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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 comorbidity 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 diagnoses. 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
Chapter 7 Summary and general discussion

The 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.

<table>
<thead>
<tr>
<th></th>
<th>Psychological abuse</th>
<th>Physical abuse</th>
<th>Sexual Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional neglect</td>
<td>0.62 (P&lt;0.001)</td>
<td>0.43 (P&lt;0.001)</td>
<td>0.27 (P&lt;0.001)</td>
</tr>
<tr>
<td>Psychological abuse</td>
<td>0.56 (P&lt;0.001)</td>
<td>0.23 (P&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Physical abuse</td>
<td>0.27 (P&lt;0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are Spearman’s correlation coefficients.

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

<table>
<thead>
<tr>
<th></th>
<th>Early parental loss</th>
<th>Divorce parents</th>
<th>Placed in care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional neglect</td>
<td>0.04 (P=0.04)</td>
<td>0.15 (P&lt;0.001)</td>
<td>0.19 (P&lt;0.001)</td>
</tr>
<tr>
<td>Psychological abuse</td>
<td>0.03 (P=0.17)</td>
<td>0.15 (P&lt;0.001)</td>
<td>0.22 (P&lt;0.001)</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>0.03 (P=0.17)</td>
<td>0.09 (P&lt;0.001)</td>
<td>0.19 (P&lt;0.001)</td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>0.03 (P=0.17)</td>
<td>0.07 (P&lt;0.001)</td>
<td>0.13 (P&lt;0.001)</td>
</tr>
</tbody>
</table>

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.
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).
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
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
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.
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, overlooking 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.
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
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
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).
References