Summary and general discussion
SUMMARY OF MAIN FINDINGS

Depression is one of societies main challenges of the 21st century, as it is currently the second most common cause of years lived with disability worldwide. Current diagnostics of depression cannot provide a clear-cut prognostic indication, since patients with the same diagnosis have extremely variable (heterogeneous) course-trajectories. Clinical staging has been suggested as a solution for how we can structure the heterogeneity in the course of depression. Staging is a tool that “aims to divide the natural course of a disorder in clinically detectable phases that reflect disease severity in terms of progression (= risk of death or residual impairment) and that possess clinical significance for prognosis and choice of treatment.” Moreover, staging allows clinicians to identify patients at risk for a progressive course and to implement treatment interventions aiming to prevent this progression. Staging can be done on different levels; it often starts on a clinical level (dividing individuals over stages using clinical characteristics, such as the number of the episode, as staging criteria) that then can be extended with a pathophysiological and/or treatment-effect levels. In cancer diagnostics and treatment planning, staging models have proven their use. However, the validity of clinical staging models developed for depression remains unclear. Therefore, the first aim of this thesis was to examine whether clinical staging of depression is an effective and valid diagnostic tool to capture the natural progressive course of depression (and as such structure the heterogeneity in the course of depression). To help answer this first aim two sub aims were formed with criteria (as suggested by Agius et al.) that must be fulfilled for the idea of a clinical staging model for depression to be valid. The two sub aims that this thesis examined were: Is each individual subsequent stage associated with a well-defined clinical presentation and specific prognosis (aim 1A) that is worse than the prior stage; and is each individual subsequent stage mirrored by a change in levels of pathophysiological or genetic markers (aim 1B) that is worse than the prior stage, and which thus can be related to the changes in the clinical picture. Another criterion that must be fulfilled for clinical staging models to be appropriate is that every subsequent stage needs a different and more ‘aggressive’ treatment than the prior stage. This was not examined in this thesis, as the available data did not allow this; however we will discuss this criterion in this chapter when information is available from other studies. Finally, to provide suggestions for possible improvement of the staging model, the second aim of this thesis was to examine whether clinical characteristics that are not included in the current staging model could be considered useful to capture the progressive course of depression.

To study these research aims, data were used of a large epidemiological longitudinal cohort study, well characterized in terms of psychiatric pathology: the Netherlands Study of Depression and Anxiety. This thesis focused on the most prominent model that consists of eight ‘clinical-level’ stages. Three stages (0, 1A and 1B) that describe people that never
experienced a depressive episode that, however, have different levels of risk for developing major depressive disorder (MDD), therefore called by us the ‘at-risk for MDD stages’; and five stages (2, 3A, 3B, 3C and 4) that describe people with an MDD diagnosis but are at different phases of progression, called by us ‘full-threshold MDD stages’. The three ‘at-risk for MDD stages’ are defined by the clinical characteristics: family history (0) and symptom level (1A, 1B). The full-threshold MDD stages are defined by the clinical characteristics: number of experienced depressive episodes (2, 3B, 3C) and the duration of the current episode (3A, 4).

For a detailed description and graphical depiction of the stages see ‘Table 1’ and ‘Figure 2’ in chapter 1 of this thesis. For a summary and reminder of stages see Box 1.

**Box 1: summary of the clinical staging model for depression examined in this thesis**

<table>
<thead>
<tr>
<th>At-risk for MDD stages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Stage 0   individuals without depressive symptoms, at risk due to having first-degree family members with depression.</td>
</tr>
<tr>
<td>· Stage 1A  individuals experiencing some mild depressive symptoms.</td>
</tr>
<tr>
<td>· Stage 1B  individuals experiencing subthreshold depressive symptoms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Full-threshold MDD stages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Stage 2   patients experiencing a first depressive episode.</td>
</tr>
<tr>
<td>· Stage 3A  patients with a first episode that does not fully remit.</td>
</tr>
<tr>
<td>· Stage 3B  patients with a first relapse, which is a second episode.</td>
</tr>
<tr>
<td>· Stage 3C  patients that have a third till umpteenth episode of depression.</td>
</tr>
<tr>
<td>· Stage 4   patients with a chronic episode.</td>
</tr>
</tbody>
</table>

In this chapter, the main findings of the previous chapters 2 through 6 will be summarized and discussed in the light of the current scientific evidence according to the aims of this thesis (see for a graphical summary of the first aim Figure 1). Considering the results presented in this thesis we will then address more general aspects connected to the optimal development of staging models designed to improve the diagnostics of depression. Moreover, we contemplate shortly on the question whether depression should be considered a progressive disorder. Finally, we address methodological considerations, review clinical implications and provide suggestions for future research.

**AIM 1: Is clinical staging of depression an effective and valid diagnostic tool to capture the natural progressive course of depression?**

In chapter 2 through 5, we examined *whether clinical staging of depression is an effective and valid diagnostic tool to capture the natural progressive course of depression*. Results from these chapters (2 through 5) are summarized in Table 1. Our first step was to examine whether *each individual subsequent (= higher) stage of depression is associated with a well-defined clinical presentation and specific prognosis (aim 1A) that is worse than the prior (= lower) stage* using both cross-sectional and longitudinal analyses (chapter 2 and 3).
### Figure 1. Summary of findings regarding aim 1

**Is clinical staging of depression an effective and valid tool to capture the natural progressive course of depression?**

#### Hypothesis

For the clinical staging model to be valid, each subsequent stage needs to have a worse (as reflected in darker blue) clinical presentation, prognosis and pathophysiological profile than the prior stage.

<table>
<thead>
<tr>
<th>Aim 1A: Is each individual subsequent stage associated with a well-defined clinical presentation that is worse than the prior stage?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chapter 2</strong> Clinical characteristic</td>
</tr>
<tr>
<td><strong>Chapter 3</strong> Clinical &amp; Etiological characteristic</td>
</tr>
</tbody>
</table>

#### Chapter 2

2-yr follow-up

- At-risk for MDD stages
- First episode
- Residual phase
- Chronic
- Full-threshold MDD stages

#### Chapter 3

2-yr follow-up

- At-risk for MDD stages
- First episode
- Recurrent (>3) episodes
- Full-threshold MDD stages

#### Aim 1B: Is each individual subsequent stage mirrored by a change in levels of pathophysiological or genetic markers that is worse than the prior stage?

**Chapter 4**

Pathophysiological mechanisms

- At-risk for MDD stages
- First episode
- Residual phase
- Chronic
- Full-threshold MDD stages

**Chapter 5**

Genetic risk

- Full-threshold stages did not carry a different number of genetic risk variants for three psychiatric (depression, bipolar, schizophrenia) disorders.

---

### Summary and general discussion
In chapter 2 we examined among 2,333 NESDA participants whether each subsequent stage of the clinical staging-model for depression had a worse clinical presentation and prognosis than the prior stage. For clinical presentation, differences between stages in clinical characteristics (e.g., severity of symptoms, age at onset, presence of comorbid anxiety) were studied. Prognoses was measured by the extent to which baseline stages predicted 2-year follow-up outcomes (e.g., MDD presence). We found that compared to early stages, individuals in later stages scored significantly poorer on most clinical characteristics and follow-up outcomes. However, the pattern of a stepwise worsening (subsequent stage scoring poorer than prior stage) was especially evident in mostly at-risk stages (0 through 2), whereas the full-threshold MDD stages (2 through 4) did not show the expected consistent stepwise worsening of clinical characteristics and 2-year outcomes. In particular, full-threshold stages defined by the number of experienced depressive episodes showed rather similar clinical profiles and prognosis. Instead, full-threshold stages defined by long-lasting symptomatology included patients with the most severe clinical profile and the less favourable prognosis. These findings suggest that the staging model for depression, in which division of individuals over stages is purely based on clinical characteristics, has overall a reasonable validity. However, among patients with full-threshold MDD, modifications to the stages are necessary to improve its validity.

In chapter 3 we focused on the absence/presence of prior MDD episodes as a potential staging criteria. NESDA respondents with a current MDD episode that had recently started (lasting shorter than 2 years) were divided in those reporting a first MDD episode (n=278) versus those with a recurrent (at least 3) MDD episode (n=375). We examined their differences in clinical characteristics (e.g. age at MDD onset, severity of symptoms, suicidality) and/or etiological characteristics (e.g. presence of childhood traumas, presence of recent life-events) and course outcomes (e.g. remission of initial MDD episode, attempted suicide, follow-up time spent with depressive symptoms). We found that first MDD episode patients experienced more recent life-events than recurrent MDD episode patients. Recurrent MDD episode patients had a significantly younger age at onset and higher neuroticism scores, and were more likely to have first-degree relatives with depression as compared to first MDD episode patients. First-episode and recurrent-episode patients did not differ in any of the other clinical or etiological characteristics. Also, the two patient groups did not differ in any of the 2-year course measures. Our findings suggest that in first episode patients environmental triggers seem important, while in recurrent episode patients the disorder
seems linked to inherited causal factors. Therefore, characteristics distinguishing first episode from recurrent episode patients may provide important indication for differential treatment needs. Nevertheless, the course of first-episode patients did not differ from recurrent-episode patients, which suggests that ‘number of MDD episodes experienced’ may not be an optimal clinical index for illness prognosis.

Our next step in answering our first aim was to examine whether each individual subsequent stage is mirrored by a change in levels of pathophysiological or genetic markers (aim 1B) that is worse than the prior stage (chapter 4 and 5). If so, it would suggest that the proposed clinical staging model could be extended to a clinical-pathophysiological staging model.

In chapter 4 we examined, among 2,563 NESDA participants, whether increasing stages are paralleled by more pronounced dysregulation in four depression-related pathophysiological mechanisms (inflammation, hypothalamic-pituitary-adrenal (HPA) axis activity, neurotropic growth and vitamin D). We found a pattern of increasing dysregulation over the three main groups: controls, the at-risk for MDD stages (0 through 1B), the full-threshold MDD stages (2 through 4). However, a stepwise increase of dysregulation (from stage to stage) was only present in the at-risk for MDD stages, while the individual full-threshold MDD stages showed no significant differences in their level of dysregulation. Consequently, a different level of pathophysiological markers mirrors the clinical picture of the at-risk stages, but not of the full-threshold stages. This suggests that the pathophysiological mechanisms investigated may be more involved in MDD’s aetiology (=cause), rather than the clinical progression from first to later MDD episodes and chronicity of MDD.

In chapter 5 we examined whether increasing full-threshold MDD stages are paralleled by an increase in the number of genetic risk variants for three major psychiatric disorders (depression, bipolar disorder and schizophrenia). We found no association between stage and polygenetic risk for any of the three major psychiatric disorders. This suggests that patients categorized in different full-threshold clinical stages do not carry a different number of genetic risk variants for psychiatric disorders.

AIM 2: Are there any other clinical characteristics useful to capture the progressive course of depression?

The examined staging model uses the clinical characteristics ‘number of experienced MDD episodes’ and ‘length of the current episode’ as criteria to divide individuals over the full-threshold MDD stages. These characteristics have previously been found to be markers of progression of MDD. However, there might be other characteristics that capture the progressive course of depression and could thus be used as staging criteria. Therefore, the
second aim of the thesis was to examine whether clinical characteristics that are not included in the current staging model could be considered useful to capture the progressive course of depression.

In chapter 5, we examined whether in 1,539 patients with MDD, clinical characteristics such as younger age at onset, longer duration of depressive symptoms, positive MDD family history, higher number of endorsed depressive symptoms, higher severity of depressive symptoms, and the presence of recurring MDD episodes are associated with an increased genetic psychiatric risk. We found that the genetic risk for MDD, bipolar disorder and schizophrenia is increased in MDD patients that endorsed a high number of depressive symptoms. Moreover, we found that the genetic risk for schizophrenia is increased in MDD patients with a high severity of depressive symptoms. And finally, we found that the genetic risk for bipolar disorder is increased in MDD patients that were younger than 18 years when they first experienced a depressive episode. These findings suggest that stratification according to these easily measured characteristics may identify subgroups of patients typified by different underlying genetic vulnerabilities that may manifest in differential clinical presentations with different prognoses. Thus, the measures ‘age at onset’ and ‘severity of depressive symptoms’ might be characteristics that could improve the current staging model.

In chapter 6 we tested the hypothesis that the prognosis of patients at baseline diagnosed with MDD is far less favourable than one might think, if we change the perspective in terms of time (longer follow-up) and the conceptualisation of affective and anxiety disorders (including dysthymia, (hypo)manic and anxiety as relevant symptoms dimensions). Thereby we moved from a small, narrow (2-year follow-up, considering only MDD diagnosis) to a long, broad (6-year follow-up, including MDD, dysthymia, (hypo)manic and anxiety diagnoses) perspective. Combining psychiatric DSM-IV based interviews and life-chart data, patients’ course-trajectories were classified as 1) recovered, e.g. no diagnoses at 2-year follow-up or thereafter; 2) recurrent without chronic episodes; 3) recurrent with chronic episodes; 4) consistently chronic since baseline. A chronic episode was defined as having symptoms consistently over 2 years. With a small, narrow perspective, the recovery rate was 58%, and 21% had a chronic episode. However, taking a long, broad perspective reduced the recovery rate to 17%, and 55% of the patients’ experienced chronic episodes. Moreover, the clinical relevance of the four course-trajectories was confirmed by the fact that the more severe course-trajectories were accompanied by significantly more functionality loss at every follow-up measure.

Furthermore, we examined which baseline socio-demographics, clinical characteristics (e.g. age at MDD onset, severity of symptoms), and psychological characteristics (e.g. presence of recent life-events, personality measures like neuroticism) predict which
individuals would experience chronic-episodes over follow-up. Moreover, we examined whether characteristics are better in predicting a shorter than a longer follow-up, and whether predictors differ if we take only MDD diagnosis or also comorbid diagnoses into account. We thus examined predictors for four perspectives (the small-narrow perspective [2-year, including MDD only], two middle perspectives [2-year, including MDD, dysthymia, (hypo)manic, anxiety disorders; 6-year including MDD only], and the long-broad perspective [6-year, including MDD, dysthymia, (hypo)mania, anxiety disorders]). We found similar predictors for a course with chronic episodes for all four perspectives: older age, younger age at onset, high depressive symptom severity, and presence of dysthymia. We found that the characteristics are similar in predicting who will have a chronic episode over a short vs. a long follow-up or a narrow vs. broad psychopathology perspective. This suggests that these characteristics ‘age at onset’ and ‘severity of depressive symptoms’ might be used to improve the current staging model, as they are associated with a different (more severe/chronic) prognosis.

DISCUSSION OF MAIN FINDINGS

AIM 1: Is clinical staging of depression an effective and valid tool to capture the natural progressive course of depression?
This thesis confirmed that only part of the staging model is a valid diagnostic tool to capture the natural progressive course of depression. The at-risk for MDD stages (individuals without a depressive diagnosis, but at risk to develop MDD due to a family history of depression or the experience of mild or subthreshold depressive symptoms) seem to reflect a valid way to capture the start of the natural progressive course of depression before the development of a full-threshold depressive diagnosis. In contrast, stratification of patients with full-threshold MDD diagnosis across proposed clinical stages did not capture the natural progressive course of depression. For the ease of reading, each sub-aim is discussed first for the at-risk stages and then for the full-threshold MDD stages.

AIM 1A: Is each subsequent stage associated with a well-defined clinical presentation and a specific prognosis that is worse than the prior stage?
At-risk for MDD stages
Individuals in each subsequent at-risk for MDD stage had a clinical presentation (chapter 2) that was worse than that of individuals in the prior at-risk stage and better than that of individuals in the first full-thresholds stage. Our findings are in line with previous studies that used the staging model of Hetrick et al.6 and examined the clinical presentation7–9 of at-risk for MDD stages. For instance, those studies found decreasing neuropsychological functionality levels,8 increasing disability levels7–9 and increasing severity levels,7 moving
from ‘low-risk for MDD onset’ stage to the ‘high-risk for MDD onset’ stage to the ‘first onset of MDD’ stage.

Similarly as the results for the clinical profile, each subsequent at-risk for MDD stage had a prognosis (chapter 2) that was worse than that of the prior at-risk stage and better than that of the first full-threshold stage. Our findings are in line with the one previous study that used the staging model of Hetrick et al. and examined the prognosis of at-risk for MDD stages. This study found that the risk of progression to a worse stage was lowest in the ‘low-risk for MDD onset’ stage and highest in those with a ‘first-onset of MDD’ stage, after ~4-years follow-up.

The studies that examined the clinical presentation and prognosis of at-risk stages, however, only focused on some of the at-risk stages, examined a combination of disorders (depressive, anxiety, and psychotic disorder), and studied a younger sample (12-30 years) as their main focus was to use the staging model to prevent full-threshold MDD. After all, the ultimate goal of staging is to prevent the development of MDD.

**Full-threshold MDD stages**

Although compared to at-risk for MDD stages, full-threshold MDD stages had in general a worse clinical presentation, and a worse prognosis; the five full-threshold stages themselves could not be clearly differentiated from each other. Each subsequent full-threshold stage did not show a worse clinical presentation (chapter 2, chapter 3) and neither a worse prognosis (chapter 2, chapter 3) than the prior stage. The only consistent difference that we found in clinical presentation and prognosis was between full-threshold MDD stages based on number of episodes (chapter 2) and full-threshold MDD stages based on longer duration of symptoms (chapter 2, 6), with the latter reporting the less favourable clinical and prognostic profile. It is difficult to compare our results to prior studies that applied Hetrick’s staging model to full-threshold stages, because they only examined patients with a first episode, or examined patients in different phases of development of their full-threshold MDD disorder as one group and compared them to at-risk stages and/or healthy controls. To our knowledge, from the studies that applied Hetrick’s staging model, only one compared the clinical presentation and only one compared the prognosis of two groups of patients: those with a first MDD episode to those with recurrent and/or chronic MDD episodes. They found that the recurrent/chronic group tended to have a worse clinical presentation and it was unclear whether the recurrent/chronic group had a worse prognosis. However, whether a worse clinical presentation or possible worse prognosis in more severe stages was driven by the return (=number) or the chronicity (=duration) of the episode could not be derived from those studies.

Although not many studies used the staging model to divide MDD patients and compare them on clinical and prognostic profile; there are quiet a few studies that examined the
clinical and prognostic profile comparing patients divided using just one of the clinical characteristics (number of episodes, duration of symptoms) that are seen as indexes of progression and used as staging criteria. Studies that divided patients using the progression index ‘number of episodes’ compared patients with a first to those with a recurrent episode. The most consistent difference in clinical presentation that those studies reported were confirmed by the findings in chapter 2 and 3 of this thesis, namely that recurrent episode patients have a younger age at onset10–16 and a higher family history of depression,10–12,14,15 while first episode patients are more linked to life-events.17–19 This thesis did not find a difference in severity of symptoms, suicide attempts and comorbid psychiatric disorders between first and recurrent MDD episode patients (chapter 2, 3). Prior studies were inconsistent in whether first and recurrent MDD episode patients differed in those clinical measures,11–15,17,20–24 One of the few studies that examined whether patients with a first or recurrent episode of depression differ in their prognosis regarding the current episode, did not find a difference in percentage that showed remission, or response after 1 year.25 In line with these findings, this thesis showed that after a 2-year follow-up (chapter 2, 3) first and recurrent episode patients did not differ in remission percentage and rate, duration of the baseline episode, disability levels at follow-up, and comorbidity with anxiety at follow-up. Interestingly, a study found that the effect of treatment on an acute episode did not differ between patients with a different number of prior episodes experienced.26 Summarized, the findings in this thesis as well as the studies that did not apply staging but used ‘number of episode’ to divide patients suggest that first and recurrent-episode patients show a few differences in clinical presentation (e.g. age at onset, life events), but do not differ in their prognosis or treatment response. Of note, however, is that all the studies examined the prognosis of a person’s current episode. It might be, as suggested by many studies,27 that those with a recurrent episode are at increased risk compared to first-episode patients to experience more episodes over a longer follow-up period. Moreover, the study25 that did not find a difference between first and recurrent episode patients in percentage remitted and responded, did find that the remitted recurrent patients relapsed sooner than remitted first-episode patients. Studies that divided patients using the progression index ‘duration of symptoms’ compared patients with a non-chronic to those with a chronic episode. Differences in clinical presentation that those studies28–30 reported were confirmed in this thesis (chapter 2). Chronic patients when compared to non-chronic patients had a younger age at onset, more severe depressive symptoms, more comorbid disorders such as anxiety, were more neurotic, had more suicidality and more often a history of childhood maltreatment.28,30 Furthermore, difference in prognostic profile that studies25,28,30 reported were similar as the ones found in the present thesis (chapter 2). Compared to non-chronic episode patients, chronic episode patients had the lowest and slowest remission rates,25 had higher severity of depressive symptoms at follow-up28 and were longer hospitalised and had a lower response and remission rates.28 Finally, studies
into treatment effects found that chronic patients tend to need combined pharmacotherapy with psychotherapy treatments\textsuperscript{10,31} and longer\textsuperscript{28} treatment than non-chronic patients. In summary, the combined results of this thesis, prior studies into the clinical and prognostic profile of (non)chronic patients and the treatment studies, suggest that separating chronic from non-chronic patient is clinically valid. To our knowledge only one study, by Rush et al.,\textsuperscript{25} divided patients using both the progression indexes that are used for staging ‘number of episode’ and ‘duration of symptoms’ comparing patients with a first-non-chronic, recurrent-non-chronic, first-chronic and recurrent-chronic to each other. This study\textsuperscript{25} found that young age at onset, high family history of depression, and suicidality are mainly driven by the episode being recurrent and not the duration of the episode. The staging model examined in this thesis, does not make a difference between first and recurrent episode patients with a chronic episode, as the chronic stage was defined regardless of the number of episodes in the past. However, we did find (chapter 2) that the stage with recurrent patients had the youngest age at onset, highest family history of depression, but not highest suicidality. Moreover the study by Rush et al.\textsuperscript{25} found that those with a chronic episode, similarly as what we found for the chronic stages, had the worst course outcomes.

Thus, first and recurrent MDD episodes show some differences in their clinical presentation, e.g. recurrent cases having a younger age at onset and more often a family history of depression; they do not show differences in important other characteristics such as severity of depressive/anxiety symptoms, suicidality, or comorbid anxiety. Moreover, they do not differ in their prognostic profile. In contrast, non-chronic vs. chronic MDD episodes show differences in both clinical presentation, e.g. chronic cases have younger age at onset, more severe depressive / anxious / disability symptoms, are more often suicidal, and more often have comorbid anxiety; and prognostic profile, e.g. chronic cases more often have MDD at follow-up, spend more time with depressive symptoms over follow up and experience more disability at follow-up.

In conclusion, this thesis found that each subsequent ‘at-risk for MDD’ stage, but not each subsequent ‘full-threshold MDD’ stage is associated with a well-defined clinical presentation and a specific prognosis that is worse than the prior stage. This thesis suggests that duration of symptoms is a useful criterion to divide patients with MDD over stages, but that the number of prior episodes experienced has poor discriminatory power and might not be the best criterion.

\textbf{AIM 1B: Is each subsequent stage mirrored by a change in levels of pathophysiological or genetic markers that is worse than the prior stage?}

\textit{At-risk for MDD stages}

Our findings showed that each subsequent at-risk for MDD stage had an increased
dysregulation in pathophysiological mechanisms, such as the HPA-axis and vitamin D, as compared to the prior at-risk stage, but less severe dysregulation as compared to the first full-threshold stage (chapter 4). These findings are in line with previous studies that examined pathophysiological changes across the staging model of Hetrick et al., and found higher salivary melatonin levels, and less severe white matter disruptions and grey matter loss in the ‘high-risk for MDD onset’ stage as compared to the ‘all full-threshold combined’ stages. The finding that these mechanisms are associated with increased dysregulation in subsequent at-risk stages and that they could discriminate between at-risk and full-threshold stages suggests that they may be involved in the aetiology (=cause) of depression, which confirms findings of prior meta-analyses and longitudinal studies. The pathophysiological mechanisms that we found to be associated with at-risk stages have been proposed to play a role in the onset of depression as follows. An up-regulation of inflammatory markers decreases the production of monoamines such as serotonin, and increases the production of tryptophan catabolites that are toxic for the brain and have been proposed to cause depression. Hyperactivity of the HPA-axis, presumably caused by malfunctioning of glucocorticoid receptors impairing the negative feedback circuit of the HPA-axis, might cause depression via impaired neurogenesis and reduced hippocampus volumes. Vitamin D might be neuroprotective by reducing neurotoxic calcium levels in the brain, low levels would then lead to depression by increased neurotoxic levels of calcium in the brain. We did not examine whether at-risk for MDD stages were associated with different levels of genetic risk as we had not enough clinical characteristic information for our non-MDD sample, which was derived from the Netherlands Twin Registration, to divide individuals over the at-risk stages. To our knowledge, no other study has either.

**Full-threshold MDD stages**

Across stages stratifying patients with a full threshold MDD disorder, no differences were found in the levels of markers that reflect four pathophysiological mechanisms (inflammation, HPA-axis, brain neurotrophic pathway, vitamin D). This suggests that the studied pathophysiological mechanisms are not associated with progression. Prior studies that suggested that pathophysiological mechanism were associated with progression of depression, did not apply staging, instead they examined just one of the clinical characteristics that are thought to reflect depression progression, such as recurrence. It could be, however, that pathophysiological mechanisms not examined in this thesis are associated with clinical progression of MDD. Mechanisms/pathways that are suggested to lead to neuroproression for instance are, neurotransmitter systems, oxidative and nitrosative stress, mitochondrial dysfunction and epigenetic influences. Indeed, compared to non-chronic depressed individuals, chronic depressed individuals had higher levels of oxidative and nitrosative damage, as found by one study. On a different level, studies that examined
structural and functional brain changes found that recurrent and chronic patients, but not first episode patient’s had more distinct brain alterations. More recent studies also found brain changes in first episode patients. Furthermore, it is very well possible that clinical progression of MDD is not driven by increased dysregulation of the studied mechanism, but rather by prolonged exposure to chronic level of dysregulation that then leads to damage/alterations of cellular components, which subsequently could cause a person to be at further risk of recurrence or chronicity. Moreover, it might be that the pathophysiological mechanism markers that we examined in this thesis are not markers of progression as we hypothesized, but instead are markers of diagnosis/trait or markers of treatment response. Markers of diagnosis/trait indicate whether a person is experiencing depression independent of the symptoms reported. Similarly, like a test for infection markers in a urine sample can define whether that person has a bladder infection independent of the symptoms a person experiences. In this thesis we found that markers for inflammation, HPA-axis and vitamin D were significantly more dysregulated in full-threshold stages than controls and at-risk stages suggesting that they are markers of diagnosis/trait (chapter 4). Markers of treatment response indicate whether an individual is likely to respond to a certain treatment or not, ideally giving the doctor the opportunity to personalise treatment to individual needs. This could be an explanation why we did not find any association between the marker BDNF and MDD groups/stages (chapter 4), and is in line with recent studies that suggest that BDNF seems to modulate the treatment efficacy, rather than being an possible cause of depression onset or progression.

Lastly, we examined the level of genetic risk across stages stratifying patients already with a full threshold MDD disorder; we found that the full-threshold stages had similar levels of genetic risk. No other studies, to our knowledge, have examined whether clinical stages are associated with similar or different levels of genetic risk. Neither did other studies compare groups of patients divided using clinical characteristics that are seen as indexes of progression (e.g. number of episodes, duration of symptoms).

In conclusion, we found that each subsequent ‘at-risk for MDD’ stage, but not each subsequent ‘full-threshold MDD’ stage is associated with an increasing dysregulation in pathophysiological mechanisms. Therefore, our results suggest that the clinical staging model for ‘at-risk for MDD stages’ could be extended to a clinic-pathophysiological staging model, but the clinical staging model for ‘full-threshold MDD stages’ cannot be extended to a clinic-pathophysiological staging model.

Combining the findings made regarding aim 1A and 1B suggests that the staging model examined, is effective and valid in capturing the natural progressive course of depression in its at-risk stages, however, not in all its full-threshold stages. Stages defined by duration
of symptoms (chronicity), but probably not by number of episodes are best able to capture progression of depression, since we found difference in clinical presentation and prognosis between chronic and non-chronic patients; and other studies suggest pathophysiological differences and treatment differences between those two groups. Still, more research needs to be done in pathophysiological mechanisms that support this distinction.

**AIM 2: Are there any other characteristics useful to capture the progressive course of depression?**

The second aim of this thesis was to examine whether clinical characteristics that are not included in the current staging model could be considered useful to capture the progressive course of depression. To be considered indicators of progression, characteristics should meet the three criteria proposed by Agius et al.\(^4\): a well-defined clinical presentation and prognosis, treatment indication, and underlying pathophysiological changes. We examined the performance of a wide array of characteristics in predicting the course trajectories for MDD patients (preliminary results in addition to chapter 6). Two clinical characteristics, age at onset and severity of depressive symptoms, showed to be relevant for the prognosis of MDD over time and will be discussed underneath to see whether they also reach the other criteria to be an indicator of progression.

Age at onset might be a characteristic useful to capture the progressive course of depression. Clearly, the younger depression starts in life, the more time is left to develop recurrent and or chronic episodes. Moreover, it could be that especially the young, developing brain is prone to the effects of a depressive state scaring the brain leading to more episodes in the future. Previous studies,\(^62–64\) also from the NESDA sample,\(^65\) found that a young age at onset is associated with a distinctive clinical presentation compared to late age at onset. Compared to those with an older age at onset of depression, those with a younger age at onset tend to have longer duration of symptoms, experience more episodes, have more suicidal thoughts and did more often do a serious suicide attempt, have more often a family history of depression, and experience more sadness; although results varied which could be caused by variability in the cut-off for a young age of onset (e.g. <18 years\(^62,6\) or <30/40yrs\(^64,65\)). We found that a young age at onset predicted a worse prognosis, e.g. a course with chronic episodes (preliminary results in addition to chapter 6). That a younger age at onset predict a worse course has been consistently found by other studies too.\(^66,67\) So, young age at onset full fills the criteria of a clear clinical presentation and prognosis that is different from an older age at onset. Whether a young age at onset is mirrored by increased pathophysiological changes is still unclear. Occasionally, it has been found that a young age at onset is associated with higher inflammation markers\(^68\) and changes in the genu of the corpus callosum,\(^69\) but other studies have shown that it is especially those with an old age at onset that show changes in the brain structures, such as the hippocampus and corpus
callosum.\textsuperscript{70,71} Again, these studies were difficult to compare, as the cut-off for young age at onset varied between studies.

Severity of a depressive episode is consistently shown to be an indicator of a worse prognosis, such as a longer duration of an episode,\textsuperscript{72,73} lower recovery rate,\textsuperscript{74,75} earlier recurrence,\textsuperscript{72} and the probability of consistent contact with the in hospital psychiatric treatment during a 10-year follow-up period.\textsuperscript{76} Consistent with these prior studies, this thesis found that more severe depressive symptoms at baseline predicted a chronic episode over 6-year follow-up (preliminary results in addition to chapter 6). However, whether the severity of an index episode of depression is associated with other differences in the clinical presentation has been barely examined. Moreover, rather than more severe depressed patients having a less favourable treatment response, they seem to have a similar or even better treatment response as less severe depressed patients, at least when psychological treatments are examined.\textsuperscript{77,78} Finally, we did not show that more severe symptoms are underlined by more dysregulation in markers of pathophysiology (chapter 3). In summary, age at onset seems a valid characteristic to define groups that are clinically and prognostic different, which would suggest that the characteristic could be considered useful to capture the progressive course of depression and therefore could be used as criteria for clinical staging. However, a clinical staging model using age at onset cannot be backed up to a clinical-pathophysiological staging model. Severity of depression seems only a valid characteristic to define groups that are different in prognosis, and therefore currently lacks evidence to be an indicator of progression that can be used for clinical staging.

Since both the characteristics ‘age at onset’ and ‘severity of depressive symptoms’ seem to be mainly relevant for the prognosis of the individual patients, it might be that they are not indicators of progression that can be used as staging criteria, but rather are profilers. Profilers are markers (e.g. clinical characteristics, neuroimaging, blood) that given the stage predict the progression rate/route over stages and/or the effect of treatment. For instance, the specific cell-type(profiler) that is involved in a patients leukaemia can indicates which treatment is necessary for the most optimal prognosis.\textsuperscript{3} (For a more in-depth discussion on profilers see paragraph on future directions). Similarly, it might be that a young age at onset, and more severe symptoms of the index-episode predict the progression rate/route over stages and/or the effect of treatment. Young age at onset of depression might be a profiler that suggest who is at risk to progress to bipolar disorder. Indeed, literature has showed that an early age at depression onset is a risk factor for developing bipolar disorder later on.\textsuperscript{79–81} Interestingly, this thesis (chapter 5) and one previous study\textsuperscript{82} found that a young age at onset was associated with an increased psychiatric genetic risk for bipolar disorder, supporting the idea that a young age at onset of depression is a profiler that selects those that are at an increased genetic risk to develop bipolar disorder later in life. Severity of depressive symptoms might be a profiler that suggests who is at-risk to develop psychotic
symptoms, a form of depression that is seen as more severe. In line with this idea, this thesis (chapter 5) found that high severity of depressive symptoms was associated with an increased psychiatric risk for schizophrenia, supporting the idea that severity of symptoms is a profiler that selects those that are at an increased genetic risk to develop psychotic/schizophrenic symptoms.

In summary, we found two clinical characteristics: age at onset and severity of depressive symptoms, which are relevant for the prognosis of MDD over time. It could be that they are indicators of progression and therefore staging, but it might be more correct to see them as profilers.

**Issues to be considered when developing a staging model for MDD**

Some major issues need to be considered in the effort of developing optimal staging models for depression, in particular: (i) the comorbidity of depression with and progression into other psychiatric disorders; (ii) the presence of subthreshold symptoms that fit various psychiatric disorders, prior to the development of a full-threshold depression disorder; (iii) the episodic nature of depression highlighted by intervals free of depressive complaints; and (iv) the consideration of treatment response as a criteria to stage patients.

The first issue that needs to be considered when developing staging models of depression is that patients with MDD often have a comorbid diagnosis or might progress to another diagnosis. Comorbidity between the MDD and anxiety has found to be as high as 67%. Anxiety can both precede and succeed the development of MDD, and often patients alternate between the two disorders. Chapter 6 of this thesis showed that nearly half of the patients that recovered from MDD after 6 years follow-up, did not recover from anxiety. Moreover, about 11% of the patients initially diagnosed with MDD continued to develop (hypo)manic episodes and would be considered bipolar (either type I or II) from that moment on (chapter 6). This comorbidity with and progression into other psychiatric disorders makes the development of staging models for psychiatric diagnoses very complicated. What is considered a first full-threshold episode (stage 2) for MDD would be considered an at-risk stage (1B) for bipolar disorder. A possible solution to overlap in diagnoses and presence of multiple mental illnesses could be to approach comorbidity as a progression of the initial illness. Staging of somatic diseases are generically divided into categories of increasing levels of severity: stage 1, conditions with no complications or problems of minimal severity; stage 2, problems limited to an organ or system, significantly increased risk of complications over stage 1; stage 3, multiple site involvement, generalized systemic involvement, poor prognosis; stage 4, death. If this would be paralleled for mental illnesses it would be stage 1: symptoms of a mental disorder not leading to functioning loss; stage 2, symptoms of mental illness limited to one disorder, that causes functioning loss; stage 3, symptoms of multiple mental illnesses, severe functioning loss, poor prognosis; stage 4 multiple mental illnesses
and inability to live independently.

A second issue that needs to be considered when developing staging models of depression, is that prior to the development of a clear-cut diagnoses as described in the DSM, patients experience subthreshold symptoms fitting to various psychiatric disorders. Something that the staging model for depression examined in this thesis already takes into account, e.g. at-risk stages are based on both depressive and anxiety symptoms. But rather than developing staging models for each individual psychiatric disorder in which at-risk stages show great overlap between disorders, it has been suggested to have one staging model for psychiatry. In this model, different disorders share their at-risk stages (like a tree trunk), but when full threshold disorders develop each different psychiatric disorder has its own stages (like different branches of that tree). Some interesting literature supports this idea. Studies suggest that different psychiatric disorders share a relevant proportion of genes, possibly causing the disorder. Our findings in chapter 6 further support this; MDD patients with a high number of DSM symptoms have not only an increased genetic risk for MDD, but also for bipolar disorder and schizophrenia (tree trunk). After this initial general increased genetic risk for any psychiatric disorder, it is suggested that it is the environment that defines what disorder you will develop during life (tree branch).

A third issue that needs to be considered when developing staging models of depression, is what to do with patients that are remitted from an episode of depression. Current staging models for depression are based on staging models for somatic disorders in which remission from the disorder is uncommon (when not treated) and thus not taken into account. Therefore, current staging-models for depression do not give directions to what to do with patient that are remitted of a first, second, or tenth episode of depression and regained their normal level of functioning. In this thesis, patients with an episode of depression that was remitted for 6 months or longer were put in the stage ‘at high risk to develop MDD (stage 1B)’. This has been an arbitrary choice based on our opinion that someone with a remitted episode could not be treated the same as someone in an active episode. Because we know that a person with a prior episode of depression is at risk to develop a new episode we staged them as ‘ultra-high risk for MDD’. Here the difference of depression with the natural course of progressive somatic disorders become clear, e.g. cancer. If these somatic disorders are not treated, they will progress and in the end lead to severe disability or death. Patients with depression, however, can experience full recovery (even without treatment) with return of normal functioning between episodes (even after many episodes), while another patient might recover from the first episode but still experience functioning loss. Moreover, while clinicians focus on symptom recovery, a patient might find function recovery much more important. It could be, therefore, that staging based on level of functioning is a better solution to map progression of depression. In bipolar disorder, for instance, Kapczinski et al. suggested to stage (bipolar) patients based on level of functioning between episodes.
In short he proposed to included in stage I ‘patients that have clear episodes of normal mood, and absence of any psychiatric comorbidity between episodes’; Stage II ‘patients who present rapid cycling or current axis I or II comorbidities’; Stage III ‘patients who present a clinically relevant pattern of cognitive and functioning deterioration’; and Stage IV ‘patients who are unable to live independently’. Our finding (chapter 6) that those with the most chronic course trajectories over 6 year follow up, had consistently worse disability scores support the idea of staging based on level of functioning. In the in this thesis examined staging model for MDD, functioning levels (GAF scores) are taken partially into account. When we applied the staging model to the NESDA data, we did not take level of functioning into account since we lacked a measure that is in accordance with the GAF score. One study that did take functioning into account, showed that those in the ultra-high risk for depression stage experienced already considerable disability that was similar as to those with a first full-threshold depressive episode.

I would like to take the thought of staging on level of functioning even further as it would be a solution to both the issues of comorbid disorders and the problem of patients with a remitted disorder. My suggestion would be to design a staging-model that fits all mental illnesses (or at least those that have great overlap) and is based on level of functioning. This would remove the problem of overlapping staging models in which a patients falls in different staging categories (stage 2 for MDD, stage 1B for bipolar disorder), would remove the problem of what to do when someone is not in an active episode, and would focus the goal of treatment to function recovery rather than symptom recovery. Staging based on level of functioning rather than the underlying pathophysiology of a disease is done in somatic disorders as well. For instance, heart failure is staged based on the level of functioning as reported by the patient (class I till IV) and as measured by the clinician (class a till d).

A final issue that I would like to be considered when developing staging models of depression is its inclusion of the effect of treatment in defining the stages. In Hetrick et al., staging model some (3A, 3B, and 4) but not all stages use the effect of treatment as staging criteria. For example, stage 3A is defined as ‘Incomplete remission from first episode of care’. Staging is supposed to describe the natural course of progression of a disease, this means without intervention of treatment. It might be difficult to find what the natural progression of the disorder is as it would require to remain from intervention in patients that present with complaints. Something that would not be ethical allowed. Therefore, if treatment has to be taken into account I would suggest doing this systematically for each stage. A possibility is to extend current staging models with the staging models that have been designed to examine whether someone is resistant to treatment (treatment resistance staging models). A systematic review showed that different treatment resistance staging models exist, some only including the number of (different) treatment tried, others also included clinical characteristics of the episode such as severity and duration. These latter characteristics are
already used in clinical staging, suggesting that combining both clinical and treatment resistance staging models could be the next step.

Summarized some major issues need to be considered in the effort of developing optimal staging models for depression, in particular: the comorbidity of depression with and progression into other psychiatric disorders; the presence of subthreshold symptoms that fit various psychiatric disorders, prior to the development of a full-threshold disorder; the episodic nature of depression highlighted by intervals free of depressive complaints; and the consideration of treatment response as a criteria to stage patients. Possible solutions for these issues are mentioned above, my preference goes to a generic model for overlapping psychiatric disorders in which stages are based on a patients’ level of functioning, rather than the number or duration of an episode.

Is depression a unique and progressive disorder? A reconsideration

Not everyone that will experience an episode of depression will continue on a path of progression towards recurrent and chronic episodes. Nowadays, it is even found that nearly half of those experiencing a first episode of depression will not recur.\(^94\) It could be that these patients received a proper intervention that has prevented them from progression. However, it might also be that depression is not a progressive disorder and recurrent and chronic episodes are the consequence of something else than progression of the disorder.

As explained in the general introduction of this thesis, the rationale for considering recurrent episodes as an index for MDD progression was based on the clinical observation that patients with multiple affective episodes tend to have progressively shorter well intervals during the course of illness (cycle acceleration), and that subsequent episodes of depression occur autonomously of stress with repeated depressive episodes.\(^95,96\) Others observed that over time patients’ subsequent episodes tend to last longer and be more severe.\(^96–98\) Post\(^99\) tried to explain these clinical observations with his kindling and sensitization hypotheses. These two hypotheses (also called scar models of depression\(^96\)) assume that prior episodes of MDD cause some form of brain damage. This brain damage makes a persons more vulnerable to new episodes that start independent of stress (kindling), and new episodes that start after life-events of less and lower severity than that were necessary to start prior (first) episodes (sensitization). In line with the kindling hypothesis, this thesis found a stronger link to environmental stress-related factors among first-episode than recurrent-episode patients (chapter 3). However, this thesis did not find any difference between first and recurrent-episode patients in the course, e.g. severity of symptoms, duration of symptoms, of their current episode (chapter 2, 3). This begs the question whether ‘number of MDD episodes experienced’ reflects progression of the disorder, or whether recurrent episodes might be caused by something else than progression (scarring of brain)?

In a recent paper\(^100\), Slater’s fallacy is used as an explanation why prior studies did find
differences between first and recurrent episode patients that actually might not exist. Prior studies, in statistical terms, did examine the between-subject effect without taken into account the within-subject effect. Meaning, that the description of the characteristics of early (first) episodes is made in a sample including patients of which some will and others will not continue to have highly recurrent episodes. When these patients are then followed over time, and characteristics are described of those with highly recurrent episodes it might seem that they have shorter inter-episode periods (and tend to be more severe). It could be, however, that those highly recurrent patients always had shorter inter-episode periods, but that this was not noticed because their first inter-episode period was averaged with those that did not developed highly recurrent episodes. Therefore suggesting that the first inter-episode period of someone who will be highly recurrent is shorter. After correction for Slater’s fallacy no differences were found in length of inter-episode periods between episodes early- versus episodes later in the course of depression. Moreover, those with highly recurrent MDD always had shorter intervals between episodes, suggesting that patients with highly recurrent MDD have a different clinical presentation than those with a single or only a few episodes. The Slater’s fallacy, might also apply to all other previously found differences between first and recurrent patients, e.g. subsequent episodes tending to last longer, being more severe, and being less dependent on stressful events. Continuing this line of thought, it might be that recurrent depression is not a progressive disorder that is a caused by ‘brain scarring, social-scarring, or psychological scarring’, but instead is the consequence of something else. One possible explanation is given by the stable liability models. Stable liability models, postulate that vulnerability factors for depression exists prior to the first-onset of a depressive episode (e.g. genetic, or non-processed youth trauma) and as long as the factor remains present after remission of the first episode, the persons remains susceptible to developing recurrent episodes of depression. This fits with the inheritance profile that we found in chapter 3 for recurrent episode patients, e.g. younger age at onset, more family history of depression and more neuroticism, which might be considered a predisposing personality trait that could reinforce return of complaints. Moreover, in chapter 5 we found that those with a young age at onset also had an increased genetic risk for psychiatric disorders.

Interestingly, liability for recurrence that is already present prior to the patient experiencing their first-episode (e.g. genetic) fits not only with the stable-liability models, but with ‘pre-kindling’ of the brain as well. Kendler et al., showed that not only prior episodes, but also genetic-risk (e.g. family history) can ‘kindle’ the brain for subsequent ‘spontaneous’ episodes. In this thesis we found evidence for both the stable liability (chapter 3, 5) model as well as the scar-model (chapter 3) as cause of recurrent episodes. To truly examine, whether recurrent episodes are the consequence of vulnerability factors or scarring, people would have to be followed for a life-time, starting prior to their first episode and followed during recurrences, prefarable till the person dies. So the consequences of depression can be
studied within persons.

**Methodological considerations**

The strong aspects of the NESDA study are its large number of well-characterized patients across the whole adult age range representing different developmental stages of MDD, its longitudinal design, the assessment of a wide range of biological and genetic variables as well as confounders relevant to the examined pathophysiological mechanisms and genetics. This gave us the unique opportunity to be the first to examine all the individual stages of the staging model for depression, as compared to previous studies that examined only a few stages of the model, like one or two at-risk stages, and one full-threshold stage that combined all proposed full-threshold stages; moreover prior studies often examined a combination of psychiatric disorders (depression and psychosis).

As with every study, some methodological aspects have to be considered. First and most important, the degree of fit between the MDD staging model developed and applied in some chapters (2,4,5) of this thesis and those currently used in clinical settings can only be approximated. Importantly, both a weakness and strength and of this thesis is that we included subjects in the whole adult range (18-65 years) that were on average older and more likely to have recurrent or persistent disorders as compared to those in the clinical studies previously conducted. The weakness was that subjects in at-risk studies might be considered relatively old (~40 years old), while research has shown that most people experience their first episode of depression around the age of ~25 years. This could limit the percentage that would truly be at-risk to develop MDD and a progressive course. Still this thesis showed that up to 17% of the participants in the at-risk stages developed MDD over time. The strength, however, was that the inclusion of the whole adult age range allowed us to examine all full-threshold stages of the model, which had not yet been done in previous studies. Furthermore important, in our study, we assigned persons to a stage regardless of their treatment status, whereas in a clinical setting, progression to a higher stage is based, among other things, on the response in those who received treatment. Our full-threshold stages, therefore, included a more heterogeneous group of patients (treated: yes/no; treatment response: yes/no); this reduced the differences between stages and might have led to an underestimation of the examined validity. Moreover, although treatment might be of influence on the course of depression, we decided not to include treatment as a covariate to our predictive analyses (chapter 2) since a previous NESDA study into the 2-year course of depression showed in a multivariate model that antidepressant use is not a predictor of course. Indeed, in the additional analyses based on chapter 6 data of this thesis, we did not find treatment to be predictive of a chronic course of depression over 6-years.

Second, during follow-up, there was selective loss of participants from the full-threshold stages with long-lasting symptoms, which could have influenced the predictive validity.
However, since those who are lost to follow-up are generally the worst affected cases (worst affected within the stages with long-lasting symptoms), selective loss tends to decrease the strength of the associations investigated and suggests that the prospective relation found might be even stronger.

Third, biological measurements were obtained via a blood draw or saliva collection, which are peripheral measurements that may not necessarily represent the ‘central/brain’ mechanism relevant for depression. However, they have been consistently associated with MDD status in previous studies.  

Fourth, to examine disease progression it would be most optimal to have a large cohort of people without depression that are than followed over time to describe the within person changes. In our sample, the proportion that had no depression at baseline and developed different stages of depression over time was too small to draw proper conclusions.

Finally, we like to acknowledge that different clinical staging models for MDD exist besides the one that we have chosen to use as our leading model. The main difference is that the models collapse the three full-threshold stages ‘incomplete remission of first episode’, ‘first relapse’ and ‘multiple recurrent episodes’ into one full-threshold stage ‘relapsing/reoccurring MDD’. We decided to use the extensive clinical staging model as it was the one mostly used in clinic and research till thus far.

Clinical implications & future directions

Current diagnostics of depression cannot provide a clear-cut prognostic indication, since patients with the same diagnosis have extremely variable (heterogeneous) course-trajectories. Clinical staging of depression might be an effective tool to capture the natural progressive course of depression and as such structure the heterogeneity in the course of depression. Findings of this thesis showed that the current clinical staging model for depression needs to be improved, especially the full-threshold stages, before it can properly directs the focus of depression diagnostics to early recognition and eventually early intervention, preventing the development of a recurrent and chronic disorder. For this, we need to carefully study the onset, and course of depression and search for predictors of both onset and course, as well as what treatment is most effective in each stage.

The current thesis showed that the staging-model seems to be effective in defining those at-risk for MDD. The ultimate goal of staging is early recognition and treatment of those that otherwise might progress to a recurrent and/or chronic disorder, and as such prevent progression of MDD. From the public health perspective prevention is only relevant if benefits (no progression to higher stage) outlay the costs. The first step of effective prevention is recognising those at risk to develop MDD and at risk for progression to more severe (higher stage) of MDD. This thesis showed that the staging-model is valid in defining those at-risk for MDD (chapter 2,4). If we could prevent those people to develop MDD in
a cheap and effective way, benefits might outlay costs. Studies that examined whether MDD onset can be prevented in those with subthreshold symptoms using psychological intervention, suggested that MDD onset can be prevented or delayed.\textsuperscript{105,106} However, no differentiation was made between patients with subthreshold symptoms with and without a prior history of MDD. Still, in both cases preventing new and recurrent episodes would stop progression. Especially, of interest are new developments such as internet-delivered self-help programmes that have shown to be an effective treatment for depression,\textsuperscript{107} but still need to be shown to be effective as a preventive tool. These treatments are costs effective, as patients can go through a program themselves, although, it has to be noted that internet delivered self-help programmes seem to be most effective when they are clinician supported.\textsuperscript{107} Still, since both the patient and clinician are not time or office restricted with this kind of treatment, costs of treatment might be massively reduced making it well suitable for prevention.

This thesis showed that age at onset and severity of depressive symptoms are predictors of a worse course. To further develop the staging model other predictors of MDD onset and MDD progression have to be found. As noted before, not everyone at-risk for MDD will develop MDD, and not everyone with a first-episode will progress towards recurrent and chronic episodes. To optimise the effect of preventive treatment, it is useful to find predictors of MDD onset for those in at-risk stages, and predictors of MDD progression for those in the first-episode stage. These predictors are known as profilers in relation to staging. Profilers are markers (e.g. clinical characteristics, neuroimaging, blood) that given the stage predict the progression rate/route over stages and/or the effectiveness of treatment. For instance, the specific cell-type(profiler) that is involved in a patient’s leukaemia can indicate which treatment is necessary for the most optimal prognosis.\textsuperscript{3} Suggested profilers for depression onset in at-risk people are lower melatonin levels\textsuperscript{12} and microstructural white matter changes.\textsuperscript{34} Suggested profilers for progression to chronic episodes (besides the ones found in this thesis) are childhood trauma,\textsuperscript{108} and comorbid anxiety\textsuperscript{109} (preliminary analyses in addition to chapter 6). In defining who is at risk for depression we should not hesitate to use new methods. A recent study showed that an algorithm could predict who would be or even become depressed using pictures posted on Instagram.\textsuperscript{110}

This thesis showed that full-threshold stages of MDD do not validly reflect the natural progression of depression. To define what are useful staging criteria, future studies should be longitudinal with high follow-up frequency in order to obtain reliable estimates of lifetime course trajectories. Preferable studies should follow individual patients from prior to onset of a first episode to death. It would help to separate between- from within patient differences. And help us answer questions like ‘is duration of a current episode relevant as an staging criteria, or should duration be defined as time exposed to depression in life’ and if the latter ‘is the effect of exposure to a depressive state similar for one episode that lasts
9 months, as for three episodes each lasting 3 months. However, long-term and frequent follow-up might be very stressful and burdensome for the patients, labour-intensive for researchers, and costly for society. Nevertheless, developments as constant data collection via minimal invasive questionnaires on phones and anonymous medical records that give the opportunity to create big-data sets, might make it possible in future to describe the course of depression over lifetime in detail, allowing the design of improved staging models.

Thus, clinical staging of depression might be an effective tool to capture the natural progressive course of depression and as such structure the heterogeneity in the course of depression. Findings of this thesis showed that the current clinical staging model needs to be improved, especially the full-threshold stages, before it can properly direct the focus of depression diagnostics to early recognition and eventually early intervention, preventing the development of a recurrent and chronic disorder. For this, we need to carefully study the onset, and course of depression and search for predictors of both onset and course, as well as what treatment is effective when. Our digitalising world gives many options to improve data collection to study all this. Moreover, if online-treatment in people with subthreshold symptoms and without prior diagnoses proves useful to prevent MDD onset, it gives us the opportunity to deliver treatment to many people at the same time, making prevention of onset an approachable option. In the future, this could lead to a noticeable effect on the disease burden and the economic costs associated with depression.

Overall conclusion
This thesis showed that the examined clinical staging model for depression is a diagnostic tool that is only partially effective and valid in capturing the natural progressive course of depression. This thesis found that the stages that indicate patients at-risk to develop MDD are valid as each subsequent (in other words: higher) had a worse clinical presentation, prognosis and more dysregulation in pathophysiological mechanisms than the prior (in other words: lower) stage. However, this thesis could not show that the model was valid for stages that reflect patients with already developed MDD, e.g. first, recurrent, chronic episodes. Patient, with different number of experienced episodes showed similar clinical presentations and prognosis. Only, patients with longer duration of their episode, e.g. chronic patients, had a clinical presentation and prognosis that was worse than those without a chronic episode. Improvement of the current staging models for depression is necessary, if clinicians want to give an indication to the prognosis of individual patients. The clinical characteristics, young age at onset and high severity of depressive symptoms might be possibilities to improve the staging model, as was indicated by this thesis. Other options to improve the staging model are discussed. The preference of the author is to design models that focus on level of functioning as staging criteria as it is a solution to both the high comorbidity between psychiatric disorders and the possibility of depression to remit. Future research, with high
follow-up frequency and length, are necessary to obtain reliable estimates of lifetime course-trajectories of depression and to examine whether staging on, for instance, functionality would be possible.
REFERENCES


Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord 2012; 139: 230–9.


Summary and general discussion


76  Musliner KL, Munk-Olsen T, Laursen TM, Eaton WW, Zandi PP, Mortensen PB. Heterogeneity in 10-Year Course Trajectories of Moderate to Severe Major Depressive Disorder A Danish National Register-Based Study. JAMA Psychiatry 2016; : 1–8.


