Staging of Major Depressive Disorder

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1 General introduction

INTRODUCTION

Epidemiology and relevance of depression

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.[1] This is due to depression's high prevalence both in high-income (life-time prevalence 14.6%) and low to middle income countries (life-time prevalence 11.1%),[2] relatively early onset (most people experience their first episode in early adulthood, e.g. before the age of 30),[2]) and its tendency to recur over time.[3] Moreover, the combination of young onset and recurrences over lifetime, make depression one of the disorders with an enormous impact on the patient's life. Depression might incapacitate someone to work or even to look after their family/children,[4] and also depression is associated with an increased risk for somatic diseases such as diabetes, cardiovascular diseases and even death.[5] The combination of high prevalence, medical costs for treatment, and productivity loss, cause depression to have a high societal-economic impact. Cost of illness studies have shown that about ~65% of the societal costs inflicted by depression are indirect costs due to productivity loss,[6–8] and in the European Union productivity loss due to depression is calculated to be twice as high as that inflicted by cardiovascular diseases.[9]

Diagnostics of depression

Depression is a term used in the general public that refers to a broad spectrum of various mood disorders, such as major depressive disorder (MDD), minor depression, bipolar depression or dysthymia. This thesis will focus on major depressive disorder.[a] According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition[10] a depressive episode is diagnosed when a person experiences a depressed mood and/or loss of interest/pleasure in almost all activities (anhedonia), combined with several other symptoms such as appetite change, sleep duration change, psychomotor agitation, loss of energy, feelings of worthlessness or guilt, concentration problems, and in severe cases thoughts of death or an actual attempt to commit suicide. These symptoms (minimum of five) need to be present for at least two weeks, cause functioning loss, and might not be caused by another psychiatric disorder (e.g. schizoaffective disorder), a somatic disorder (e.g. hypothyroidism) or a substance use disorder.

The goal of diagnostics is to give meaning to a patients' complaints (diagnosis), the ability to find the cause of these complaints (aetiology of the diagnosis), and to give the patient treatment for the complaint and a prognosis (belonging to the diagnosis). Today, the cause of depression is thought to be multifactorial, probably a combination of genetics and environmental factors, still no established mechanism can explain all aspects of the disorder.[11] Similarly, the diagnosis of MDD cannot provide a clear-cut prognostic indication,

[a] In this thesis I will use the terms depression and major depressive disorder interchangeable for the ease of reading, although major depressive disorder is the official medical term.

since patients with the same diagnosis have extremely variable course-trajectories. In the newest DSM-5 this has been recognized, and specifiers can be added to the diagnosis of MDD in an attempt to create more homogenous groups of patients with distinctive clinical profiles and moreover a different prognosis. For instance, the DSM-5 allows addition of specifiers that attempt to take the course of MDD over life into account, the specifiers code whether the current episode is a first, a recurrent or a chronic (lasting >2 years) episode. These specifiers show the diverseness (heterogeneity) in the course of MDD.

The course of depression

The course/prognosis of patients with MDD is highly heterogeneous, varying from a benign self-limiting disorder that only occurs once, to a recurrent and sometimes chronic disorder regardless of treatment (see Figure 1 for a graphical presentation of the heterogeneity in the course of MDD). For instance, when patients that experience a first episode of depression are followed-up over time, at least half of them recover within 6 months, but a quarter will still be depressed after two years (chronic MDD).[12] Moreover, of those that recover from a first episode it is estimated that around sixty percent will have at least one recurrence.[3,12] Furthermore, some people might not fulfil the criteria for MDD because they experience 'only' three or four symptoms of depression. We know, however, that these people are at risk to develop an episode of MDD.

Preventing these recurrent and chronic courses to develop might have serious impact on a person's quality of life as well as on depression's impact on society. From a public health perspective it is therefore essential to understand the course of depression and which factors

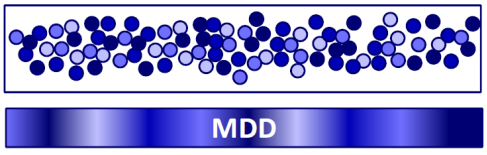

Figure 1: Graphical presentation of the heterogeneity in the course of MDD.
We see depicted persons with an MDD episode diagnosis and the variety in their course, as some will have no diagnoses due to lack of enough symptoms but are at risk to develop one (lightest blue), some will experiences their first episode (light blue), some a recurrent episode (middle blue) and some will experience a chronic episode (dark blue).

may impact on its trajectory (e.g. who will develop recurrent and/or chronic episodes, why do they develop recurrent and/or chronic episodes, and how can we prevent development of recurrent and/or chronic episodes). Clinical staging might be a solution for how we can structure the heterogeneity in the course of depression.

Clinical staging

A possible solution to structure the heterogeneity in the course of depression is clinical staging. Staging is a diagnostic tool to describe, the progression of a disorder/disease

that happens over time. "Staging aims to divide the natural course of a disorder/disease 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."[13] Clinical staging is a simple and practical solution used in medicine for somatic disorders for more than a hundred years.[14]

Clinical staging in somatic disorders

In 1902 Dorothy Reed recognized that patients with Hodgkin's disease could be staged in those with lymphadenopathy and those with lymphadenopathy plus systemic symptoms (e.g. night sweats). This simple staging model based on just clinical symptoms has since than be extended with pathophysiological disease characteristics into a clinic-pathophysiological staging model with 4 stages and 4 modifying features, with for each stage specific treatments and prognosis.[15] Since this earliest model hundreds of staging-models have been developed for again hundreds of somatic diseases, such as diabetes,[16] and kidney disease.[17] Moreover, besides clinical and/or pathophysiological staging-models, functionality staging models for somatic syndromes, such as heart failure[18] were designed based on level of disability. These somatic diseases/syndromes are all characterised by a natural course that is progressive, meaning that if nature takes it course the disease will ultimately lead to severe impairment or early death. Staging of a disorder is often followed by profiling. Profilers are markers (e.g. from neuroimaging or 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.[19] Staging plus profiling improved the diagnostics for somatic disorders, since they helped devise specific treatments for specific stages, and to make the case for early detection. Ultimately, early detection leads to early intervention with treatments that have less side-effects than treatments for later stages and that stop the process of progression giving a better prognosis. This is a positive result for patients, and secondly for public health. It has been hypothesized that some mental disorders such as MDD might have similar benefits from application of staging.

Clinical staging in psychiatry

In 1993 Fava and Kellner[20] were the first to suggest that the diagnostics of psychiatry might benefit from clinical staging. They attributed the lack of the existence of staging models for psychiatry to the focus on cross-sectional descriptions of the disorder rather than longitudinal studies that examine prodromal symptoms, the fully developed disorder and residual symptoms. Most evidence in that time came from studies on patients in secondary and tertiary health care, there were the most severe cases with end stages of the disorder will be found; rather than the general population, were persons with rather early

symptoms ofthe disorders might be found. Fava and Kellner proposed staging models for schizophrenia, MDD, bipolar disorder and panic disorder in 1993. Since then different staging models have been designed for MDD that fit different purposes,[21,22] not only staging disease progression based on clinical characteristics of the presenting disorder, but also staging of disease progression based on level of treatment resistance of the presenting disorder.[22,23] In this thesis we will focus on a staging model that stages depression progression based on clinical characteristics. The model presented by Hetrick et al.,[24] is in current epidemiological work the most applied and examined. This model is based on the original staging model by McGorry and colleagues[14] that was developed for severe psychotic and affective disorders. Hetrick et al.,[24] model consists of eight stages. Three stages that describe people that never experienced a depressive episode that, however, have different levels of risk for developing depression, therefore called by us the 'at-risk for MDD stages'; and five stages that describe people with an MDD diagnosis but at different phases of progression, called by us 'full-threshold MDD stages'. In table 1, the eight clinical stages of depression are shown, and figure 2 is a graphical depiction of the stages.

Table 1: Stages of depression as suggested by Hetrick et al.[24] based on earlier work of McGorry.[14]

Stage			Description
AT-RISK for MDD	0		Increased risk of anxiety or depressive disorder; no symptoms currently. (e.g. First degree teenage relatives of probands).
	1	A	Mild or nonspecific symptoms of anxiety or depression, with mild neurocognitive deficits and functional change or decline.
		B	Ultra-high risk: moderate but sub-threshold symptoms of anxiety or depression, with moderate neurocognitive changes and functional decline to caseness (GAF < 70).
FULL-TRESHOLD MDD	2		First episode of MDD; full-threshold disorder with moderate to severe symptoms, neurocognitive deficits and functional decline (GAF 30-50).
	3	A	Incomplete remission from first episode of care.
		B	Recurrence or relapse of depressive disorder which stabilizes with treatment at a level of GAF, residual symptoms, or neurocognition below the best level achieved following remission from first episode.
		C	Multiple relapses, provided worsening in clinical extent and impact of illness is objectively present.
	4		Severe, persistent OR unremitting illness as judged on symptoms, neurocognition and disability criteria.

Abbreviations: GAF= global assessment of functioning; MDD= major depressive disorder

The three 'at-risk for MDD stages' are divided to relative risks for developing depression. In stage 0 are people without any depressive symptoms but that are at risk because they have first-degree family members with depression. In stage 1A are people experiencing some mild depressive symptoms, in stage 1B are people experiencing subthreshold depressive symptoms. The five 'full-threshold MDD stages' are divided according to increasing level of MDD progression. In stage 2 are patients experiencing a first depressive episode. In stage 3A are patients with a first episode that does not fully remit. In stage 3B are patients with a first relapse, which is a second episode. In stage 3C are patients that have a third till umpteenth episode of depression. And finally in stage 4 are patients with a chronic episode, an episode

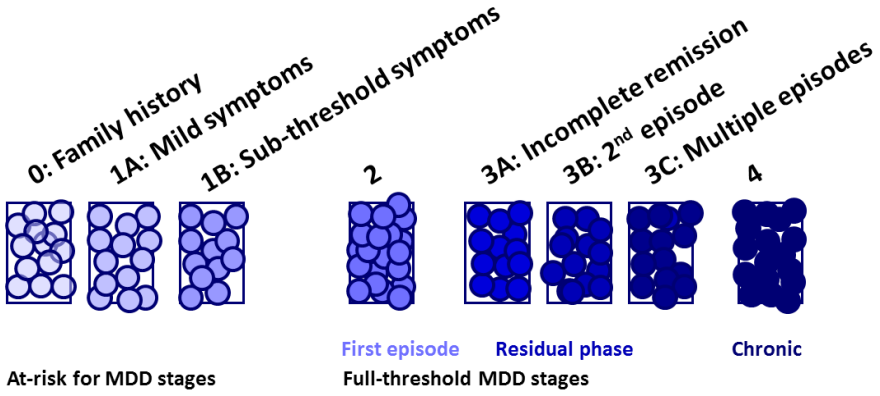

Figure 2: graphical presentation of how clinical staging can structure the heterogeneity in the diagnosis of MDD along the line of the natural progressive course of depression.
Based on the stages for unipolar depressive disorders as proposed by Hetrick et al.,[24] and based on the stages for psychotic and severe mood disorders made by McGorry et al.[14]

lasting for 2 years regardless of the number of the episode.

As described before, clinical staging is a tool to describe the progression of a disorder over time. So what evidence did Fava and Kellner have that depression is a progressive disorder?

Is depression a progressive disorder?

In 1993, Fava and Kellner found evidence for progression of MDD in the fact that a first full-blown episode of MDD is nearly always preceded by less severe symptoms of depression, what they call the prodromal phase of MDD. This prodromal phase is characterized by generalized anxiety, anhedonia, irritability, fatigue, initial and delayed insomnia.[20] This prodromal phase is later by McGorry subdivided in the at-risk stages 1A and 1B described above. Extensive evidence exist that people with a family history of depression or even other mental-health disorders are at increased risk to develop depression themselves.[25] McGorry therefore included a stage 0 to his staging model.

Both Fava and McGorry than define a first episode of MDD as the first stage of full-threshold MDD, and recurrent MDD as a more severe stage, and both see chronic MDD (an episode lasting longer than 2 years) as the final stage of MDD progression. The rationale for considering recurrent MDD as an index of disease progression is based on the clinical observations first made by Kraepelin in 1921, he noted: that patients with multiple affective episodes tend to have progressively shorter well intervals between episodes later than between episodes early in their course of illness, which is also called cycle acceleration; and that subsequent episodes of depression occur autonomously of stress with repeated depression episodes, in other words while early episodes are dependent on stress, later episodes start spontaneous without (severe) stress.[26,27] Others observed that over time

patients' subsequent episodes tend to last longer[28] and be more severe.[27,29] Post tried to explain these clinical observations with his kindling and sensitization hypotheses.[30] The *kindling hypothesis* assumes that subsequent episodes of depression occur autonomously of stress with repeated depression episodes; as a consequence of prior episodes causing some brain damage making a person more vulnerable to new episodes independent of stress. Indeed it has been found that with each new episode a patient experiences, the risk for a new episode increases;[31] that patients whom have experienced multiple episodes show more distinct brain alterations[32,33] and that recurrent episodes seem to start without a stressor.[34] The *sensitisation hypothesis* assumes that due to the brain scarring, events of less and lower severity trigger episodes with successive recurrences. This phenomenon has been studied less, but some evidence supports this hypothesis.[35]

Evidence for chronic depression being a more progressed form of MDD has been found in that those with chronic symptoms tend to have a worse prognosis over time.[36–38] In addition, in patients with a chronic episode, long-lasting and/or more intensive specialised psychotherapeutically treatment are often necessary.[36] Moreover, some studies suggest recurrent episodes are a risk factor for a chronic episodes.[37]

Both Fava&Kellner and McGorry recognize the importance of residual symptoms after an acute episode of depression (Stage 3A first episode with incomplete remission). Studies have consistently shown that patients who remitted from their acute episode but remain having residual subthreshold symptoms are at higher risk to develop a recurrent episode.[39]

In summary, for those who in life develop a first episode of depression, at least half will develop subsequent episodes. In those patients, depression seems to follow a progressive course. For those that do not develop a recurrent episode after experiencing a first episode, we assume for now that they have received a proper intervention that has prevented them from progression. However, it might also be that depression is not a progressive disorder and that recurrent and chronic episodes are the consequence of something else than progression of the disorder. This is an interesting thought that will be discussed in the general discussion of this thesis.

Thus, assuming that depression is indeed a progressive disorder, diagnostics of depression might improve by implementing staging, focusing the patients and clinicians attention to early identification of those at risk for a progressive course and leading to treatment intervention that might prevent this progression. Clinical staging models for depression have been developed and its stages are based on clinical characteristics (number of episodes, duration of symptoms) that seem to indicate progression of the disorder. However, whether these staging models are truly valid has barely been examined. In 2010 Agius and collegues[40] suggested three criteria that must be fulfilled for the idea of a clinical staging model to be appropriate: 1) each individual stage must be associated with a well-defined clinical presentation; 2) the application of a staging system must actually help in

assessing the patient and deciding appropriate treatment as well as planning research into the treatment of the illness 3) stages must be mirrored by anatomical or pathological changes which can be observed in the brain which can be related to the changes in the clinical picture.[40] This final step could be seen as the development from a clinical staging model to a clinic-pathophysiological staging model. Examination of these criteria requires a large cohort of patients in different phases of their disease. At the start of this thesis, the staging model had only been examined in young persons in early phases of their illness.[41]

General objectives of this thesis

The first aim of this thesis is 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 based on the criteria (according to Agius et al.,[40]) that need to be fulfilled for the idea of depression staging to be valid. First (aim 1A), is each individual subsequent stage associated with a well-defined clinical presentation and specific prognosis that is worse than the prior stage? In addition (aim 1B), is each individual subsequent stage mirrored by a change in levels of pathological or genetic markers that is worse than the prior stage, and which thus can be related to the changes in the clinical picture? The second aim of this thesis is 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. Examined is the performance of a wide array of characteristics in predicting the course trajectories for MDD patients. To study all these research aims an epidemiological perspective is taken, based on a large longitudinal cohort well characterized in terms of psychiatric pathology: the Netherlands Study of Depression and Anxiety. A unique dataset as it includes a cohort of patients that at their first assessment are in different phases of their depressive disorder, whom than have been followed for 6-years, allowing me to study the course of depression in relation to those different phases and including aspects such as long-term comorbidity and disability.

This is an innovative thesis, since it is one of the first to examine all the individual stages of the staging model for depression, rather than only the at-risk stages or including a combination of disorders. Findings of this thesis could help improving a staging model that directs the focus of depression diagnostics to early recognition and eventually early intervention, preventing the development of a recurrent and chronic disorder.

Cohorts studied in this thesis

Netherlands Study of Depression and Anxiety (NESDA).

NESDA is an on-going longitudinal cohort study that started in 2004 and examines the course and consequences of depressive and anxiety disorders.[42] At baseline 2981 persons

between the age of 18 and 65 years with a current depression and/or anxiety disorders (57%), a remitted depression and/or anxiety disorder (21%) and controls with no lifetime history of any psychiatric disorder (22%) were recruited from the general population, primary health care and secondary mental health care, to represent persons along the whole developmental range of psychopathology. Excluded were those who: 1) had insufficient command of the Dutch language, and 2) had a primary clinical diagnosis of bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, severe substance use disorder or a psychotic disorder. The baseline assessment was a 4-hour face-to face interview at one of our clinics, were participants were assessed on demographic and personal characteristics, and received a standardized diagnostic psychiatric interview and a medical assessment. The Ethical Review Boards of all the participating centres approved the study and all participants signed an informed consent. Every 2-year after baseline, a face-to-face assessment was conducted; they had a response rate of 87.1% (n=2596) at 2-year, 80.6% (n=2402) at 4-year, and 75.7% (n=2256) at 6-year follow-up.

For the genetic analyses, described in the chapter 5 we made use of two more cohorts.

The Netherlands Twin Register (NTR)

The Netherlands Twin Register (NTR) has collected longitudinal data on Dutch twin families involving nearly 40.000 adult participants. Since the start in 1989, extensive data has been collected on participants' demographics, health, lifestyle, personality, and psychopathology mostly via self-report questionnaires, but also via interviews. Presence of a psychiatric diagnosis was made if reported by the participant or if the participant had a consistently high factor score based on a multivariate analyses of depressive complaints, anxiety, neuroticism and somatic anxiety.[43,44] The ethical review board of the contributing university has approved this study and all participants have signed an informed consent.

RADIANT-UK

RADIANT-UK is a subset with only United Kingdom (UK) participants of the larger RADIANT study that also includes cases from Europe and the United States of America.[45] RADIANT-UK comprises three cohorts from which depressed cases were selected. Two studies that focused on recurrent depression: the Depression Case Control (DeCC) study, and the Depression Network (DeNt) study; and one pharmacogenetics study: the Genome-Based Therapeutic Drugs from Depression (GENDEP) study.[46–48] The GENDEP study included only cases with current MDD of at least moderate severity and consisted for 60.4% of recurrent cases. Controls, derived from the DeCC and from the BACCS a bipolar case control study, were collected in the UK and screened for absence of lifetime depressive symptoms via a telephone interview. MDD diagnoses were made with the Schedules for Clinical Assessment

in Neuropsychiatry (SCAN) interview.[49] All study participants provided informed consent and ethical approval was obtained from relevant institutional review boards.

Aims & outline of this thesis

Assembling the observations addressed in the general introduction, the outline of this thesis is presented here.

Regarding the first aim: is clinical staging of depression an effective and valid diagnostic tool to capture the natural progressive course of depression (and as such to structure the heterogeneity in the diagnoses of depression)? We first (aim 1A) examine whether each individual stage is associated with a well-defined clinical presentation and specific prognosis that is worse than the prior stage. In **chapter 2** we examine whether the eight stages of depression defined by the model of Hetrick et al.,[24] are associated with a stepwise worsening of a range of clinical characteristics (clinical presentation) and whether they predict the subsequent 2-year course of MDD (prognosis). In **chapter 3** we focuse on the absence/presence of prior MDD episodes as a potential staging criteria: we examine whether patients divided in first- versus recurrent episode MDD differ in clinical and/or etiological characteristics and course outcomes. Next (aim 1B), we examine whether each individual subsequent stage is mirrored by a change in levels of pathological or genetic markers that is worse than the prior stage, and which thus can be related to the changes in the clinical picture. In **chapter 4** we examine whether increasing stages are paralleled by more pronounced dysregulation in four central depression-related pathophysiological mechanisms (inflammation, hypothalamic-pituitary-axis, neurotropic growth and vitamin D). In **chapter 5** we do this for the number of genetic risk variants for three major psychiatric disorders (depression, bipolar disorder and schizophrenia).

Regarding our second aim: which 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 further examine whether younger age at onset, longer duration of depressive symptoms, positive MDD family history, more depressive symptoms, higher severity of depressive symptoms, and the presence of recurring MDD episodes are associated with an increased genetic psychiatric risk. Finally in **chapter 6** we describe the 6-year course of patients initially diagnosed with MDD, regardless of staging but including potential comorbid psychopathology. Moreover, in preliminary analyses applied to the data of chapter 6, we examine the potential value of a wide array of clinical characteristics predicting the disorders course.

REFERENCES

1 Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2163–96.

2 Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health 2013; 34: 119–38.

3 Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT et al. Multiple recurrences of major depressive disorder. Am J Psychiatry 2000; 157: 229–233.

4 Ormel J, Oldehinkel AJ, Vollebergh W. Vulnerability Before, During, and After a Major Depressive Episode. A 3-Wave Population-Based Study. Arch Gen Psychiatry 2004; 61: 990–996.

5 Penninx BWJH, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med 2013; 11: 129.

6 Sobocki P, Jönsson B, Angst J, Rehnberg C. Cost of depression in Europe. J Ment Health Policy Econ 2006; 9: 87–98.

7 Olesen J, Gustavsson A, Svensson M, Withchen H–., Jonsson B. The economic cost of brain disorders in Europe. Eur J Neurol 2012; 19: 155–162.

8 Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Costs of nine common mental disorders: implications for curative and preventive psychiatry. J Ment Health Policy Econ 2006; 9: 193–200.

9 Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. 2006.

10 American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders Fifth Edition. 5th ed. American Psychiatric Association Pusblishing: Arlington, 2013.

11 Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M et al. Major depressive disorder. Nat Rev Dis Prim 2016; 2: 160-65.

12 Spijker J, de Graaf R, van Bijl R, Beekman ATF, Ormel J, Nolen WA. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry 2002; 181: 208–213.

13 Gonella J, Hornbrook M, Louis D. Staging of disease. A case-mix measurement. JAMA 1984; 251: 637–644.

14 Mcgorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry 2006; : 616–622.

15 Eyre TA, King AJ, Collins GP. Classical Hodgkin's lymphoma: past, present and future perspectives. Br J Hosp Med 2013; 74: 612–618.

16 Seino Y, Nanjo K, Tajim N, Kadowaki T, Kashiwagi A, Araki E et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010; 1: 212–228.

17 National Institute for Health and Care Excellence (NICE). Chronic kidney disease early identification and management of chronic kidney disease in adults in primary and secondary care.. NICE clinical guideline 182, 2015.

18 American heart association. Heart failure classes. 2016. http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp (accessed 19 Sep 2016).

19 Huijgens PC. [Disease profiling in haemato-oncology]. Tijdschr Psychiatr 2012; 54: 921–5.

20 Fava GA, Kellner R. Staging: a neglected dimension in psychiatric classification. Acta Psychiatr Scand 1993.

21 Cosci F, Fava GA. Staging of mental disorders: systematic review. Psychother Psychosom 2013; 82: 20–34.

22 Ruhé HG, van Rooijen G, Spijker J, Peeters FPML, Schene AH. Staging methods for treatment resistant depression. A systematic review. J Affect Disord 2012; 137: 35–45.

23 Fekadu A, Wooderson S, Donaldson C, Markopoulou K, Masterson B, Poon L et al. A Multidimensional Tool to Quantify Treatment Resistance in Depression: The Maudsley Staging Method. J Clin Psychiatry 2009; 70: 177–184.

24 Hetrick SE, Parker a G, Hickie IB, Purcell R, Yung a R, McGorry PD. Early identification and intervention in depressive disorders: towards a clinical staging model. Psychother Psychosom 2008; 77: 263–70.

25 Klein DN, Glenn CR, Kosty DB, Seeley JR, Rohde P, Lewinsohn PM. Predictors of first lifetime onset of major depressive disorder in young adulthood. J Abnorm Psychol 2013; 122: 1–6.

26 Kraepelin E. Manic-depressive insanity and paranoia. Translated. Translated by RM Barclay, Edited by GM Robertson. Edinburgh: E & S Livingstone. Reprinted New York: Arno Press 1976: York:, Edinburgh: E & S Livingstone., 1921.

27 Post RM. Mechanisms of illness progression in the recurrent affective disorders. - PubMed - NCBI. Neurotox Res 2010; 18: 256–271.

28 Kessing LV. Course and cognitive outcome in major affective disorder. Dan Med J 2015; 62: B5160.

29 Kessing LV. Severity of depressive episodes during the course of depressive disorder. Br J Psychiatry 2008; 192: 290–293.

30 Post RM. Transduction of Psychosocial Stress Into the Neurobiology of Recurrent Affective Disorder. Am J Psychiatry 1992; 149: 999–1010.

31 Bockting CLH, Spinhoven P, Koeter MWJ, Wouters LF, Schene AH. Prediction of Recurrence in Recurrent Depression and the Influence of Consecutive Episodes on Vulnerability for Depression: A 2-Year Prospective Study. J Clin Psychiatry 2006; : 747–755.

32 Lorenzetti V, Allen NB, Fornito A, Yücel M. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J Affect Disord 2009; 117: 1–17.

33 Mckinnon MC, Yucel K, Nazarov A, Macqueen GM. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. J Psychiatry Neurosci 2009; 34: 41–54.

34 Stroud CB, Davila J, Moyer A. The Relationship Between Stress and Depression in First Onsets Versus Recurrences: A Meta-Analytic Review. J Abnorm Psychol 2008; 117: 206–213.

35 Stroud CB, Davila J, Hammen C, Vrshek-Schallhorn S. Severe and nonsevere events in first onsets versus recurrences of depression: Evidence for stress sensitization. J Abnorm Psychol 2011; 120: 142–154.

36 Cuijpers P, van Straten A, Schuurmans J, van Oppen P, Hollon SD, Andersson G. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. Clin Psychol Rev 2010; 30: 51–62.

37 Hölzel L, Härter M, Reese C, Kriston L. Risk factors for chronic depression--a systematic review. J Affect Disord 2011; 129: 1–13.

38 Rush a J, Wisniewski SR, Zisook S, Fava M, Sung SC, Haley CL et al. Is prior course of illness relevant to acute or longer-term outcomes in depressed out-patients? A STAR*D report. Psychol Med 2012; 42: 1131–49.

39 Fava GA, Ruini C, Belaise C. The concept of recovery in major depression. Psychol Med 2007; 37: 307–17.

40 Agius M, Goh C, Ulhaq S, McGorry PD. The Staging model in schizophrenia, and its clinical implications. Psychiatr Danub 2010; 22: 211–220.

41 Hickie IB, Scott EM, Hermens DF, Naismith SL, Guastella AJ, Kaur M et al. Applying clinical staging to young people who present for mental health care. Early Interv Psychiatry 2013; 7: 31–43.

42 Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen W a, Spinhoven P et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res 2008; 17: 121–40.

43 Boomsma DI, Vink JM, van Beijsterveldt TCEM, de Geus EJC, Beem AL, Mulder EJCM et al. Netherlands Twin Register: a focus on longitudinal research. Twin Res 2002; 5: 401–6.

44 Willemsen G, Vink JM, Abdellaoui A, den Braber A, van Beek JHDA, Draisma HHM et al. The Adult Netherlands Twin Register: Twenty-Five Years of Survey and Biological Data Collection. Twin Res Hum Genet 2013; 16: 271–281.

45 Power R a., Keers R, Ng MY, Butler AW, Uher R, Cohen-Woods S et al. Dissecting the Genetic

Heterogeneity of Depression Through Age at Onset. Am J Med Genet Part B Neuropsychiatr Genet 2012; 159 B: 859–868.

46 Cohen-Woods S, Gaysina D, Craddock N, Farmer A, Gray J, Gunasinghe C et al. Depression Case Control (DeCC) Study fails to support involvement of the muscarinic acetylcholine receptor M2 (CHRM2) gene in recurrent major depressive disorder. Hum Mol Genet 2009; 18: 1504–1509.

47 Farmer A, Breen G, Brewster S, Craddock N, Gill M, Korszun A et al. The Depression Network (DeNT) Study: methodology and sociodemographic characteristics of the first 470 affected sibling pairs from a large multi-site linkage genetic study. BMC Psychiatry 2004; 4: 42.

48 Uher R, Huezo-Diaz P, Perroud N, Smith R, Rietschel M, Mors O et al. Genetic predictors of response to antidepressants in the GENDEP project. Pharmacogenomics J 2009; 9: 225–233.

49 Wing JK. SCAN: Schedules for Clinicial Assessment in NEuropsychiatry. Arch Gen Psychiatry 1990; 47: 589.