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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 embarrassment (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.

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

Type of trauma: emotional abuse (EA) physical abuse (PA) sexual abuse (SA), emotional neglect (EN), physical neglect (PN), witnessing interpersonal violence (WV), significant 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 considered 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), number of perpetrators (Nop), duration (Dur), age of onset, of the trauma (Aoo) and the effects that trauma had on the victim (impact).


Interrater reliability kappa > 0.6 fair, kappa >0.8 substantial
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 cardiovascular 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-esteem (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 psychopathology, 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
Emotional Scars  Impact of childhood trauma on depressive and anxiety disorders

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 comingle 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.

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.
References

Chapter 1 General introduction and outline of the thesis


88. Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry 2007; 64:49-56.


