun leven een depressieve en/of angststoornis gehad. Wij vonden dat een voorgeschiedenis van jeugdtrauma een belangrijke voorspeller was voor het optreden van zowel een 'eerste' als een 'recidief' depressieve en/of comorbide episode tijdens de 2-jarige follow-up. Hierbij maakte het geen verschil of de patiënten ooit (versus nooit) een eerdere episode hadden gehad voorafgaand aan de eerste (baseline) meting. Van alle trauma domeinen, bleek emotionele verwaarlozing de enige onafhankelijke voorspeller te zijn in multivariabele modellen. Deze bevinding impliceert dat emotionele verwaarlozing de meest cruciale rol speelt in de relatie tussen jeugdtrauma en depressie en angst op latere leeftijd. De relatie tussen jeugdtrauma en het optreden van een 'eerste', dan wel 'recidief' episode van depressieve en angststoornissen, bleek verder grotendeels af te hangen van de aanwezig-heid van meer en ernstiger angst of depressieve symptomen en/of de aanwezigheid van een eerdere angst of depressieve episode in de voorgeschiedenis. Onze bevindingen wijzen erop dat jeugdtrauma een belangrijke risicofactor is in de omgeving, die kwetsbaar maakt voor het optreden van nieuwe en recidiverende depressieve en comorbide episoden. Deze longitudinale resultaten kunnen bijdragen aan een beter inzicht in *hoe* jeugdtrauma kan leiden tot depressieve en angststoornissen bij volwassenen.

De laatste studie in dit proefschrift (**hoofdstuk 6**) beschrijft jeugdtrauma en het beloop van depressieve en angststoornissen in een bredere context. In deze studie hebben we gekeken naar het psychosociaal functioneren op volwassen leeftijd (in het kader van werk, inkomen, sociaal netwerk, partner/vrienden en negatieve levensgebeurtenissen) en de rol van psychologische kenmerken, zoals persoonlijkheid, cognitieve reactiviteit (i.e. de mate van dysfunctionele gedachten tijdens een sombere stemming) en 'locus of control' (i.e. mate van controle die iemand ervaart over de gebeurtenissen in zijn/haar leven). Een gangbare manier om persoonlijkheid in te delen is aan de hand van het Big Five model. Dit model gaat ervan uit dat persoonlijkheid bestaat uit vijf min of meer onafhankelijke dimensies, namelijk de mate van extraversie (versus introversie), openheid voor nieuwe ervaringen en ideeën, meegaandheid (versus competitiviteit), neuroticisme (versus emotionele stabiliteit) en consciëntieusheid (versus onverschilligheid). Iedereen heeft elk van deze vijf persoonlijkheidstrekken in een bepaalde mate, en de combinatie van deze vijf trekken bepaalt iemands karakter.

Blootstelling aan jeugdtrauma wordt in verband gebracht met een verstoorde hechting tussen ouder en kind, die kan leiden tot een ongunstige persoonlijkheidsontwikkeling en copingstijl (i.e., hoe omgegaan wordt met problemen en gebeurtenissen) en tot nadelige psychosociale omstandigheden op de volwassen leeftijd. In deze studie gebruikten we van 1474 patiënten, met een angststoornis en/of depressieve stoornis, de baseline meting en werd het beloop (met name de duur tot herstel) van hun psychiatrische ziekte tijdens een 4-jarige follow-up in kaart gebracht. Wij vonden dat jeugdtrauma, met name emotionele verwaarlozing en misbruik, een negatieve invloed had op het psychosociaal functioneren op volwassen leeftijd en het risico verhoogde op blootstelling aan later negatieve levensgebeurtenissen. Daarnaast was jeugdtrauma geassocieerd met een ongunstiger persoonlijkheidsprofiel. Uit de resultaten kwam naar voren dat patiënten met jeugdtrauma in de voorgeschiedenis, hoger scoorden op de domeinen neuroticisme, openheid, hopeloosheid, rumineren en externe 'locus of control' en lager scoorden op de domeinen extraversie, meegaandheid en consciëntieusheid, in vergelijking met de niet-getraumatiseerde patiënten. Het lijkt er daarom op dat bepaalde persoonlijkheidsdimensies een belangrijke rol spelen bij de relatie tussen jeugdtrauma en het ongunstige ziektebeloop van depressie en angst. Hoge scores op neuroticisme, hopeloosheid en externe 'locus of control' en lage extraversie scores hadden een belangrijk aandeel in het voorspellen van de relatie tussen jeugdtrauma en het ongunstige ziektebeloop. De bevindingen uit deze studie kunnen van belang zijn voor de klinische praktijk, met name bij de behandeling van deze prognostisch ongunstiger subgroep van depressieve en angststoornissen. Vroege interventies, gericht op het verminderen van neuroticisme en hopeloosheid en het versterken van extraversie en 'locus of control', kunnen de prognose van deze 'hoge risico' groep mogelijk verbeteren.

Algemene discussie

Dit proefschrift eindigt met een algemene discussie (**Hoofdstuk 7**), waarin de bevindingen van hoofdstukken 2 tot en met 6 worden besproken. Deze studies hebben tot nieuwe inzichten geleid in de onderlinge samenhang tussen jeugdtrauma en depressieve en angststoornissen. De bevindingen laten zien dat jeugdtrauma een belangrijke risicofactor is voor het ontwikkelen van depressieve en angststoornissen, met name voor depressieve en comorbide stoornissen, en een chronisch en prognostisch ongunstig ziektebeloop voorspelt. Emotionele verwaarlozing is een kernelement van jeugdtrauma, en heeft een overwegende en sterke negatieve invloed op het ontstaan en beloop van depressieve en angststoornissen op volwassen leeftijd. Daarnaast hebben we een aantal risicofactoren geïdentificeerd die individuen, blootgesteld aan jeugdtrauma, kwetsbaar maken voor het ontwikkelen van depressieve en angststoornissen op volwassen leeftijd. Deze risicofactoren spelen op hun beurt een cruciale rol in het ongunstiger ziektebeloop van depressieve en angststoornissen,

Jeugd	**Jeugdtrauma:** Emotionele verwaarlozing Psychologisch misbruik Lichamelijk misbruik Sexueel misbruik	Negatieve levensgebeurtenissen: Overlijden ouder Echtscheiding ouders Uit huis plaatsing

Factoren van invloed	**Cognitieve reactiviteit:** Hopeloosheid ▲	**Persoonlijkheid:** Neuroticisme ▲ Extraversie ▼ Locus of control ▼

Klinische factoren:
Aanwezigheid van psychopathologie in de voorgeschiedenis ▲
Aantal en ernst van de depressieve symptomen (IDS-SR) ▲

Volwassenheid	Angst stoornissen: Risico op vroeg begin Risico op recidief Risico op chroniciteit	**Depressieve stoornissen:** Risico op vroeg begin ▲ Risico op recidief ▲ Risico op chroniciteit ▲	**Depressieve en angststoornissen:** Risico op vroeg begin ▲ Risico op recidief ▲ Risico op chroniciteit ▲

bij patiënten met een jeugdtrauma in de voorgeschiedenis. Het onderliggend mechanisme van hoe jeugdtrauma leidt tot depressieve en angststoornissen op volwassen leeftijd, hebben we weergegeven in een schematisch overzicht (zie Figuur). In dit op onze resultaten gebaseerde verklaringsmodel wordt een oorzakelijk verband beschreven waarin: (a) blootstelling aan jeugdtrauma de persoonlijkheidsontwikkeling en copingsstrategieën beïnvloedt via een mechanisme van "litteken vorming", (b) dit een ongunstig persoonlijkheidsprofiel kan induceren, gekenmerkt door hoog neuroticisme, lage extraversie, een negatieve cognitieve stijl en externe 'locus of control', (c) een hoge mate van neuroticisme en maladaptieve depressieve cognities vervolgens kan leiden tot depressieve symptomen en uiteindelijk tot (d) syndromale depressieve en comorbide stoornissen met een chronisch beloop. Dit model benadrukt de relatie tussen jeugdtrauma en depressieve en angststoornissen op volwassen leeftijd via het mechanisme van de cognitieve kwetsbaarheid. Het is natuurlijk van belang om dit model te plaatsen in de context van eveneens aanwezige neurobiologische kwetsbaarheidsfactoren, die in dit proefschrift buiten beschouwing zijn gebleven.

Implicaties voor de klinische praktijk

De studies in dit proefschrift onderschrijven het belang van aandacht voor de mogelijke aanwezigheid van jeugdtrauma in het verleden, in het bijzonder bij een subgroep van patiënten met comorbide depressieve en angststoornissen en/of met een chronisch beloop. Expliciet en gedetailleerde navraag naar aanwezigheid van jeugdtrauma in de voorgeschiedenis moet onderdeel zijn van de diagnostische evaluatie van patiënten met angst en depressieve stoornissen en draagt bij aan de profilering van een prognostisch ongunstiger subgroep. Zo zou men tot een snellere identificatie van patiënten met een groot risico voor een slechter en chronischer beloop kunnen komen. Verder kan dit bijdragen tot een verfijning van de diagnostiek en behandeling voor de individuele patiënt. De standaard behandelingen volgens de richtlijnen voor depressieve en angststoornissen zijn ontoereikend voor deze subgroep van patiënten. Niet alleen moet er aandacht zijn voor de traumatische gebeurtenisssen in de jeugd, maar de behandeling moet zich ook richten op ontwikkelings-specifieke en relationele facetten. Hiermee refereren we aan de verstoring van de hechtingsrelatie, problemen met het zelfbeeld en met het vertrouwen van belangrijke anderen. (Psycho)therapeutische technieken zoals het verbeteren van de emotieregulerende vaardigheden en hechtingsstijlen en het vergroten van het probleemoplossend vermogen en de persoonlijke controle worden aanbevolen. De therapeutische benadering die uitgaat van 'empowerment' binnen de veiligheid van een therapeutische relatie, is essentieel voor deze patiënten met jeugdtrauma in de voorgeschiedenis. Het is verder belangrijk om nieuwe behandelmodules te exploreren die zijn gericht op de psychologische en biologische kwetsbaarheid van deze subgroep, en om deze te implementeren in toekomstige richtlijnen voor de behandeling van depressieve en angststoornissen.

Maatschappelijke implicaties

De resultaten in dit proefschrift benadrukken de link van jeugdtrauma met a) een verhoogd risico op het ontwikkelen van, en b) een ongunstig ziektebeloop van depressieve en angststoornissen. Vroegtijdige interventies gericht op het voorkomen van negatieve effecten van jeugdtrauma op volwassen leeftijd zijn aanbevelingswaardig. Aandacht voor vroegtijdige herkenning en signalering van jeugdtrauma is een belangrijke eerste stap in het kader van preventie. Hoewel emotionele verwaarlozing en emotioneel misbruik een groot maatschappelijk probleem vormen, zijn de schadelijke gevolgen hiervan voor het ontwikkelen van psychopathologie bij volwassenen lange tijd onvoldoende erkend en aanzienlijk ondergewaardeerd. Hulpverleners in de jeugdzorg zouden standaard moeten screenen op emotionele verwaarlozing en emotioneel misbruik naast lichamelijk en seksueel misbruik. In gezinnen met een hoog risico is tijdige detectie en het bieden van opvoedingsondersteuning van belang. Vroege detectie biedt de mogelijkheid om snel in te grijpen in het gezin en de duur en de ernst van (de gevolgen van) verwaarlozing/misbruik te beperken. Bovendien kunnen dan vroegtijdige interventies plaatsvinden die zijn gericht op het weerbaarder maken van het kind, zoals het verbeteren van zelfwaardering, emotionele stabiliteit en negatieve cognities. Kortom, toegenomen maatschappelijke bewustwording en kennis over de lange termijn gevolgen van jeugdtrauma, onder de algemene bevolking en onder professionals in de jeugd- en volwassen zorg zullen hopelijk leiden tot meer rapportage van verwaarlozing/misbruik onder jeugdigen en op termijn tot een afname van de prevalentie van jeugdtrauma.

Perspectieven voor toekomstig onderzoek

Een grote uitdaging voor de toekomst is het opzetten van lange termijn studies die aandacht besteden aan de complexe wisselwerking tussen de gezinscontext, de ouder-kind relatie, psychosociale bronnen en psychologische en biologische kwetsbaarheden, die allen interacteren met jeugdtrauma tijdens de transitie naar volwassenheid. Voor toekomstig onderzoek naar depressieve en angststoornissen, lijkt de parameter 'met jeugdtrauma' van belang om subtypes van depressieve en angststoornissen te onderscheiden, waardoor deze populaties gestratificeerd kunnen worden binnen een onderzoeksdesign. Daarnaast zou ook het soort jeugdtrauma nader gespecificeerd moeten worden. Hierdoor kunnen we meer inzicht verwerven in de verschillen in klinische presentatie, beloop en behandelrespons. Verder zijn gerandomiseerde gecontroleerde studies gericht op geïntegreerde behandelmodules van belang om de behandeling van deze subgroep te optimaliseren.

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Curriculum Vitae

Jacqueline Hovens werd op 2 augustus 1962 in Linne (Limburg) geboren. Na het behalen van haar VWO-B diploma aan de Rijksscholengemeenschap in Roermond, studeerde zij geneeskunde aan de Universiteit van Maastricht. Eind 1986 behaalde zij haar artsexamen. Aansluitend werkte zij als arts-assistent psychiatrie (AGNIO) in het Maaslandziekenhuis in Sittard. Vanaf 1988 volgde zij de opleiding psychiatrie in het Psychomedisch Centrum Vijverdal in Maastricht (opleider prof. M. Richartz). Van 1991 tot medio 1992 deed zij in het kader van haar opleiding psychiatrie een wetenschapsstage in de kinder- en jeugd-psychiatrie aan de David Geffen School of Medicine aan de Universiteit van Californië Los Angeles (UCLA) (opleider prof. Dennis Cantwell), met een SIR-beurs van NWO. Voor haar opleidingsjaar sociale psychiatrie kwam ze terug naar Nederland (RIAGG Eindhoven 1992-1993). Sinds augustus 1993 is zij BIG-geregistreerd als psychiater en psychotherapeut (psychoanalytisch georiënteerd). Van 1993 tot 1997 was ze opnieuw verbonden aan de Universiteit van Californië Los Angeles (UCLA), nu als fellow kinder- en jeugdpsychiatrie. In 1997 voltooide ze het artsexamen (USMLE) cum laude in de Verenigde Staten. Vanaf 1998 werkt ze als psychiater op de afdeling psychiatrie van het LUMC in Leiden, sinds 1999 als staflid. Ze is verantwoordelijk voor de psychiatrische consultatieve dienst en daarnaast actief op de polikliniek psychiatrie met als aandachtgebieden zieken-huispsychiatrie, transplantatiegeneeskunde, geneesmiddelenverslaving en zwangerschaps gerelateerde psychiatrie. Ze participeert in vele liaison activiteiten in het LUMC, ondermeer bij de HIV groep, spoedeisende hulp, transplantatie afdelingen, oncologie, psychosomatische gynaecologie en seksuologie. Verder is ze betrokken bij het onderwijs voor medisch studenten, bij de opleiding van de arts-assistenten psychiatrie en participeert ze in het onderwijs van diverse medisch specialistische opleidingen (oa interne geneeskunde, neurologie en spoedeisende geneeskunde) in het LUMC. In 2008 startte ze haar promotie-onderzoek binnen de Nederlandse Studie naar Depressie en Angst (NESDA), dat resulteerde in dit proefschrift.