Summary and general discussion
The aim of this thesis was to further disentangle the association between childhood abuse and late-life depression. We had four research questions. First, we looked at the association between childhood abuse and two possible underlying biological mechanisms, namely HPA-axis and telomere length. Next, we investigated the role of chronic somatic diseases, psychosocial and lifestyle factors in the association between childhood abuse and, respectively, late-life depression and functional disabilities. Third, we were interested in the association between childhood abuse and the course of late-life depression. Fourth, we examined the test-retest reliability of the retrospective self-reports concerning childhood abuse in older adults.

This chapter will give a short overview of the main findings and will discuss the results per research question. Next, it will reflect on methodological considerations and the strengths and limitations of the studies. Finally, clinical implications of the findings will be discussed and future research suggestions will be made.

Findings per chapter

In chapter 2 and 3, we studied the association between childhood abuse and two biological mechanisms, namely HPA-axis functioning and telomere length, and its link with late-life depression. In chapter 2, we examined the association between childhood abuse and the hypothalamic-pituitary-adrenal (HPA)-axis, which is a biological stress system that was measured by cortisol levels in saliva during the day. We found that childhood abuse was associated with lower basal cortisol levels at awakening, irrespective of depression state. In addition, a higher reactivity of the HPA axis during the hour after awakening (elevated AUCi) was found in non-depressed older adults only. In the depressed group, this elevated peak after awakening was not found. The age at onset of depression had no major influence on these associations. Our findings suggest that older adults with a history of childhood abuse might be more negatively affected by stress or stressful events, which is reflected by dysregulations of the HPA axis.

Another biological mechanism that might be associated with childhood abuse is cellular aging, reflected by telomere length. Some studies among younger adults have shown that psychosocial stressors and higher risks on mental and somatic health problems are linked to shortened telomere length. In chapter 3, we examined the association between childhood adversity (childhood abuse, childhood adverse events) and recent psychosocial stressors (recent negative life events and loneliness) and telomere length in older adults. In our study, we found that childhood abuse, recent negative life events and loneliness were unrelated to telomere length in both depressed and non-depressed older adults. There was a significant, but weak, negative association with telomere length for having experienced any childhood adverse event. We concluded that there is no clear, consistent association between psychosocial stressors (early and later in life) and shortened telomeres in older adults. We assumed that in older adults other telomere length-damaging factors, such as physical health problems, might blur the putative influence of psychosocial stressors on telomere length.
In chapter 4 and 5, our goal was to investigate the effect of childhood abuse on early- and late-onset depression, as well as functional disabilities, and the role of depression characteristics, psychosocial factors, chronic somatic diseases and lifestyle factors. Therefore in chapter 4, we studied whether psychosocial factors, specifically partner status, social network size and feelings of loneliness, mediate the association between childhood abuse and both early-onset and late-onset depression. In particular, we were interested whether the strength of the mediation effect differed between early- and late-onset depression. Overall, we found that childhood abuse was significantly associated with early- as well as late-onset depression. Only for early-onset depression, a smaller social network and loneliness partly mediated this association. Loneliness appeared the strongest mediator, leading to a reduction of almost 25% of the direct effect between childhood abuse and early-onset depression. The mediation effects were strongest for emotional neglect and psychological abuse. No psychosocial mediators were found for the association between childhood abuse and late-onset depression.

Childhood abuse as well as depression has an effect on functional disabilities, such as mobility, self-care, household activities and participation in society. The question remained whether childhood abuse is associated with functional disabilities later in life, and which factors mediate this association. In chapter 5, we therefore examined the association between childhood abuse and functional disabilities in older adults, and whether depression, chronic somatic diseases and life style factors mediate this association. The results showed that older adults reporting childhood abuse had more functional disabilities compared to those adults that did not report a history of childhood abuse, irrespective of depression state. Furthermore, this association was fully explained by having more depressive symptoms, a younger age at depression onset and more chronic diseases. Lifestyle factors were no mediators in the association between childhood abuse and functional disabilities.

Longitudinal studies showed that childhood abuse is associated with chronicity of depression in younger adults. Later in life, depression often has a chronic course. However, no consensus exists on the impact of childhood abuse and the factors that explain chronicity of late-life depression. So, in chapter 6, we studied the course of late-life depression over a period of two years in older adults that provided information on the childhood trauma questionnaire. In addition, we examined several mediating variables, namely severity of depression, age at onset of depression, neuroticism, number of chronic diseases, and psychosocial factors such as loneliness and social network size. Our study showed that childhood abuse is strongly associated with a poorer course of late-life depression. This poorer course was explained by having more depressive symptoms at baseline, younger age at depression onset, higher levels of neuroticism and loneliness and more chronic diseases. This also implicates that childhood abuse has predominantly an indirect effect on the course of depression. These findings strengthen the general idea that childhood abuse negatively influences the course of
depression, even in late life. Especially depression severity seems an important predictive course factor.

Last, but not least, we wanted to validate our findings by examining the reliability of retrospective self-reports on childhood abuse in older adults. This is described in chapter 7. Since the use of retrospective reports, controversy exists on the reliability of acquired information on childhood abuse obtained in adulthood. Although reasons for under- or overreporting might even be more prominent in old age, no studies have been done in older adults. We investigated the test-retest reliability and agreement of retrospective reports on childhood abuse and the role of age, cognitive functioning and depression. Our results showed that most answers were consistent (yes-yes or no-no) on two separate interviews, varying from 85 to 94%. This was most stable concerning the no-answers, whereas yes-answers were more fluctuating. The test-retest reliability was moderate to good over time, but slightly dependent on the type of abuse. Of all types of childhood abuse, sexual abuse was most reliably reported in both confirmative (positive) answers and denying (negative) answers, whereas the reliability of positive answers on physical abuse was lowest. The consistency of the answers was not significantly influenced by age or cognition. Depression seemed to influence the answer consistency on emotional neglect, but importantly not the other types of childhood abuse.

Discussion per research question (RQ)

**RQ 1: What is the role of the HPA-axis and telomere length in the association between childhood abuse and late-life depression?**

In older adults, childhood abuse was associated with the stress response, reflected by the cortisol awakening response. On the other hand, we did not find an association with telomere length. In younger adults, more consistent associations were found with these two biological mechanisms. In previous studies in older adults, findings are more diverse and inconsistent, which might be due an accumulation of other factors that come with age, such as somatic diseases, comorbidity, medications, or frailty. These other factors could confound the true relationship. In addition, large differences between studies in sample characteristics, measurements and methods are noticed (e.g. Strüber et al., 2014) and raise difficulties when comparing our findings on biological mechanisms with current literature. Furthermore, studies on HPA-axis functioning and telomere length in older persons with a history of childhood abuse are limited. Initially, we only found one study in older adults from a population-based sample showing an association between childhood adversity (including abuse) and lower morning cortisol (Gerritsen et al., 2010). Our findings were in line with this study, since we also found lower morning cortisol, independent of depression state. In addition, we found a higher reactivity during the hour after awakening (AUCi), only in non-depressed older adults with a history of childhood abuse, especially psychological and sexual abuse. The cortisol awakening response in childhood abused older adults has not been studied yet, and findings in younger
adults vary from greater reactivity to reduced reaction to stressors (Heim et al., 2010; Strüber et al., 2014). Accelerated cellular aging, which is measured by telomere length, was also predominantly studied in younger adults, showing that psychosocial stressors, mental and somatic health problems can be linked to shortened telomere length (e.g. Verhoeven et al., 2015; Verhoeven et al., 2014; Epel et al., 2004). Due to ageing and its associated physical changes, this might be different in older adults. However, in older adults from NESDO, depression was unrelated to telomere length (Schaakxs et al., 2015). In our study, we also concluded that psychosocial stressors (childhood abuse, recent negative life events and loneliness) were unrelated to telomere length. Our explanation is that in older adults other telomere length-damaging factors might blur the putative influence of psychosocial stressors on its length, such as physical health problems (Price et al., 2013) or alternatively, that NESDO contains the more ‘physically healthy’ depressed older adults.

Recently, Nemeroff (2016) wrote a review on neurobiological and clinical consequences of childhood abuse, particularly in children and younger adults. He concluded that findings on HPA-axis functioning after childhood abuse were divergent and conflicting, predominantly showing it is a complex area. The complexity is probably due to other (confounding) factors, such as type and timing of childhood abuse, presence of psychosocial support and more recent traumatic events, family history of psychiatric disorders and (epi)genetic factors. Looking at conflicting results on telomere length between younger and older adults one could suggest also a complex interaction of these and other factors that might have a combined negative effect on telomere length. Overall, studies among younger adults showed that childhood abuse has a negative effect on neurobiological mechanisms and this is intertwined with many factors. Comparing our findings with these studies seems to imply that age does differentially affect biological mechanisms, and need to be disentangled per age group. At old age, neurobiological mechanisms may still be influenced by childhood abuse but it seems particularly important to investigate explaining, mediating factors.

In addition, independent of the growing literature on childhood abuse consequences, there is still paucity concerning other biological mechanisms, such as certain hormones, neuroanatomical changes in certain brain areas and in brain functioning (Nemeroff, 2016). Teicher et al. (2016) reviewed neuroimaging studies and found that there is a clear association between childhood abuse and changes in the brain, but that the link between these changes and psychopathology is complicated. This complements our studies, showing that childhood abuse negatively affects other biological mechanisms and that particularly the link between neurobiology and late-life depression could be complicated. In two reviews (Teicher et al., 2016; Teicher & Samson, 2016), they concluded that childhood abuse probably was an unrecognized confounder in psychiatric imaging studies since it affects brain development, even in ‘healthy’ adults with a history of childhood abuse. This was also suggested by Heim et al. (2010; 2008; 2004) who showed that many biological changes were characteristic for childhood abuse. Apart from the impact of childhood abuse on psychopathology, the literature lacks a comprehensive
overview of the consequences of childhood abuse over the life course. The increasing number of meta-analyses and reviews published in the last years expands our understanding in younger age groups, but also shows the importance of continuity and persistence in research to disentangle the impact of childhood abuse on neurobiological and other mechanisms later in life. Especially since childhood abuse and its neurobiological alterations seems to create increased vulnerability for a poorer health and, hence, suggests a window of opportunities for a preventive approach (McCrorly et al., 2017; Berens et al., 2017).

**Answer RQ1:** Later in life, childhood abuse is associated with dysregulation of the HPA-axis, but not with telomere length. The association between childhood abuse and dysregulation of the HPA-axis is independent from depression status.

**RQ 2:** What is the impact of childhood abuse on depression characteristics, psychosocial and lifestyle factors, chronic somatic diseases and functional disabilities later in life.

Cross-sectionally, we investigated the consequences of childhood abuse later in life on several important factors. Most clearly, childhood abuse has a strong influence on depression and its characteristics. Depression most often develops earlier in life and with more depressive symptoms, which has been predominantly found in younger adults (e.g. Bernet & Stein, 1999; Green et al., 2010; McLaughlin et al., 2012). Our studies were clearly in line with these findings. However, some people develop their first depression later in life, suggesting that they were able to stay mentally healthy until late life. We therefore wondered which factors mediate the association between childhood abuse and the onset of depression.

Adults with a history of childhood abuse more often have problems with psychosocial functioning (Horan & Widom, 2015; Pitzer & Fingerman, 2010), for instance their social networks are smaller and they more often feel lonely (Gibson & Hartshorne, 1996; Sperry & Widom, 2013; Wilson et al., 2006), and we hypothesized this could also be related to the onset of depression. We found that a smaller social network and feeling more lonely partly explained the association between childhood abuse and late-life depression; however, especially in early-onset and not in late-onset depression. So, psychosocial problems seem to be more important in depression with an onset at a younger age or a recurrent depressive episode. This might point at difficulties in developing social skills, long-lasting relationships and a strong social network. Therefore, early interventions should focus on developing better psychosocial functioning. Although results vary, even later in life interventions can improve psychosocial skills (Hagan et al., 2014; Masi et al., 2011).

Another factor that partly explained the onset of depression was the presence of chronic somatic diseases. Contrary to psychosocial factors it partly explained a late onset of depression (Comijs et al., 2013). In chapters 4 and 5, we showed that in older adults chronic somatic diseases often play a significant mediating role between childhood abuse and late-life depression, and functional disabilities. Chronic somatic diseases may be due to aging, but also
to long-term effects of an unhealthy lifestyle, which is also often associated with childhood abuse. Childhood abuse has been associated with lifestyle factors, such as smoking, obesity and risky behavior (Walker et al., 1999; Anda et al., 2006; Rehkopf et al., 2016). This seems particularly important at a younger age, since we did not find a mediation effect of lifestyle factors between childhood abuse and functional disabilities later in life. In our study, childhood abuse was not related to lifestyle factors. It might be that later in life the consequences of an unhealthy lifestyle become more important, such as more chronic somatic diseases, and explains why the presence of chronic somatic diseases was a significant mediator (chapters 4 and 5). At least we did find a significant association between certain lifestyle factors and functional disabilities later in life, meaning that it has an effect on daily life functioning. Furthermore, it could be that the sum of unhealthy lifestyle factors is more important than each separate lifestyle factor. Future longitudinal research is needed to explain the nature of this association.

As was earlier shown, childhood abuse as well as depression has an effect on functional disabilities (Walker et al., 1999; Chartier et al., 2007; Wegman and Stetler, 2009; van der Werff et al., 2010; Verhaak et al., 2014), particularly shown in younger adults. In older adults, we found that higher depression severity, younger age at depression onset and more chronic somatic diseases fully explained the association between childhood abuse and functional disabilities on domains such as cognition, mobility, household activities and participation in society (chapter 5). Functional disabilities are also related to depression and may increase the impact of childhood abuse on these two concepts, since the association between depression and functional disabilities seems reciprocal. Studies that have looked specifically into this association suggested a two-way association: depression has an effect on functional disabilities as well as the other way around (Ormel et al., 2002). This could explain why we found that depression was a significant mediator, and hints towards a vicious circle.

Answer RQ2: Childhood abuse is associated with an early age at depression onset and higher severity of late-life depression, an increased number of chronic somatic diseases and functional disabilities. Psychosocial factors are particularly associated with early-onset depression.

RQ 3: What effect has childhood abuse on the course of late-life depression?
In NESDO, the two-year course of late-life depression in older adults with a history of childhood abuse is significantly worse. This was fully explained by several factors, namely more depressive symptoms at baseline, younger age at depression onset, higher levels of loneliness and neuroticism and more chronic diseases (chapter 6). First of all, this indicates that childhood abuse particularly has an indirect, negative effect on the course of depression, even in late life. This is in line with other studies predominantly in younger adults (Wiersma et al., 2009a; Hovens et al., 2012; Rhebergen et al., 2011), leading to the conclusion that childhood abuse is
significantly associated with the course of depression, independent of age. Surprisingly, in contrast to previous studies, that have shown a dose-response relationship between frequency of childhood abuse and course of depression, especially in younger adults (Kessler et al., 1997; Green et al., 2010; Nanni et al., 2012; Norman et al., 2012), but also in older adults (Ege et al., 2014), we could not confirm this dose-response relationship. This could be due to the fact that just a few participants reported only a single childhood abuse event.

Most interesting were the mediating factors. Depression severity was the strongest factor associated with the course of depression in older adults with a history of childhood abuse. Also the age at depression onset was a significant mediator. A younger age at depression onset has been linked to more depressive symptoms, more depressive episodes and chronic depression (Bernet & Stein, 1999; Zisook et al., 2007; Rhebergen et al., 2012). So, this shows an important interplay between depression characteristics that are influenced by childhood abuse as well. Loneliness was also a significant explanatory factor for a poorer course of late-life depression. This concept consists of different aspects (e.g. van den Brink et al., 2018), such as having less contacts than one would prefer as well as feeling more emotionally isolated. At old age, it has been shown that childhood abuse more often led to smaller social networks and feeling more isolated (Wilson et al., 2006). In our study, only loneliness, not a smaller social network, influenced the course of depression and might be an important aspect to consider in treatment. Wilson et al. (2006) also found childhood abuse was related to neuroticism. We showed that neuroticism was another important mediating factor in the association between childhood abuse and a poor course of late-life depression. Other research in adults of 50 years and older also showed that neuroticism, particularly self-consciousness (shame and embarrassment), was more often reported by individuals with a history of childhood abuse and associated with more severe depressive symptoms (Gamble et al., 2006). Furthermore, this study showed that severe childhood abuse was related to higher levels of neuroticism and might explain why neuroticism only mediated between the association between the childhood abuse index and not the dichotomous childhood abuse variable, and the course of depression. In this study only the mediation effect of neuroticism was investigated. We did not consider other personality traits, particularly since earlier studies showed the strongest associations with neuroticism and diverse findings for extraversion, agreeableness, openness and conscientiousness (Moran et al., 2011; Hengartner et al., 2015). It has been suggested that cognitive styles (e.g. hopelessness) are important coping skills (e.g. Alloy et al., 1999). In younger adults, hopelessness was an important mediator between childhood abuse and a poor course of depression (Hovens et al., 2016). Neuroticism and cognitive styles have also been associated with each other (Hong & Paunonen, 2011). In old age, cognitive styles and its influence on coping skills and depression after childhood abuse could be interesting topics for future research. Lastly, a small, but significant, explanatory factor was the number of chronic somatic diseases. This is in line with earlier cross-sectional findings (chapters 4 and 5), and fits with a declining physical health later in life. Poor physical health was associated with a poor course of depression (Comijs et al., 2015) and has an effect on daily functioning (Ormel et al.,
Furthermore, there is overlap in depressive symptoms and symptoms of somatic diseases. At old age, it seems important to simultaneously focus on treatment for mental and physical health problems.

*Answer RQ3:* Childhood abuse has a strong negative effect on the course of late-life depression, but this association was fully explained by depression characteristics, loneliness, neuroticism and chronic somatic diseases.

**RQ 4:** How consistent are retrospective self-reports concerning childhood abuse in older adults?

Based on our findings on test-retest reliability of retrospective reports on childhood abuse, we conclude that these reports were sufficiently reliable, also later in life. Although studies in younger adults were somewhat cautious and careful in their conclusion, most of them concluded the same (e.g. Da Silva & Da Costa Maia, 2013; Naicker et al., 2017). Especially negative (no) answers were highly reliable in our study, while positive (yes) answers were more fluctuating. So, positive answers require more in-depth questioning such as specific examples of the abuse experiences to ensure reliable reports. This is in line with earlier suggestions by other researchers (Yancura & Aldwin, 2009; Hardt et al., 2006). Furthermore, we found (small) differences per type of abuse, where childhood sexual abuse was reported most reliably. Surprisingly, the positive (yes) answers for physical abuse were more fluctuating over time although, at first glance, it seems a more objective type of abuse. Since it was not influenced by depression or cognition, it remains unclear why participants answered differently on two interviews. Only the retrospective reports on childhood emotional neglect were influenced by depression. In 2015, Humphreys & Zeanah argued that it would be useful to distinguish research in two different types of childhood abuse, namely neglect and abuse. Our findings also seem to correspond with their suggestion to split childhood abuse into what they call inadequate (neglect) and harmful (physical abuse) input, experiences. In earlier studies, we did compare emotional neglect and psychological abuse (inadequate input) with physical and sexual abuse (harmful input) and did find different associations with depression (chapter 4). However, this is also a difficult methodological issue since most people experienced more than one type of childhood abuse leading to overlapping categories and distorted conclusions. Other components of childhood adversity in the assessment were shown to be important and could be missing in our study, e.g. financial situation, substance abuse by parents/caregivers, parental mental illness, exposure to criminal behavior (Kessler et al., 2010). However, these components could also be interrelated with the reported childhood neglect and abuse. Furthermore, the duration of the childhood abuse might be important with respect to the reliability of the assessment. Future research can be helpful to further explore this framework.
Answer RQ4: Retrospective reports on childhood abuse are sufficient reliable and largely consistent. To enhance its test-retest reliability, it is important to ask concrete and specific questions that can be completed with examples.

Overarching discussion points

Overall, several remarks need to be made. First, protective personality characteristics, such as resilience, mastery and coping style, were not included in this thesis. Although we included some factors that could be viewed as the inverse of positive coping and resiliency, it would still be an interesting point of view for future research. In a review, Meng et al. (2018) found 85 studies of low to middle quality that investigated resilience and protective factors after childhood abuse. Although protective factors and resilience were associated with better (health) outcomes, the authors accentuated that there was wide variation in measurements and outcomes which made it difficult to draw firm conclusions. In NESDO, unfortunately adequate measures on protective factors and resiliency are not available.

Next, previous research has shown that major depressive disorder can be a precursor (prelude, prodromal) for dementia. There is a strong association between late-life depression and dementia (Byers et al., 2011; Haigh et al., 2018). Since, older adults with a history of childhood abuse have a higher chance of developing a depression, their chances to develop dementia may also be higher. It is still unexplored territory, but would be an interesting topic. Attrition in NESDO was associated with the severity of depression and with worse cognition. This might indicate that the most severe cases fell out of the study. However, there was no difference in attrition rates between adults that reported childhood abuse and those who did not, except for physical abuse, which could also mean that a history of childhood abuse is not directly related to cognitive problems. At a younger age, childhood abuse seems to influence cognitive functioning (Sideli et al., 2014). In this study, they showed that childhood abuse was associated with poorer performance on tasks concerning working memory and executive functioning. In addition, childhood abuse is related to brain changes on several levels (Teicher et al., 2016), which might be related to cognitive deficits. So there might be an association between childhood abuse and cognitive function, also later in life. If childhood abuse is also associated with an increased risk on dementia remains to be investigated. Future (longitudinal) research could shed some light on this issue.

Finally, in the general population, the role of gender was an important factor that was suggested to cause differential risks for adult psychopathology after childhood trauma (Tiwari & Gonzalez, 2018). Indeed, Teicher et al. (2003) found gender differences due to childhood adverse experiences and suggested these could be related to the nature of these adverse experiences, and to brain and hormonal developments. Other studies also suggested sex differences related to a differential role of sex steroids in plasticity of brain regions (McEwen,
In a recent meta-analysis, Gallo et al. (2018) concluded that there were no statistically significant gender differences although the associations between childhood abuse and depression/anxiety were larger for women. In our studies, we did consider gender in the statistical analyses; however, odds ratios changed less than 10% in our sample. This suggests that in old age gender is less important in the association between childhood abuse and depression.

**Methodological strengths**

Concerning our studies, several strengths and limitations have to be considered. Major strength of all studies is the extensive assessment of childhood abuse that enquired information on four specific types of childhood abuse using concrete and specified operationalisations. This was shown to be important to get more veracious answers on this sensitive topic (e.g. Hardt et al., 2006; Yancura & Aldwin, 2009). Furthermore, it allowed us to use a categorical (‘yes-no’) as well as a dimensional variable considering childhood abuse and enabled a more thorough investigation. In addition, NESDO is a longitudinal cohort study, meaning that we had two-year and six-year follow-up data. Furthermore, NESDO consists of a large sample size of older adults with detailed information about formal DSM-IV diagnoses (APA, 2000) and related symptom questionnaires, as well as a wide array of (potential) explanatory factors and covariates. Consideration and possibility to incorporate multiple covariates in the statistical analyses allowed us to control for confounding effects, especially those that are important later in life.

**Methodological limitations**

Overall, there has been a lot of research concerning childhood abuse and its consequences in children, adolescents and younger adults (<60 years). It is however difficult to compare our results in older adults with those studies because there is a great variety of measurements and methods limiting the overarching conclusions. For example, some studies looked at one generic question on childhood abuse or adversity, while others considered specific types of childhood abuse or even broader childhood adversities (e.g. Gerritsen et al., 2010; Kessler et al., 2010). There were studies that also looked at the frequency or duration of childhood abuse (Schalinski et al., 2016). Some studies only considered retrospective reports, while others compared those with official records (e.g. Sperry & Widom, 2013). Although the general message is that childhood abuse has a large negative impact on mental health, uniformity in measures and methods seem essential to generate clear and unequivocal answers. Second, information was mostly gathered through retrospective reports in NESDO. Apart from our own study on test-retest reliability of childhood abuse, this concerns also reports about the age at onset. However, Toren et al. (2006) concluded in their study that age at disease onset was reliably and accurately reported with a 10-year interval in adults aged 18-60 years, indicating that we gathered reliable information. Third, studies showed that childhood abuse has also been related to post-traumatic stress disorder (PTSD); however, this information was not available in NESDO.
Furthermore, due to sample size and power issues we were not able to consider specific subtypes, course types or course trajectories of depression, such as atypical or melancholic depression (Lamers et al., 2010; Rhebergen et al., 2012). In addition, a mediation model applies stricter implicit rules to heighten its applicability (Preacher & Hayes, 2008) that, for instance, could lead to a reduced power by using smaller sample sizes. Sixth, in general, a larger amount of statistical tests could lead to type-I error. However, we did not perform a Bonferroni correction since this would have led to an increased chance of making a type-II error for all tests and would not have detected a real association (Perneger, 1998; Gelman et al., 2012). Seventh, the naturalistic design and the use of cross-sectional data in some studies in this thesis impede us to make causal inferences and study changes over time. Furthermore, detailed information on treatment was not available in NESDO. Therefore the impact of various treatment regimens on depressive symptoms in victims of childhood abuse could not be thoroughly examined. No firm conclusions can be drawn on important aspects concerning specific treatments. Last, our results came from a depressed sample of older adults, so no conclusions can be drawn for the general population. However, some results were independent of depression status, so it would be interesting to investigate the impact of childhood abuse in the general population.

**Clinical implications: diagnostics**

Childhood abuse affects daily life negatively, also later in life, so it requires clinical awareness. Most importantly, it requires skills of the clinician to enquire and detect childhood abuse. One might think only mental health clinicians need to be vigilant but it seems also important in other health areas (physical and public health). In addition, in older adults, it seems important to consider the overlapping symptoms of somatic health and depression, and its impact on functional disabilities. One aspect that needs to be emphasized is that when people answer positively ('yes') on questions concerning childhood abuse it requires more in-depth and concrete questioning to ensure the true nature of the childhood experiences. As was already suggested by Yancura & Aldwin (2009) and Hardt et al. (2006), specific and concrete questions heighten the reliability of the answers on personal, confidential issues. Also, independent of its reliability, the combination of late-life depression and positively answered questions about childhood abuse, could give some clues about the underlying causes for the diagnosis and the course of the (depressive) disorder. Childhood abuse is strongly associated with an early onset of depression and the symptoms are often more severe. It gives an indication of the prognosis and might help with treatment selection. However, childhood abuse is also associated with late onset depression, therefore in all cases, when older adults have a depression it is important to take childhood abuse into account during the diagnostic process and during the treatment.

**Clinical implications: treatment**

When someone has reported a history of childhood abuse, it is important to integrate this in treatment of current psychopathology. Nemeroff (2016) discussed that a history of childhood
abuse often leads to poorer response to (conventional) treatment, suggesting a distinct biological endophenotype for depression and childhood abuse, and should be taken into account to increase treatment effectiveness. In late-life, the treatment selection might be driven by several factors. First of all, it is and should be based on evidence-based guidelines for depression, suggesting pharmacotherapy and/or psychotherapy. A review showed that psychological interventions were effective treatments in late-life depression, although there were fewer studies on pharmacotherapy or combined treatment to draw firm conclusion (Cuijpers et al., 2014). Second, during treatment of depression childhood abuse needs to be taken into account. A study of Williams et al. (2016) showed that there was a poorer response to commonly prescribed antidepressants in adults with a history of childhood abuse, which also seems to depend on the timing of the abuse. This needs to be considered in the treatment selection. From our findings several other factors can be considered, such as psychosocial factors. As was described in chapter 4, we found that social network size and loneliness were partly explanatory of early-onset depression. The focus of treatment in this specific group could be on ways to reduce feelings of loneliness and increase the size of their social network. Furthermore and in line with Tunvirachaisakul et al. (2018), we found several baseline depression characteristics that have a prognostic value, such as age at depression onset and depression severity. A younger age at onset and more severe depression explained a poor course of depression in older adults with a history of childhood abuse. These factors can be assessed at the first contact and might be used as an indication for a more specialized, individualized treatment. It might even be considered to choose upfront for a treatment that has been effective in case of chronic depression such as Cognitive Behavioral Analysis System of Psychotherapy (CBASP; Wiersma et al., 2009b; McCullough, 2003). Next, in older adults, it seems important to consider chronic somatic diseases and its overlap with depression. In chapter 5, we also showed that depression as well as chronic somatic diseases explain increased functional disabilities in childhood abused older adults. Combined treatment for depression as well as chronic somatic diseases might be useful to reduce both diseases as well as functional disabilities in daily life. Availability and access to treatment, for example videoconferencing or blended treatments, can also be considered promising (Renn & Aréan, 2017; Hagan et al., 2014). Furthermore, if childhood abuse becomes the focus of treatment, it could be that the therapeutic relationship and specific relational experiences are important (Parry & Simpson, 2016). It would also be interesting to consider different treatments for childhood neglect versus childhood abuse. Humphreys & Zeanah (2015) suggested to split these forms of abuse based on the way of ‘input’, where neglect is considered as the absence of certain behaviour while abuse is related to the presence of (traumatic) behaviour. Studies on post-traumatic stress disorder (PTSD) considered different treatments for neglect versus abuse childhood experiences (Cloitre et al., 2012; Arntz et al., 2012), and might be interesting to consider in late-life depression as well.
**Clinical implications: prevention**

Childhood abuse is a major public health issue (e.g. Cuijpers et al., 2011), since it has a large negative impact over the life course. Predominantly, prevention strategies need to focus on children and their development (Garner et al., 2015). After childhood, other preventive strategies can be considered. As was mentioned earlier, childhood abuse is associated with a younger age at depression onset, and psychosocial functioning partly explained the earlier age of depression onset (chapter 4). So, prevention of late-life depression could focus on social skills, social network and loneliness. Creating new or maintaining existing social contacts can be helpful later in life. In addition, effective strategies have been found to decrease feelings of loneliness such as structured group interventions, experimental interventions using new technologies, focusing on new maladaptive social cognitions (Lang, 2001; Hagan et al., 2014; Masi et al., 2011).

**Future research**

Qualitative studies could be very informative and enhance knowledge of important but less quantifiable factors. This could consist of in-depth interviews on childhood abuse, coping strategies, mental health issues and resiliency. As was mentioned earlier, resiliency was missing in our study, but seems quite important (Meng et al., 2018). Qualitative studies might be particularly interesting for the mentally healthy adults with a history of childhood abuse. Related to that, a study in the general population could be helpful and might give more clues on differentiating factors between childhood abused adults with and without health issues. Currently, our sample consisted predominantly of depressed older adults, but it would have been interesting to study the effects of childhood abuse, independent of depression, e.g. study the association between childhood abuse and cognitive problems. Especially since some reviews suggest that current findings in psychiatry might have been confounded by the independent effect of childhood abuse (e.g. Teicher et al., 2016; Heim et al., 2008). This could mean that studies need to adjust for childhood abuse, but particularly implicates that more research is needed on the specific effects of childhood abuse. Furthermore, long-term prospective studies are needed to enable reliable life-course data, particularly life course developments and enabling comparison of younger and older adults. Although many studies focused on depression, Haigh et al. (2018) already showed that there is insufficient evidence of depressive symptom profiles over the life course; let alone, the impact of childhood abuse. It would be valuable to specify long-term course trajectories, as was already done in younger adults (Lamers et al., 2010; Rhebergen et al., 2012). In addition, as a future direction, it would be interesting to see which treatment is most effective for late-life depression in adults with a history of childhood abuse and what should be the primary focus of the treatment. So, evaluating the effectiveness of medication for this specific group of patients or a randomized-controlled trial comparing psychological treatments for depression with and without a primary focus on traumatic events would be interesting.
Concluding remarks

Childhood abuse affects a person's life with an enormous burden, also later in life: a higher risk of depression, a poorer course of depression, chronic somatic diseases and functional disabilities. As became clear in this thesis, it is truly important to enquire childhood adversities independent of timing and nature of the problem, especially when someone is presenting his or herself with mental health problems. In-depth questioning and empathic listening are key components when enquiring something so important and disastrous.

Mrs. de Jonge, 75 years old, was chronically depressed and got treatment from mental health care for a long period of time. Recently, she told a mental health care practitioner for the first time that she was sexually abused during her childhood. She wanted to know whether she could get some help with childhood memories that became more lively with increased care for her grandson. It took her a long time to be able to speak about her childhood experiences. Mrs. de Jonge had difficulty trusting people, and hence found it difficult to start talking about this topic. She was grateful that someone actively explored her childhood experiences with her.
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