Time after time: biological factors in the course of recurrent depression
Lok, A.

Citation for published version (APA):
Lok, A. (2013). Time after time: biological factors in the course of recurrent depression
General discussion

Summary, conclusions and general discussion

Lok A

Submitted to J of Psychotraumatology to be published.
In this chapter, the conclusions of our studies will be summarized and the findings will be discussed. Possible limitations and strengths of this thesis as well as the implications for future research will be addressed.

Summary
The primary focus of this dissertation was to increase the knowledge about possible biological factors and psychopathological mechanisms (including HPA/axis functioning, one-carbon and fatty-acid metabolism), as well as some gene-environment interactions for the course of recurrent MDD (MDD-R). Studying MDDR is important because there are indications that it represents a more biological and genetic determined MDD-subtype, which may be specifically linked to recurrence and CVD-risk. For this reason we expected these patients to deviate the strongest from healthy controls in the (patho)physiological and genetic mechanisms and to have more pronounced alterations in their course of MDD.

We considered two leading hypotheses that potentially could explain the underlying mechanism for the high risk for recurrence: (I) the vulnerability-accumulation or scarring hypothesis and (II) the premorbid vulnerability hypothesis. Our aim was to investigate specific premorbid factors (e.g. genetics, childhood trauma) that are present before MDD onset as well as the specific biological factors that could play a premorbid role and/or are involved in vulnerability-accumulation (‘scarring’). These biological variables were collected in different stadia in the course of MDD-R, i.e. the remitted phase, subsyndromal phase and acute depressive state.

Studies in this thesis are mostly based on data collected from the participants of the DELTA study: a well-defined high-risk population for relapse and recurrence as it includes exclusively remitted patients with at least two previous depressive episodes.
Research questions

This thesis consists of substudies conducted to answer the following questions regarding some pathophysiological mechanisms, which possibly influence the course of MDD-R:

1. What is the relation between recurrent depression, being overweight, and obesity in patients with MDD-R and is this relation explained or modified by use of antidepressant (AD) medication?

2a. In what ways does the HPA-axis functioning differ between MDD-R patients and healthy controls?

2b. Does this reflect a persistent trait or is this influenced by depressive state, stress or previous episodes, associated with recurrence?

2c. Can this relation be modulated by cognitive therapy?

3. Do HPA-axis measures predict time to recurrence in MDD-R patients?

4a. Do polyunsaturated fatty acid (PUFA) levels and the n-6/n-3 ratio differ between MDD-R patients compared to non-depressed controls?

4b. Are these possible alterations “state” dependent, or do they reflect a trait (i.e. are they independent of the current depressive status)?

5. What is the relationship of the Ala54Thr fatty acid-binding protein 2 (FABP2) polymorphism in MDD-R and are fatty acid concentrations associated with the CVD risk factor waist circumference?

6. What is the prevalence of the MTHFR polymorphism and its relationship with 1-C-cycle components in MDD-R patients compared to matched controls, and are the latter influenced by depressive state and/or AD use?

7. What is the relation between recurrent MDD patients carrying the T allele in the MTHFR gene with time to recurrence and is this relation associated with having been exposed to traumatic childhood events (TCE)?

8. What is the association between medically unexplained physical symptoms (MUPS) and time to recurrence in MDD-R and what is the association between MUPS and FA metabolism and MUPS and the serotonin transporter gene?

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Timeline figure DELTA with assessments
Summary of the results of the studies

Obesity

In chapter 2 (research question 1) we show that overweight and obesity were more prevalent in patients with MDD-R than in the reference group, although this was only statistically significant in women (74% of the sample). MDD-R patients using ADs (mostly SSRIs) continuously showed significantly more abdominal overweight and obesity than those using ADs intermittently or not at all. Compared with SSRIs, other types of ADs used (e.g. tricyclic ADs) did not have a significant impact on the anthropometric measures. However, we did find a small positive association between AD equivalent dosage and waist circumference and waist-to-hip ratio.

This was studied in MDD-R patients (n=134) and compared with reference data of BMI, waist-to-hip ratio and waist circumference, derived from the cross-sectional monitoring project on risk factors for chronic diseases (MORGEN project), a large Dutch population-based study of time trends on obesity prevalence rates.

A better understanding of the relationship between obesity and depression, and the beneficial and adverse effects of psychotropics on appetite, eating behavior, body weight and metabolism, may improve our ability to prevent and treat both obesity and depression. This supports the development of person-tailored interventions for MDDR including effective non-pharmaceu-tical preventive treatment and extra physical activities which may - as added benefit - protect against AD-induced weight gain.

HPA-axis

In chapter 3 (research question 2), we describe that MDD-R patients had higher cortisol concentrations than gender and -age matched controls. This did not change during new MDD-episodes during follow-up (3 months and 2 years). HPA-axis activity was not related to daily hassles or childhood life events. Interestingly, cortisol concentrations were lower in patients with more previous episodes, but were not associated with recurrence(s) during follow-up. Finally, randomly assigned cognitive therapy at study-entry enhanced cortisol declines over the day throughout the twoyear follow-up.

These results indicate that remitted MDD-R patients have a persistent trait of increased cortisol concentrations, irrespective of stress. In combination with the finding that patients’ cortisol concentrations do not change during new MDD-episodes (and thus do not represent epiphenomenal or state-effects), our results support that hypercortisolemia fulfills the state-independence criterion for an endophenotype for MDD-R.
Moreover, in this chapter (research question 3) we addressed the observation that lower mean morning cortisol levels predicted earlier time to recurrence over 5.5 year after correction for residual symptoms. Residual symptoms and childhood trauma slightly confounded the association between cortisol and recurrence. Lower cortisol levels were associated with having experienced traumatic childhood life events (42.3% in patients with lower cortisol versus 19.2% in patients with higher cortisol).

This study provides further support for the predictive role over 5.5 year of HPA axis dysregulation (i.e. lower morning cortisol levels) for recurrence in recurrently depressed patients. Childhood trauma was associated with having lower cortisol levels. This might have long-term consequences for dealing with (psychological) stress and dealing with the accompanying HPA-axis alterations.

Fatty acid metabolism
Chapter 4.1 (research question 4 a) first describes an explorative study in which we randomly selected patients from our total DELTA cohort. Homocysteine (tHcy) levels were measured together with saturated fatty acids (FAs), monounsaturated fatty acids (MUFAs) and polyunsaturated FAs (PUFAs) of the omega (N)-3, omega-6 and omega-9 series in plasma and erythrocytes. Compared to laboratory reference values our study sample showed lower levels in erythrocytes of C22: n-3, C22: 6 n-3, C24: 1 n-9 and C20: 3 n-9 and in plasma a decrease in C24: 1 n-9 and C20: 3 n-9. These differences were only statistically significant for the total of n-6 fatty acids and plasma tHcy. The fact that most patients in our sample were clinically recovered suggests that the FA alterations may represent a biological “trait” marker for MDD-R.

In chapter 4.2 (research question 4 a and b) we confirmed the results of chapter 4.1. using the results of a case-control study with 137 patients with MDD-R and 65 matched non-depressed controls. This study confirmed the results of our explorative pilot study. The most striking finding is that in both plasma and erythrocytes of patients with MDD-R the concentrations of most of the SFAs and MUFAs, and additionally erythrocyte PUFAs, all with a chain length of 20 carbon (C) atoms, were significantly lower than in the controls. In contrast, the concentrations of most of the shorter chain members (18C) of the SFAs and MUFAs were significantly higher in patients. Estimated activities of several elongases in plasma of patients were significantly altered, whereas delta-9 desaturase activity for C14:0 and C18:0 was significantly higher.

The fatty acid status of patients with MDD-R not only differed with regard to omega-3 and omega-6 PUFAs, but this was also the case for other fatty acids. The alterations observed may be
due to differences in diet, changes in synthesizing enzyme activities or higher levels of chronic (oxidative) stress. However, these alterations may also be the result of adaptive strategies by providing protection against enhanced oxidative stress and production of free radicals.

In chapter 4.3 (research question 5) we investigated whether the Thr54-polymorphism in the \textit{FABP2}-gene: (I) was more prevalent in MDD-R patients than in sex- and age-matched controls, (II) was associated with observed alterations in FA-metabolism, and (III) was associated with the CVD-risk factor waist circumference. \textit{FABP2}-genotype distribution did not significantly differ between the 137 MDD-patients and 73 matched controls. However, patients with the Ala54Thr-polymorphism had higher concentrations of especially eicosadienoic acid and other 20-carbon FAs, and was associated with lower waist circumference. In addition, \textit{FABP2}-genotype effects on waist circumference in patients seemed mediated by its effect on C20:2 n-6, and different from controls.

Although Ala54Thr-polymorphism distribution was not associated with MDD-R, our results indicated that \textit{FABP2} may play a role in the explanation of observed FA-alterations in MDD. For patients with the Ala54Thr-polymorphism, potentially adaptive conversion of increased bio-available dietary precursors into eicosadienoic acid instead of arachidonic acid might be related to a low waist circumference.

One Carbon metabolism

In chapter 5 (research question 6), we studied the genetic variation in the enzymes of the one-carbon (1-C)-metabolism and integratively investigated key 1-C-components (folate, homocysteine, vitamin B6 and B12), while including the possible effects of antidepressant medication and depressive state to gain more insight in the possible association between the \textit{MTHF}-polymorphism and MDD-R. We compared the \textit{MTHFR} C677T-polymorphism together with the key 1-C-components in clinically ascertained patients with MDD-R (n=137) to age- and gender-matched healthy controls (n=73). Despite our specific recurrently depressed patient population, we found no clear associations with the 1-C-cycle, except for higher homocysteine and lower vitamin B6 during the depressed state. This suggests that 1-C-cycle alterations in MDD-R are state-dependent, possibly resulting from high levels of acute (psychological) stress. Stress reduction may be a treatment target to lower cardiovascular risk in this population.

In chapter 5 (research question 7) we also showed that the relation between the C677T \textit{MTHFR} variant and depression recurrence, over a 5.5-year follow-up, was modified by previous
exposure to traumatic childhood events (TCEs) in a clinical sample of 124 patients with MDD-R. This finding was supported by the fact that in an independent replication sample of 665 healthy individuals from the general population the relation between the C677T MTHFR variant and self-reported depressive symptoms was also modified by TCEs. In summary: T-allele carriers exposed to childhood trauma may be at increased risk for depressive symptoms or MDD recurrence.

Medically unexplained physical symptoms
In chapter 6 (research question 8), we show that medically unexplained physical symptoms (MUPS) are a risk factor for recurrence in recurrent depression over 3.5 years. The relation between MUPS and recurrence of depression could not be explained by an association between sustained high level of MUPS and omega (ω)-3 and −6 fatty acid (FA)-status and/or functional polymorphisms in the promoter region of the serotonin transporter gene (5-HTTLPR). We conclude that recognition and reduction of MUPS within this subsample of patients in an early state could prevent a (depressive) relapse.

General discussion
MDD is a heterogeneous disorder with a highly variable and recurrent course, an inconsistent response to treatment, and so far no established (biological) mechanism. When taking into account the recurrences of MDD, it is a challenge to understand dynamic changes in psychobiological systems over time and investigating different biological systems in the course of MDD. During the time-period in which the studies that contributed to this thesis were conducted, many manuscripts in the field of metabolic and biological factors in the course of MDD have been published. This stipulates the importance of stress-related factors in particular, which has led to a growing awareness that this topic may be considered as an important research and clinical focus.

Epidemiologic findings point to an association between MDD and increased cardiovascular morbidity and mortality. In many patients, cardiovascular disorders precede depression, but in others, depression precedes the cardiovascular disorder. Both n−3 fatty acid deficiency and elevated plasma homocysteine levels have been implicated in cardiovascular disease (CVD) and in MDD. Elevated cortisol levels in depression might increase the risk of CVD, given that cortisol increases visceral fat.

So, among the pathophysiological systems that may play a role in the etiology of MDD and its recurrent nature are the hypothalamic-pituitary-adrenal (HPA) axis and some metabolic abnor-
malities. HPA-axis hyperactivity has been demonstrated in depressed persons compared with controls, and has been further implicated as a potential mechanism through which depression increases the risk of CVD and other somatic diseases. Related to this, other metabolic abnormalities such as obesity and adverse lipoprotein patterns are also associated with MDD and several studies reported an association between MDD and the metabolic syndrome, a cluster of risk factors for type 2 diabetes mellitus and CVD.

In this thesis, we simultaneously assessed these biological factors (HPA-axis functioning, fatty acid metabolism and the 1-C cycle components) in a population with recurrent MDD. We considered two hypotheses presented in the introduction to explain the high risk for recurrence: (I) the vulnerability-accumulation or scarring hypothesis and (II) the premorbid vulnerability hypothesis. We did so by investigating premorbid factors (e.g. genetics, childhood trauma), which are present before MDD onset, as well as biological factors that can play a premorbid role and/or are involved in vulnerability-accumulation (‘scarring’).

Although the results of our studies could not yield a clear direction to either one of the two hypotheses, they both showed an effect of premorbid and scarring factors in the course of recurrence in our MDD patients. In addition, we found some evidence for a premorbid (genetic) vulnerability in the FA and 1-C metabolism, suggesting a premorbid vulnerability for CVD-risk and MDD. Furthermore, we found (biological) stress vulnerability factors, e.g. a persistent trait of increased cortisol concentrations and 1-C alterations. These metabolic alterations, possibly in combination with a changed lifestyle, were associated with a worse course of MDD-R. When integrating the findings concerning these pathophysiological mechanisms (HPA-axis, FA and 1-C metabolism), a common pattern of specific biological alterations emerges in MDD-R patients. In this discussion we choose to zoom in on two specific topics, namely the concept of oxidative stress and the effects of childhood trauma.

Oxidative stress
We argue that oxidative stress - defined as an imbalance between production and inactivation of reactive oxygen species (ROS) - may play a fundamental role in the pathogenesis of both MDD and CVD, and so may function as their common denominator. Oxidative stress is associated with alterations in the intrinsically linked FA-metabolism and 1-C-cycle. Both are essential for adequate neurocognitive functioning and mood regulation, as well as a proper functioning of the cardiovascular system.
Altered FA-metabolism has been consistently reported in MDD\textsuperscript{11, 12, 13}, both in acutely depressed and remitted patients\textsuperscript{11}. The main findings, also in our studies, are lower concentrations of n-3 long chain polyunsaturated fatty acids (LCPUFA) [e.g. eicosapentaenoic acid (C20:5 n-3; EPA) and docosahexaenoic acid (C20:6 n-3; DHA)]\textsuperscript{11, 12}, and decreased overall FA unsaturation, chain length and peroxidizability\textsuperscript{14}. FAs together with their (non)enzymatic peroxidation products may very well explain (part of) the overlap of the clinical picture between CVD-risk factors and MDD.

To understand the effects of oxidative stress on FA- metabolism, we suggest that the 1-C-cycle plays an essential integrating role in modulating the effects of oxidative stress on FA-metabolism. The 1-C-cycle shifts away from the methylation pathway and production of methylgroups needed for PUFA- production, neurotransmitters, and DNA-methylation, to the transsulfuration-pathway resulting in synthesis of the major intracellular antioxidant glutathione.

Increased oxidative stress may be intrinsically involved in the shared disposition for both MDD and CVD. Increasingly, evidence indicates that disturbances of the antioxidant defense system and presence of oxidative stress may play a role in the biochemical mechanisms underlying psychiatric disorders, e.g. MDD\textsuperscript{15, 16}. It is likely that the proposed mechanism also occurs at the level of the neuronal membrane, which is the site of neurotransmitter receptors, ion channels, signal transduction, and drug effects. Biological systems have evolved complex protective strategies against free radical toxicity. Under physiological conditions the potential for free radical-mediated damage is kept in check by the antioxidant defense system, which is comprised of a series of enzymatic and non-enzymatic components\textsuperscript{16}.

In short, oxidative stress is a state of dysequilibrium between pro-oxidant processes and the antioxidant defense system in favor of the former. Since the role for toxic radicals in the etiology of schizophrenia was proposed in the 50s\textsuperscript{17}, there are several studies linking free radical mechanisms to the pathophysiology of psychiatric disorders.

Recently, MDD was shown to be related to lower plasma concentrations of several key antioxidants, such as vitamin E, zinc and coenzyme Q10, as well as lower antioxidant enzyme activity\textsuperscript{18}. These deficiencies in antioxidant defenses impair protection against reactive oxygen species (ROS), and lead to damage of fatty acids, proteins and DNA. Moreover, there is an association between depression and polymorphisms in genes involved in oxidative pathways, affecting enzymatic activity\textsuperscript{18}. Taken together, this suggest a role of free radicals and antioxidants in the pathophysiology of (recurrent) MDD.
Both heritable genetic factors and environmental factors including dietary fatty-acid composition may act in concert to sustain elevated immune-inflammatory signaling. Converging translational evidence has shown elevated immune-inflammatory signaling activity in the pathophysiology of mood disorders, including MDD, and even suggesting different MDD-subtypes (e.g. inflammatory and metabolic dysregulation associated with atypical depression).

Long term effects of Childhood Trauma

Our data suggest that exposure to traumatic events during childhood (TCE) influences or changes the regulation of the HPA-axis. We found an indication that childhood trauma slightly confounded the prediction of recurrence by mean morning cortisol. In our other study, we found that CLEs, not specified as trauma, did not explain the observed hypercortisolemic trait. Finally, our study showed that MDD patients with a childhood trauma history and carriers of the thermolabile variant of the MTHFR gene constitute a subgroup of patients that had a worse course of recurrence. These biological alterations may in turn be a vulnerability factor for the onset of MDD-R itself. Our findings indicate that childhood trauma contributes to the risk on recurrences of MDD. The effect of environmental factors on the course of MDD, and childhood trauma in particular, is in line with a recent meta-analysis and a study by Peyrot et al.

The experience of traumatic events in childhood may have a crucial role on the HPA-axis, in dealing with stress, and subsequently, in onset and course of depression (chronicity). Childhood traumas have been reported before as an independent determinant of chronicity of depression. This is in line with our finding that lower cortisol levels within this patient group were associated with having experienced more traumatic life events in childhood. Lower cortisol levels were also predictive of prospective recurrence (42.3% of the patients with lower cortisol experienced traumatic life events while 19.2% experienced childhood trauma in patients with higher cortisol). Treadway et al. suggest that chronic stress subsequent to childhood maltreatment may initiate glucocorticoid-related injury to the anterior cingulate cortex. This damage may impair cortico-limbic circuits involved in emotion regulation.

Carpenter and colleagues reported that especially emotional childhood abuse might dampen cortisol reactivity and that this effect is cumulative overtime, as was shown in a study amongst 230 adults without major Axis I Disorders that completed the Dex/CRH test. Unfortunately, we do not have data on emotional abuse in childhood to examine this hypothesis. However, we did indeed find an indication that childhood trauma in general (such as sexual abuse) slightly confounded the prediction of recurrence by mean morning cortisol. Our finding that CLEs, not
specified as trauma, did not explain the observed hypercortisolemic trait, is in line with previous literature 26.

Childhood trauma may be conceptualized as a developmental risk factor triggering a chain of risks such as subsequent depressive episodes that might progressively potentiate the vulnerability to poor course of illness 27. In order to understand the origins of this chain of risks, future studies should explore the cognitive and biological correlates of trauma in childhood before the accumulation of MDEs 28.

Furthermore, it is important to characterize the gene-environment interplay underlying the effects of childhood trauma on MDD outcomes. Childhood trauma may be conceptualized as an environmental risk factor for poor MDD course and a moderator of treatment outcome, complementing the emerging genetic markers of vulnerability to recurrent depression 29 and poor treatment response 30.

The experience of a traumatic event during childhood may disrupt major beliefs regarding personal invulnerability, benevolence of the world, meaning, self-worth, and relations with others. An individual may feel vigilant, depressed, powerless, vulnerable or guilty about not being able to change the situation, and these feelings may color the way the individual sees the world. This may increase vulnerability for psychiatric disorders such as MDD. The association of childhood trauma with MDD in adulthood could be due to common factors linking family perpetrators of abuse and their victims, including not only shared genes but also a shared environment (e.g. poverty, poor nutrition and poor prenatal care) 31. Moreover, Nederoff & Schmidt 32 propose that individual differences in sensitivity to early programming in combination with the environments encountered during sensitive periods determine whether the cumulative stress hypothesis (disease risk increases as adversity accumulates) or the mismatch hypothesis (a stressful childhood leads to developmental changes to prepare for a stressful adulthood) is more applicable.

Clinical relevance
What are the consequences of our findings for clinical practice? Knowledge of specific predictors and underlying mechanism(s) of MDD recurrences is essential for making treatment decisions. About half of the patients with MDD in mental health care have recurrences and the risk increases with higher (HRSD>10) inter-episodic symptomatology 33. It is important to closely monitor these high-risk patients for relapse, for instance by using mobile devices that are users friendly for daily life (such as mobile phones, Apps 34).
Long-term use of antidepressants is recommended for patients that remitted with antidepressants by leading international guidelines for recurrently depressed patients. However, a recent meta-analysis demonstrated that with an increasing number of episodes a relative resistance against the protective effect of antidepressant medication is developed.

Several meta-analyses demonstrated that psychological interventions applied in the acute phase of the depressive episode, have an enduring effect after remission. In addition, rather than a relative resistance with increasing numbers of episodes, an increasing protective effect is found for psychological interventions, including MBCT.

Recent studies indicate that psychological preventive interventions might be an alternative strategy for long-term use of antidepressants for this recurrent patient group as first studies already indicate. However, further large-scale studies are needed to validate this positive effect of psychological interventions as an alternative for antidepressant maintenance treatment.

A sequential approach in which a brief psychological intervention (i.e. Preventive Cognitive Therapy, Maintenance Cognitive Therapy, and Mindfulness based Cognitive therapy) is started after recovery on other treatment (including AD treatment) is effective in preventing recurrence as demonstrated by several meta-analyses, especially for patients with MDD-R. Presently, relapse rates are still (too) high. To reduce recurrence rates in MDD, a personalized medicine approach using specific markers, including clinical, genetic, biological and psychological markers, might help us to examine which preventive strategy works for whom at what stage. A potential target for relapse prevention is the ability to better handle or cope with recurrent stressors and daily hassles.

Additionally, development and evaluation of new interventions specifically focused on the subsample of these patients with MUPS might also improve outcome over time. Especially an intervention that focuses on the ability to notice, but not over-react to MUPS and its negative bodily sensations and experiences, might be promising. More empirical evidence in support of these potential strategies is needed, however, before firm conclusions may be drawn.

The larger part of the variance in recurrence remains unexplained. This makes more and prospective research needed to better identify (biological) predictors play a role in recurrences.
It could also be useful to apply different outcome variables (severity, time between recurrences, number of recurrences) because different factors could predict different outcomes. Moreover, as a result, recurrence of MDD remains difficult to predict and stays a complex and only partially understood phenomenon.

Treatment of the high-risk MDD-R group should aim for the reduction of biopsychosocial risk factors for recurrence. This approach has been successful in other disciplines in medicine. For example, in our intention to treat analysis, CT had an effect of steeper cortisol declines over the day throughout the 2-year follow-up. The mechanisms underlying the observed effect of CT on the HPA-axis are not elucidated yet. It could be hypothesized that the preventive CT changes coping strategies, e.g. stress perception, management of stress and generation of subsequent stress. These effects could mediate its recurrence-preventive effects. As this evidence accumulates it may be possible to design more effective and efficient models of relapse prevention, to reduce the burden that MDD-R places on those who are affected.

MDD-R patients with early trauma and specific psychotherapies
This section focuses on two, in our opinion, important topics of clinical relevance: (I) patients that premorbid experienced factor Childhood Trauma and (II) interventions targeting the 1-C cycle and thereby lowering CVD-risk.

A meta-analysis including epidemiological studies demonstrates that maltreated individuals were twice as likely as those without a history of childhood maltreatment to develop both recurrent and persistent depressive episodes. The results from clinical trials corroborated these epidemiological observations. Further, compared with depressed individuals without a history of childhood maltreatment, depressed and maltreated individuals appeared to benefit less from treatment (and particularly from combined treatment), thereby incurring greater risk of recurrent and persistent depressive episodes.

Our results suggest a subgroup of patients for whom interventions should focus on both MDD recurrence and the consequences of childhood trauma. The gene-environment interaction we found in two independent samples suggests benefit from the integration of two types of therapeutic approaches. Psychotherapeutic interventions specifically aimed at the consequences of childhood trauma while there is no PTSD (including psychotherapeutic treatment of trauma related problems), which could be combined with interventions aimed at the 1-C cycle.
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Information about a history of childhood trauma and maltreatment helps to identify individuals who are at high risk of developing a recurrent and persistent subtype of depression and those who will respond poorly to current treatments. Clinicians may consider that the routine inquiry about childhood maltreatment is not harmful and could add important prognostic information to their assessment. Clinicians may also consider more intensive and alternative treatment options for recurrent MDD individuals with a history of childhood trauma.

The meta-analytical evidence that maltreated and depressed individuals have a poor response to combined treatment with structured psychological therapy and antidepressant medications indicates that simply combining these two common options is not sufficient. It is important to consider exploring the response of maltreated and depressed individuals to new treatments targeting the biological vulnerabilities described in this subgroup.

Interventions aimed at reducing childhood maltreatment could help to reduce the large health and economic burden linked to poor MDD course. Childhood years are thought to be a sensitive developmental window for the maturation of emotion regulation. Therefore, early preventive and therapeutic interventions (even in childhood or adolescence) may be more effective (and cost-effective) in preventing a poor longitudinal recurrent course of MDD than interventions at later ages, when harmful developmental trajectories have already been established.

Interventions aimed at the 1-C cycle, and lowering CVD-risk

In patients with recurrent MDD, their cardiometabolic risk factors and MetS status should be carefully monitored, and proper treatment and lifestyle changes could be advised if the patients are at a higher risk of diabetes/CVD.

( Oxidative) stress may be mitigating by improving anti-oxidant defenses through dietary modification and (add-on) exercise. MDD is commonly associated with lower levels of physical activity. While data derived from epidemiological and correlational studies do not necessarily confirm causation, a consistent relationship does exist across a number of populations. In adults, an active lifestyle was associated with reduced depressive symptoms independent of education and physical health status. In overweight/obese adults, a reduced risk of MDD was associated with increasing moderate-to-vigorous-intensity physical activity and decreasing sedentary time. Another study using data from over 4,000 men and women aged 20 years or older confirmed that adults with depression spent significantly less time both in light and moderate physical activity than non-depressed adults. In a longitudinal study of over
9000 people, regular physical activity was associated with a reduced likelihood of depressive symptoms at follow-up 55.

The efficacy of exercise as a treatment for MDD is summarized in a lot of recent reviews. In a meta-analysis on supervised and unsupervised physical activity interventions among healthy adults, Conn 56 concluded that physical activity interventions had a moderate inhibitory effect on depressive symptoms in adults with and without clinical depression. Carek et al. 57 concluded from a review of the literature that exercise compared favorably to AD medications as a first-line treatment for mild-to-moderate depression and also improved depressive symptoms when used as an adjunct to medications. Similar antidepressant effects were also found in trials comparing exercise with cognitive-behavioral therapy 58. Despite these positive findings there is a paucity of research demonstrating long-term beneficial effects of exercise in patients with clinical MDD 59, 60.

Prevention and/or treatment of CVD and MDD-R should primarily combat underlying oxidative stress. Therefore, we propose an effective approach, lowering oxidative stress by physical exercise, a healthy diet, reducing psychological stress (e.g. cognitive therapy and/or antidepressants), and weight loss. All have been proven beneficial for psychiatric symptomatology and CVD-risk 61, 62. These interventions should be routinely implemented in clinical care for MDD-R patients.

Moreover, (adjuvant) novel oxidative stress relieving treatments seem promising. For example, effects on oxidative stress of N-acetylcysteine through the 1-C-Cycle, but also psychotherapy 62, 63, may be an interesting focus of future investigation.

Finally, in spite of consensus recommendations and guidelines, proper monitoring of anthropometric and metabolic parameters has not yet been strictly implemented in psychiatric care. Obstacles to implementation need to be overcome by making CVD-risk monitoring mandatory. The concept metabolic syndrome (MetS) encompasses a cluster of CVD-risk factors and may be a helpful tool for clinicians to assess CVD-risk. Although there is continuing debate regarding the MetS-criteria and -concept, this clustering of risk factors is unequivocally linked to an increased risk for developing CVD 64. 9. The concept MetS could help clinicians which recurrent MDD patients that should receive treatment for their increased CVD-risk 10.
Methodological considerations

Limitations

Limitations of the studies in this thesis were discussed in each chapter. However, we will summarize the most important ones in the next paragraph.

First: Our study sample is comprised only of patients with recurrent depression. It is not clear whether our results will generalize to patients with MDD in general. Restricting ourselves to MDD-R patients, however, had as a benefit that this subgroup represents a more biologically determined MDD-subtype, which may be specifically linked to recurrence and CVD-risk. For this reason, we expect these patients to deviate strongest from healthy controls in the (patho)physiological and genetic mechanisms and to have more pronounced alterations in their course of MDD which is the main focus of our thesis.

Second: We applied a prospective cohort approach in some of the studies used in this thesis to the data of patients who originally participated in a randomized controlled preventive cognitive therapy (PCT)-trial. Where possible, the analyses were performed on the total sample, with and without instant drop-outs (PCT plus treatment as usual (TAU), n=172; early drop-outs immediately after inclusion, n=15). To account for the fact that our sample participated in a RCT, we assessed whether the intervention (PCT) modified or the relation between potential risk factors and the outcomes and if this was the case performed the analyses only in the control group (n=84), it is therefore unlikely that the intervention has biased our results.

For some analyses we only included those patients (a) who attended the study-protocol specific follow-up moments and had a valid research variable (e.g. PSC-questionnaire, cortisol, 1-C-components) and who were euthymic (had no DSM IV-R diagnosis of major depressive episode) in the observed period. In these cases, we always tested whether the study-protocol specific included subgroups of patients was comparable to the other (excluded) patients on demographic and clinical variables.

Third: The issue of multiple imputation in some studies of this thesis. Although we used multiple imputation to reduce bias introduced by missing values, it is possible that the missing values influenced our result. Multiple imputation is based upon the assumption that data are missing at random. This means that missingness (i.e. whether data are missing or not) may depend on observed data, but not on unobserved data. In our studies, we were able to include several predictors in the imputation model (e.g. psychopathological, demographic, and other biological...
variables), which increases the chance that missingness is accounted for by observed data. In addition, most missing data in our studies is missing completely at random, e.g. due to laboratory or logistic accidents, which in any case would not result in biases. Furthermore, there is some evidence that even in the case that missing is not completely at random, analyses using multiple imputation will yield less biased results than analysis using other methods like for instance complete cases analysis. Furthermore, bias by missing values would not easily explain the observed relations. Comparing results with and without multiple imputations should be done with caution. However, replication of our findings would strengthen the evidence.

Fourth: One could question whether our patient sample is a representative (sub) group of high-risk recurrent MDD patients. This may not be completely the case. The patients in the studies described in this thesis, although remitted, were willing to participate in a preventive CT trial and therefore are self-selective.

Fifth: We assessed childhood trauma with a self-report questionnaire rather than an interview. This might on the one hand underestimate the actual prevalence of childhood trauma, or on the other hand due to social desirability lead to over-estimate.

Strengths
First, a major strength of this thesis is that all the research aims were investigated within in a specific sample of highly recurrent depressed patients, which can be considered characteristic for those patients particularly representative of a more biologically determined MDD-subtype, which may be specifically linked to recurrence and cardiovascular co-morbidity. Therefore, the included patient group can be considered characteristic for those patients particularly causing the large MDD-associated burden of disease. Moreover, these patients give the biggest contrast. Where there are biological differences to find than they are most likely to be found in this group.

Second, by using a prospective design it was possible to study the predictive value of various potential biological risk factors for the recurrent course of MDD during a follow-period (maximum of 5,5 years).

Third, it is rather unique to study biological, psychological, cognitive and somatic processes in a comprehensive battery ranging from self-reported measures, interview based measures to biological and genetic tests in such a well-defined clinical population.
Future perspectives
Based on the findings and conclusions from the studies that were presented in this dissertation, we suggest that it should be considered good practice to include healthy controls in studies examining recurrent MDD, HPA-axis regulation, and metabolic and genetic mechanisms and thereby following both groups prospectively. In studies examining the relationship between trauma exposure and polymorphisms and/or metabolites, adequate trauma assessment, not only of the patients but also of the controls should take place. This trauma assessment should not only cover trauma exposure in adulthood but more importantly, also trauma exposure during childhood.

Finally, it would be very intriguing to compare healthy controls, individuals before onset of MDE, patients with one MDE and the recurrent MDD patients on the biological factors longitudinal investigated in this thesis. Especially, examining biological factors (in combination with environmental factors) over time in these groups, may resolve the issue that for some patients MDD is an acute time-limited condition, while for others it results in recurrent episodes over the life course. Currently, there is little information available to guide researchers and clinicians in understanding which of these two life course pathways any particular person with a first MDE eventually will follow.
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*ND richtlijnen 2010-2013 (update komt elk moment uit)*


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