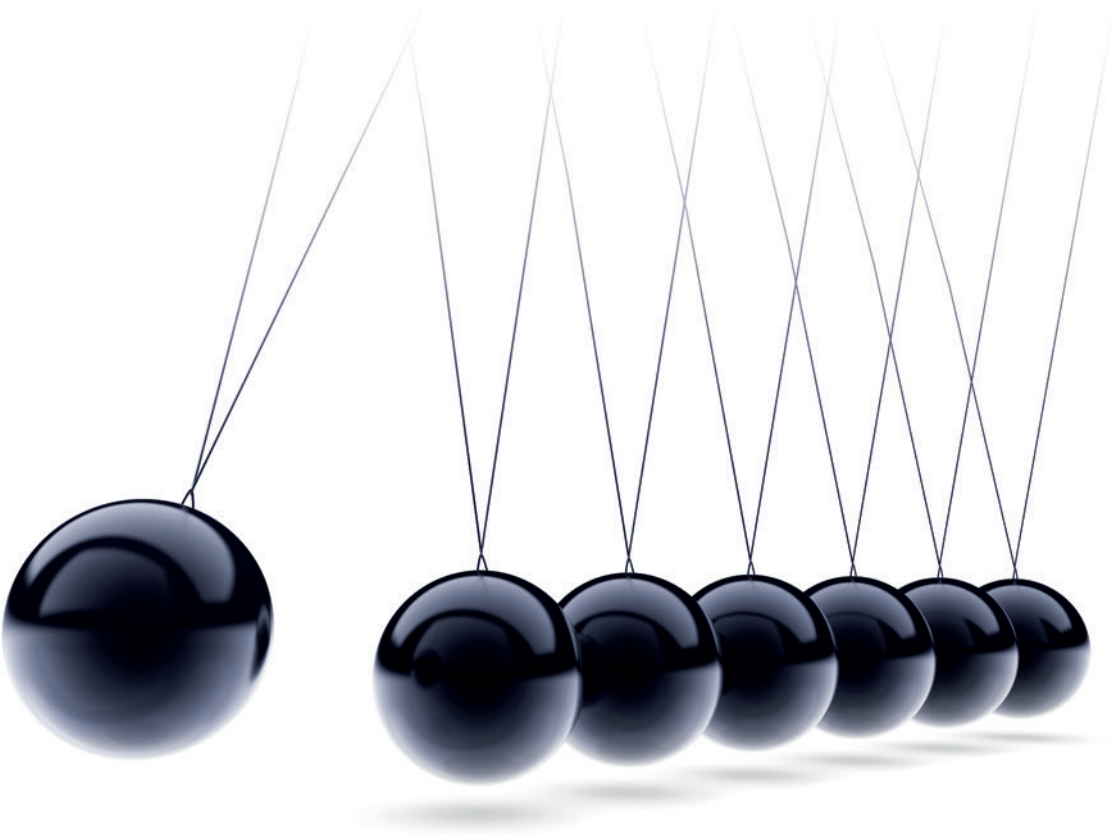
RECURRENCE OF MAJOR DEPRESSIVE DISORDER

TOWARDS A MODEL OF RISK



F. Hardeveld

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RECURRENCE OF MAJOR DEPRESSIVE DISORDER

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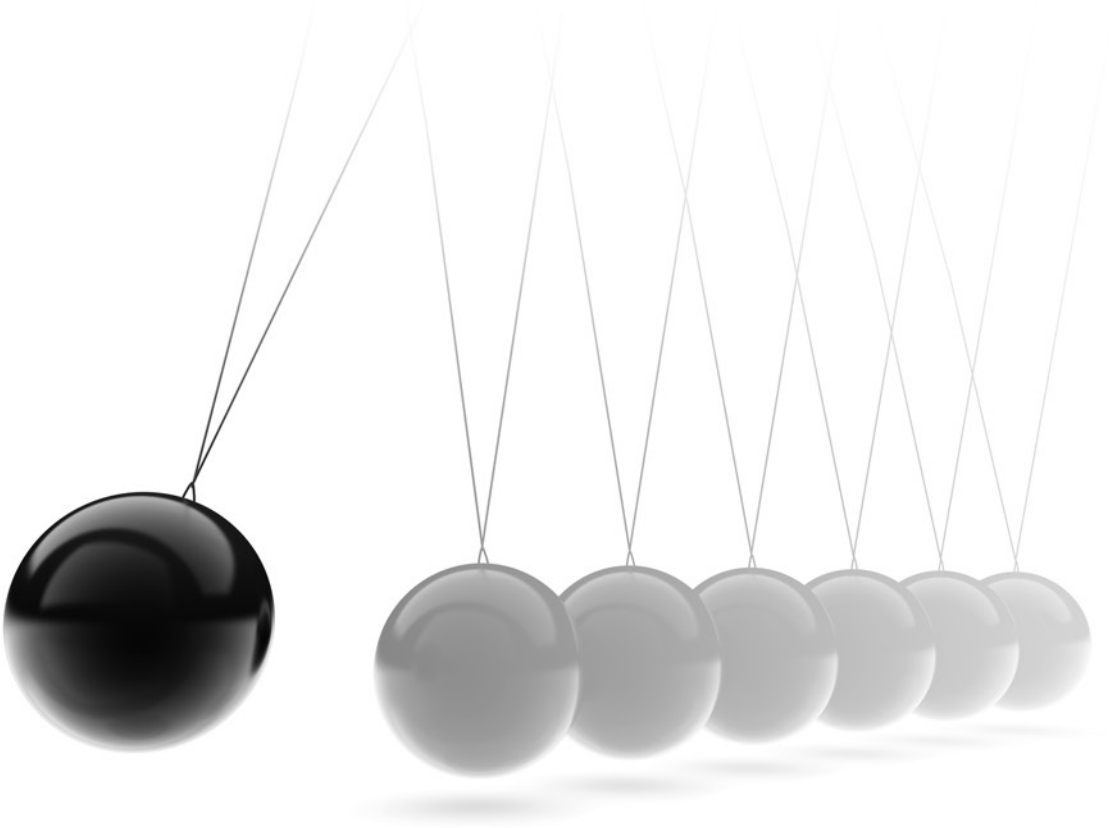
Introduction



Suppose the following patient visits the psychiatrist.

Miss C, 34 years old, has suffered her third depressive episode. The first was at the age of 22, and the second at age 31, but this is the first time she has sought medical help. Her mother experienced depression at age 40. Following treatment with the antidepressant escitalopram, Miss C recovers but still experiences mild insomnia and difficulties with concentration. Both the patient and psychiatrist are glad that the depression is in remission. She asks the psychiatrist about the chances for recurrence. This is a basic question in everyday practice, but is it possible to predict recurrence? What are the main risk factors and can patients with a high level of risk be identified? This thesis attempts to provide answers to these questions.

1.1. Burden of depression

Unipolar major depressive disorder (MDD) is a highly prevalent condition associated with a high level of disability. In the ten high-income countries participating in the World Mental Health Survey Initiative, the average lifetime and 12-month prevalence of MDD was estimated at 14.6% and 5.5%, respectively (Bromet et al., 2011). In the Dutch population, the lifetime and 12-month prevalence of MDD is estimated at 18.7% and 5.2%, respectively (de Graaf et al., 2012). Despite effective treatment strategies for MDD (Vöhringer et al., 2011), its prevalence has not fallen in recent years (de Graaf et al., 2012). Rather, the disease burden is expected to worsen (WHO, 2008). Currently, depression is one of the leading causes of sickness leave (de Graaf et al., 2012) and years lost to disability (WHO, 2001). By 2020, depression is projected to rank second in terms of disability-adjusted life years (DALYs) calculated for all ages and both sexes, and this is already the case for the 15-44 age-group (WHO, 2008). The burden is partly explained by the course of the disease, as recurrence and chronicity are common (Keller et al, 1992; Spijker et al, 2002). Health economic studies show that prevention of recurrence is likely to be effective in reducing the population burden of MDD (Vos et al., 2004). Psychological interventions (number needed to treat (NNT=5)) and maintenance treatment with antidepressants (NNT=13) are effective in preventing recurrence of MDD (Biesheuvel-Leliefeld et al., 2014). It remains to be seen which subjects are prone to recurrence and should be advised to undergo such therapies.

1.2. Historical overview

The importance of describing the course of psychiatric disorders in a systematic manner was first highlighted by Kahlbaum (1874) and further applied in research by Kraeplin (1899). Kraeplin described an average duration of two to three months of depressive episodes in bipolar disorder and nine to twelve months in depressive disorder with a minority of patients with MDD experiencing a chronic course of melancholic symptoms for more than two years (Kraeplin, 1899). This pioneering work set the stage for research on the course of affective disorders (Angst, 2002). The course of depressive disorder was, in Kraeplin's view, influenced by external factors; he wrote:

> '*The attacks of depressive or manic-depressive illness begin not infrequently after the illness or death of near relatives. In spite of the removal of the discharging cause, the attack follows its independent development. But, finally, the appearance of wholly similar attacks on wholly dissimilar occasions or quite without external occasion shows that even if there has been external influence, it must not be regarded as a necessary presupposition for the appearance of the attack'* (Kraeplin 1899).

Anecdotally, in 1921 Kraeplin reported on a patient with depression related to the death of her husband. A second episode occurred after the death of her dog and a subsequent episode following the death of her pigeon. This anecdote is in correspondence with the theory later formulated by Post (1992). This theory holds that less severe life events could provoke a depression in those with multiple episodes of depression in the past. According to Post, the course of the condition is influenced by both sensitization to stressors, i.e. increased sensitivity to psychosocial stressors, and episode sensitization, i.e. increased vulnerability to recurrence with shorter intervals of remission as a function of the number of episodes. Both mechanisms could affect the level of gene expression of neurotransmitters, receptors and neuropeptides in the long term. Thus, both stressors and episodes may leave residual traces and vulnerabilities to further occurrences of affective illness. This suggests that the biochemical and anatomical substrates underlying affective disorders evolve over time as a function of recurrences. Research prior to 1970 postulated that depression was a relatively benign disorder with occasional recurrences. After 1970, long-term longitudinal studies found that the course of depression was more unfavourable than previously understood (Paykel, 1994). As a result, the perception of major depressive disorder shifted from that of an acute disorder to a chronic disorder. Nowadays, the course of depressive disorder is described as a highly variable continuum of depressive symptomatology (Judd et al., 1998; Spijker et al., 2002).

1.3. Recurrence of MDD

Approximately 50% of the subjects who recover from an initial depressive episode will experience one or more additional episodes (Kupfer et al., 1996; Post, 1992). The risk of further episodes increases with each new episode: two major depressive episodes (MDEs) confers a 70% risk of a third, while three MDEs confer a 90% risk of a fourth (APA, 2000). Over a lifetime, the average number of major depressive episodes ranges between four and eight episodes and a considerable amount of time may pass between episodes (Keller et al, 1996). Although many studies have been published on the recurrence of MDD, it is difficult to compare the results due to differences in definitions of recurrence. In order to provide a clear definition, Frank et al. (1991) suggested describing the course of depression in terms of the 5 R's: *response, remission, recovery, relapse,* and *recurrence* (Fig. 1). Response is defined as a significant improvement of symptoms after starting treatment and is often operationalized as an improvement of symptoms of more than 50% on the Hamilton Rating Scale for Depression (HRSD). The patient is deemed to be in remission when there are no symptoms or minimal symptoms of depression operationalized as a score on the HRSD of 8 points or lower. Recovery may be reached after remission when the patient has no symptoms of MDD within a fixed period. Previous research did not set a strict fixed period for remission. For example, one of the most important studies on the course of depression, the Collaborative Study of the Psychobiology of Depression (CDS) by the National Institute for Mental Health (NIHM) (Mueller et al., 1999) defined remission as minimal or no symptoms for two consecutive months. Other studies used other

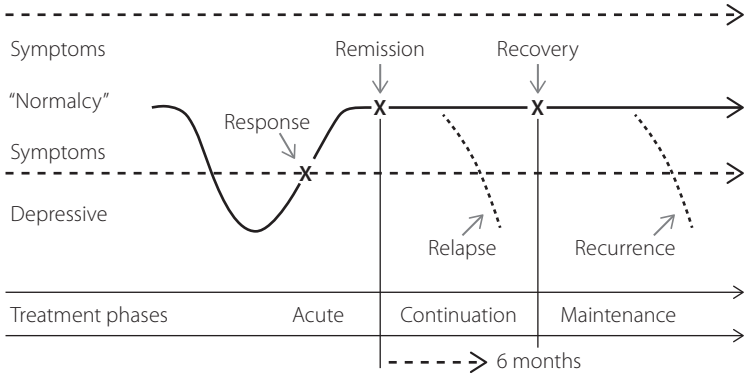


Figure 1 Course of major depressive disorder

Derived from Kupfer et al., 1991

definitions for remission and recovery and are therefore difficult to compare (Thase, 1999). Furthermore, the classification has not been validated (Riso et al., 1997; Furakawa et al., 2008). Furakawa et al. (2008) recommended 4 or 6 months of remission. Relapse is defined as a return of symptoms during remission, and recurrence as a return of symptoms after recovery.

1.4. Predictors of recurrence

Knowledge of recurrence of MDD and its predictors is of major importance for treatment decisions. Predicting MDD recurrence is a complex task because many interacting factors are involved. Over the past 20-30 years, a number of studies have assessed putative predictors for MDD recurrence. The factors considered include demographic variables (such as age, sex, and level of education), psychosocial characteristics (such as personality and social support), clinical characteristics of the depressive disorder (such as the severity and duration of the index episode) and biological parameters (HPA-axis, genetics). Predictors are frequently modelled in the dynamic stress vulnerability model (Ormel et al., 2001). An adapted version is presented in Fig. 2. According to this model, biological factors, clinical features, psychosocial factors and life events interact to generate a depressive

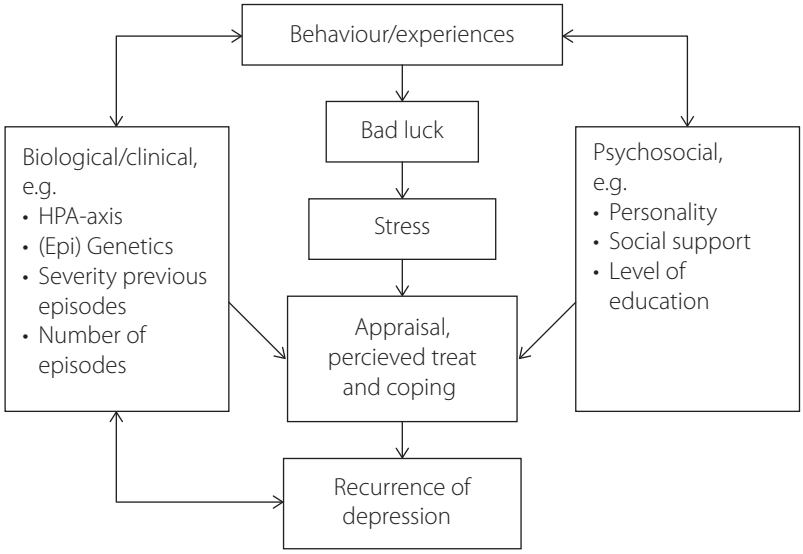


Figure 2 Adapted version of the dynamic stress vulnerability model

state. Fluctuations in symptom levels may be caused by stressors and could depend on individual coping skills. In this model, stressors are seen as predisposing factors in depression (first or recurrent episodes).

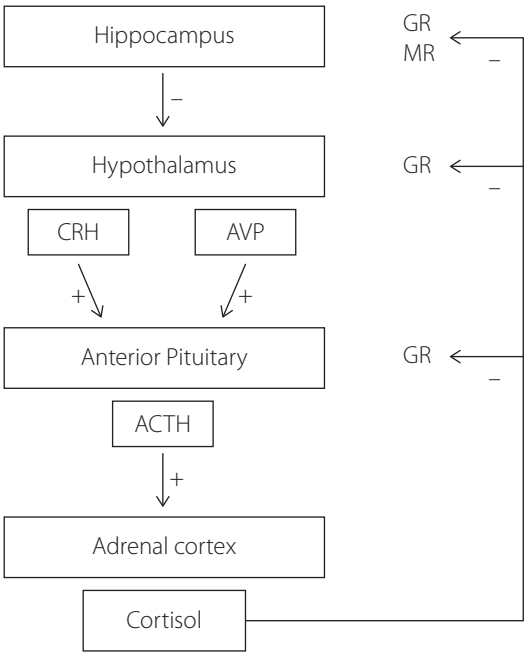
1.5. Predictors of recurrence across care settings

A small number of review studies have described the recurrence rate and predictors of recurrence (Zis & Goodwin 1979; Lavori et al., 1984; Belsher & Costello 1988; Piccinelli et al. 1994; van Weel-Baumgarten et al., 2000; Burcusa & Iacono, 2007). These reviews mainly focused on patients treated in specialized mental health care and did not use strict selection criteria**.** The focus on specialized care settings (with more severe, complex, recurrent and long-term disorders) constitutes a major limitation to current knowledge on predictors of recurrence, whereas the natural course of depressive disorders and the risk factors for recurrence are best studied using a general population sample free from selection bias (Eaton et al., 2008). Moreover, as most depressed patients are treated in primary care, risk factors for recurrence in specialized mental health care may differ from those in primary care. Research on the recurrence rate and risk factors in primary care versus specialized mental health care is still sparse.

1.6. Stressors, HPA-axis and recurrence

Stressors are thought to play an important role in the pathogenesis and recurrence of MDD (Burcusa et al., 2007; Ten Doesschate et al., 2010; Hovens et al., 2012). It seems likely that individual vulnerability to stress is key to the development of depression and subsequent recurrence, since stressful events do not automatically result in depression (de Kloet et al., 1998; de Kloet et al., 2005). The neuroendocrine response to stress includes the activation of the sympathetic nervous system and the release of cortisol from the adrenal glands mediated by the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 3) (Pariante & Lightman 2008).

Cortisol affects various systems in the body, including the HPA axis itself, the cardiovascular system, the immune system, metabolism, and cell growth. Levels of cortisol are high upon awakening, increase 50-60% in the first 30-40 minutes thereafter (known as the cortisol awakening response), drop quickly in the subsequent few hours and slowly decline to reach the lowest point near midnight (Pruessner et al., 2007). Although the HPA-axis has been studied extensively during depression (Stetler et al., 2011), and alternations to the HPA-axis has been reported to be one of the most consistent findings in psychiatry (Pariante et al., 2008), there is no consensus as to whether HPA-axis alternations have a predictive value for recurrence of MDD.



Parvocellular neurons from the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) which stimulate adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary. ACTH stimulates the release of cortisol from the adrenal cortex, which has a number of biological functions involved in the stress response. Cortisol exerts negative feedback on the hypothalamus, anterior pituitary and most importantly via the hippocampus.

GR=glucocorticoid receptor; MR=mineralocorticoid receptor. GR=glucocorticoid, MR=mineralocorticoid, ACTH=adrenocorticotropic hormone, CRH=corticotropin releasing hormone, AVP=arginine vasopressin.

Derived from Claire Abou-Seif et al., 2012.

Figure 3 The hypothalamic-pituitary-adrenal axis. Schematic diagram of the hypothalamic-pituitary-adrenal (HPA) axis

1.7. Genetic factors associated with recurrence

The effects exerted by cortisol are mediated by two brain corticosteroid receptor types, the mineralocorticoid receptor (MR), with a high affinity already occupied under basal conditions and the glucocorticoid receptor (GR), with a low affinity and activated predominantly under stress (Fig. 3). Response to stress is influenced by genetic factors (Wüst et al., 2004); the availability and efficiency of corticoid receptors are influenced by variation in the genes coding for them. Small variants, called single nucleotide polymorphisms (SNPs) are commonly present in the GR and MR receptor gene and genetic variation within the GR and MR produces differences in receptor function (Stevens et al., 2004). The GR gene (NR3C1) is located on chromosome 5 and the MR gene (NR3C2) is located on chromosome 4. Associations have been found between a number of SNPs and depression (v. Rossum et al., 2006; v. West et al., 2006). It has also been postulated that certain SNPs, which are associated with glucocorticoid sensitivity could be the weak link in the pathogenesis of depression (Pariante et al., 2008) but it is not known whether these SNPs are also associated with recurrence of MDD.

1.8. Datasets

For this thesis, data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl et al., 1998a) and the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008). NEMESIS is a prospective naturalistic psychiatric survey among the Dutch adult general population (aged 18-64) with 7076 persons recruited at baseline. Data were recorded in three waves: at baseline in 1996, at 12-month follow-up in 1997 and after three years (1999). NESDA is an ongoing longitudinal cohort study, launched in 2004, which examines the long-term course of depressive and anxiety disorders in various health care settings. The NESDA cohort (N=2981) consists of respondents (18-65 years) with (i) a current anxiety and/or depressive disorder, (ii) a prior history of a depressive and/or anxiety disorder and (iii) healthy controls. All respondents were administered a baseline assessment, which included psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Respondents were recruited in primary care through a screening procedure, in specialized mental health care when newly enrolled and in the community.

1.9. Aims and outline of the thesis

The objectives of this thesis are to examine the risk of recurrence of major depressive disorder across care settings and to study its predictors and the way they interact. On the basis of this knowledge, it might be possible to distinguish subjects at high risk for recurrence of MDD from those at low risk. Accurate identification of these groups may help to improve both the efficacy and efficiency of mental health care.

This thesis is divided into seven chapters. Following an introduction (**Chapter 1**), **Chapter 2** gives an overview of previous research on prevalence and predictors of MDD recurrence. In **Chapter 3**, the incidence and predictors of MDD recurrence in the general Dutch adult population are investigated based on NEMESIS data. In **Chapter 4**, predictors of recurrence are analysed across treatment settings. **Chapter 5** examines HPA-axis alterations as a predictor of recurrence and the glucocorticoid and mineralocorticoid receptor polymorphism associated with recurrence of MDD are examined in **Chapter 6**. Chapters four through six are based on NESDA data. In **Chapter 7** the results of the studies are summarized and discussed. The studies are summarized in Figure 4 (mind map).

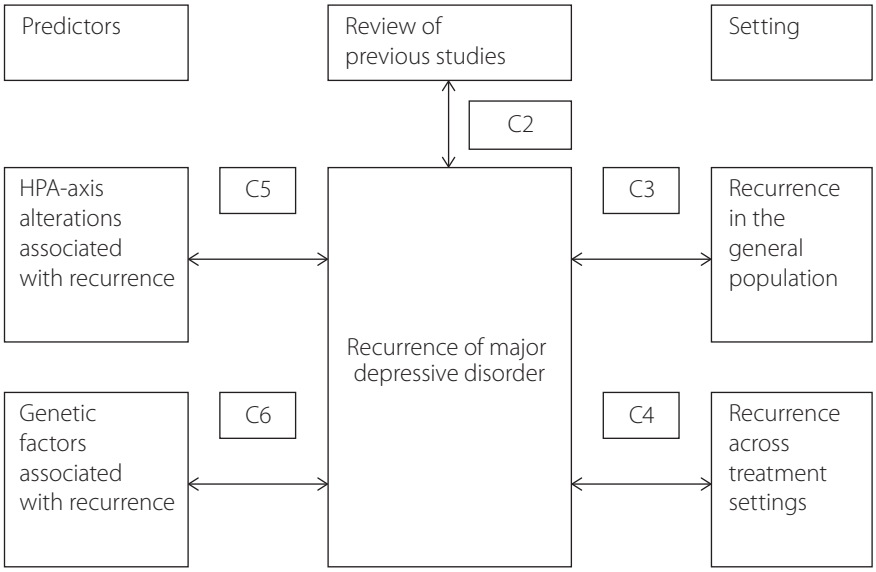


Figure 4 Overview of studies in this thesis

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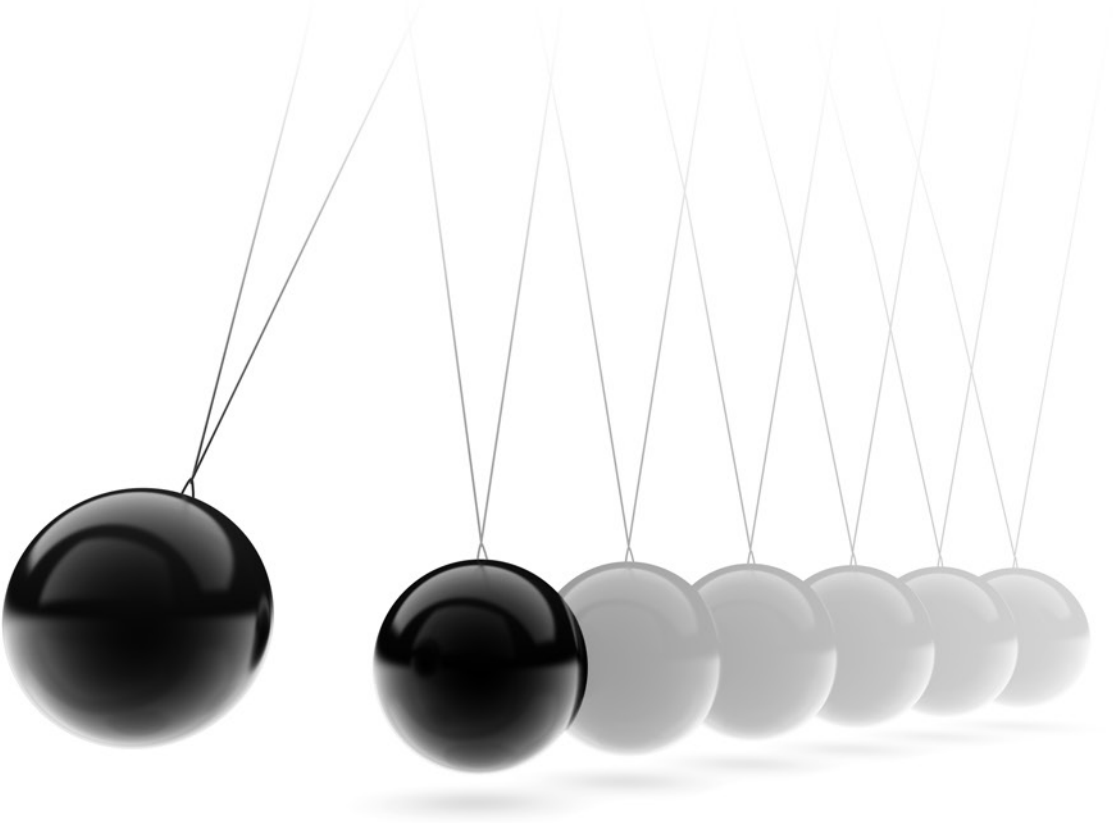
Prevalence and predictors of recurrence of major depressive disorder in the adult population



F. Hardeveld, J. Spijker, R. de Graaf, W.A. Nolen, A.T.F. Beekman.

Acta Scandinavica Psychiatrica. 2010:122(3);184-191.

Abstract

Objective: Knowledge of the risk of recurrence after recovery of a major depressive disorder (MDD) is of clinical and scientific importance. The purpose of this paper is to provide a systematic review of the prevalence and predictors of recurrence of MDD.
Method: Studies were searched in Medline en PsychINFO using the search terms 'recur*', 'relaps*', 'depress*', 'predict*' and course.
Results: Recurrence of major depressive disorder in specialised mental health care settings is high (60% after 5 years, 67% after 10 years and 85% after 15 years) and seems lower in the general population (35% after 15 years). Number of previous episodes and subclinical residual symptoms appear to be the most important predictors. Gender, civil status, and socioeconomic status seem not related to the recurrence of MDD.
Conclusion: Clinical factors seem the most important predictors of recurrence. Data from studies performed in the general population and primary care on the recurrent course of major depressive disorder are scarce.

2.1. Introduction

Major depressive disorder (MDD) is one of the most prevalent mental disorders with a high morbidity. The lifetime prevalence in the United States of America (US) is estimated at 16.2% (Kessler et al., 2003). Currently, MDD is worldwide the third leading cause of burden of disease and will rise to the first place in 2030 (WHO, 2008).

Long-term studies performed in the US (Keller et al., 1982) showed that MDD has a less favourable course than initially thought. Knowledge about the course of MDD and its determinants is of clinical and scientific importance. It would seem reasonable to treat patients with a high risk of recurrences as a chronic disorder (Andrews, 2001), while treatment of those with a low risk of recurrence may be limited to the index episode. Accurate differentiation of these groups may help to improve both the efficacy and the efficiency of mental health care. The treatment of the high risk group should not only include maintenance treatment with antidepressants, but also aim for the reduction of risk factors for recurrence. This approach has been successful in other disciplines in medicine. The prevention of myocardial infarction for example targets its risk factors (e.g. smoking, high blood pressure, and hypercholesterolemia) and this approach has lowered the incidence of myocardial infarction (Pais, 2006). Moreover, prevention programmes for diabetes have been successful in the prevention of the long-term complications, such as reducing diabetic retinopathy and nephropathy (Nathan, 1998). Identification of predictors of recurrence can help to select which patients should be offered longer term preventive care. Furthermore, it is likely that patients treated in specialised mental health care have a higher risk for recurrence than patients treated in primary care. If proven true, this would lead to different recommendations for patients treated for MDD in specialised mental health care vs. primary care.

Over the past 20-30 years several studies have been able to assess putative risk factors for recurrence of MDD. The factors that have been considered include demographic data (such as age, sex, and level of education), psychosocial characteristics (such as personality and social support) and clinical characteristics of the depressive disorder (such as the severity and duration of the index episode).

Aims of the study

To perform a systematic review of prevalence and risk factors predicting recurrence of MDD, comparing patients in specialised mental health with those seen in primary care and community settings.

2.2. Material and Methods

Relevant articles were searched in PsychINFO and Medline with the search terms 'recur*', 'relaps*', 'depress*', 'predict*', and course. The flow chart is shown in Fig. 1.

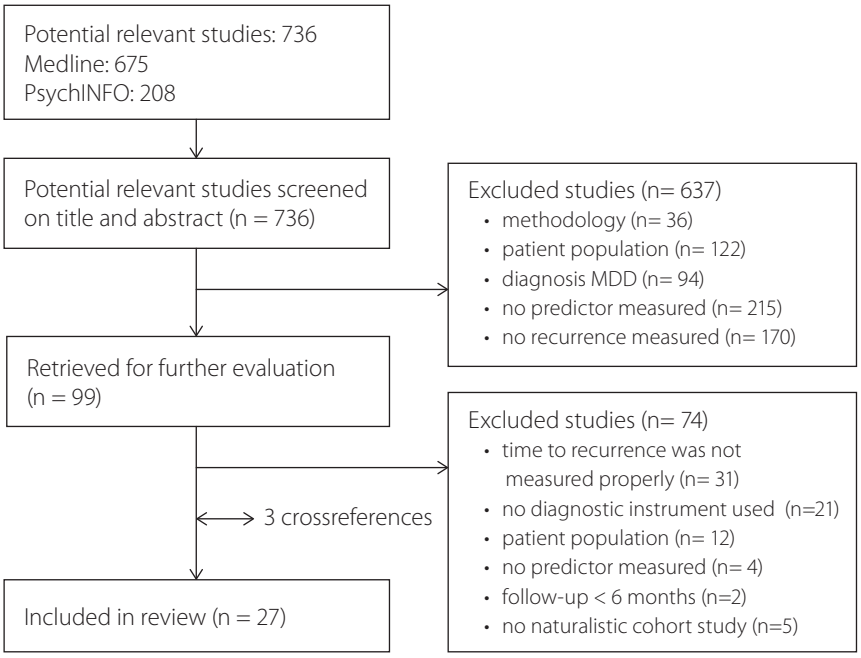


Figure 1 Flow chart of selection of studies that researched the prevalence and predictors of recurrence of MDD

Only articles written in English which studied the adult population and which were published between January 1980 and August 2008 were included (n = 736). These articles were screened on relevance, methodology, and study population by the first author (FH), using the title and summary. Ninety-nine articles were retrieved for further evaluation. Another three articles were included after examining the references. Of these 102 articles two authors (FH & JS) studied the full text. The following selection criteria were applied: i) naturalistic cohort study, ii) including subjects with MDD, iii) MDD diagnosed using a diagnostic interview or checklist based on Research Diagnostic Criteria/Bedford College Criteria (RDC/BCC) criteria, DSM III/III-R/DSM IV criteria or ICD-9/10 criteria, iv) the course had to be measured with a standardised instrument or checklist, v) with a minimum follow-up of six months, vi) and including at least 50 subjects. Moreover, vii) the criteria of

remission, recovery, relapse and recurrence according to Frank et al. (1991) had to be applied; relapse is a return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission but before recovery, recurrence is the appearance of a new episode of major depressive disorder and can occur only during a recovery, remission is a period during which an improvement of sufficient magnitude is observed that the individual no longer meets syndromal criteria for the disorder, recovery is a remission that lasts for X days or longer. Frank et al. (1991) did not formulate the time to recovery but made suggestions depending on the course instrument used. All included studies had to fulfil all the applied selection criteria. Studies that included patients with bipolar disorder, depression with a seasonal pattern, postpartum depression, or specific age groups were excluded because this may unduly influence the risk of recurrence. We did not subdivide the studies according to MDD subgroups (e.g. melancholic, with psychotic features, catatonic, atypical) because too few studies differentiated according to subgroups and in those who did the subgroups were usually too small to compare. The articles were screened independently on the selection criteria by FH & JS. When there were inconsistencies (n=3) both reviewers reached consensus by analysing the articles on the applied selection criteria together.

2.3. Results

Twenty-seven studies were included for further evaluation. The articles were subdivided in studies that included patients from the general population, primary care, and specialised mental health care. The characteristics of the included studies are summarised in Table 1.

Prevalence

The prevalence depends on the setting in which is measured. Table 2 gives an overview of the percentage of recurrence by setting.

Specialised mental health care

The majority of the available studies were carried out in specialised mental health care. Considering all studies, the overall risk of recurrence after recovery during the first year ranges between 21% and 37%. The high percentage of 37% was observed in a study that selected patients with a high number of previous episodes (Maj et al., 1992). The lowest percentage of 21% was found in a Japanese study, that included patients treated in specialised mental health care as well as primary care (Kanai et al., 2003). An important study is the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression (CDS). In this study 431 patients with a MDD were followed 15 years, the first five years half yearly and then yearly. During the first year after recovery, the risk of recurrence was 25%, increasing to 85% over 15 years (Mueller et al., 1999).

Table 1 Characteristics of studies that researched the association between predictors and recurrence risk

Author	Maximum follow-up (years)	Diagnostic instrument	Diagnosis	Number of patients 'at risk'	Duration of remission (months)	Course instrument	Predictor measured
Specialised mental health care							
Holma et al. 2008	5	SCAN	DSM-IV	140	2	LCI	demographic, clinical, personality, social
Ilardi et al. 1997	7	DIS	DSM-III-R	50	0.5	LIFE	Personality
Judd et al. 1998	10	SADS	RDC	238	2	LIFE	clinical
Judd et al. 2000	12	SADS	RDC	238	2	LIFE	clinical
Kanai et al. 2003	6	COALA	DSM-IV	82	2	COALA	demographic, clinical
Kennedy et al. 2003	11	CID	RDC	65	2	LIFE	demographic, clinical
Kennedy et al. 2004	10	CID	RDC	59	2	LIFE	clinical
Keller et al. 1983	2	SADS	RDC	234	2	LIFE	demographic, clinical
Lavori et al. 1994	5	SADS	RDC	359	2	LIFE	demographic, clinical
Maj et al. 1992	9	SADS	RDC	72	2	LIFE CPRS SADS	demographic, clinical
Melartin et al. 2004	1,5	SCAN	DSM-IV	198	2	LCI	demographic, clinical, personality, social
Mueller et al. 1999	15	SADS	RDC	380	2	LIFE	demographic, clinical
Naz et al. 2007	4	SCID	DSM-III-R	60	2	SCID	demographic, clinical
Paykel et al. 1995	1.25	CID	RDC	60	2	BDI	clinical
Paykel et al. 1996	1.25	CID	RDC	60	2	BDI	demographic, social
Pintor et al. 2003	2	SCID	DSM-III-R	183	2	HAMD	clinical
Pintor et al. 2004	4	SCID	DSM-III-R	138	2	HAMD	clinical
Ramana et al. 1995	1.25	CID	RDC	60	2	BDI	clinical
Simpson et al. 1997	15	SADS	RDC	176	2	LIFE	demographic

Solomon et al. 2000	10	SADS	RDC	318	2	LIFE	clinical
Solomon et al. 2004	15	SADS	RDC	290	2	LIFE	social
Winokur et al. 1993	5	SADS	DSM-III-R	172	2	LIFE	demographic, clinical
Primary care							
Conradi et al. 2008	3	CIDI	DSM-IV	110	2	CIDI BDI	demographic, personality, social, clinical
Gopinath et al. 2007	1	SCID	DSM-III-R	386	3	LIFE, SCID	demographic, clinical, social
General population							
Eaton et al. 1997	15	DIS	DSM-IV	80	12	DIS, LCI	demographic, clinical
Eaton et al. 2008	23	DIS	DSM-IV	78	12	LCI, DIS	demographic, clinical, social

Abbreviations:BDI, Beck Depression Index, CID, Clinical interview for Depression, CIDI, Composite International Diagnostic Interview, COAL A, Comprehensive Assessment List for Affective disorders Raskin Scale, CPRS, Comprehensive Psychopathological Rating Scale, DIS, Diagnostic Interview Schedule , DSM, Diagnostic and Statistical Manual of Mental Disorders, LCI, Life Chart Interview, LIFE, Longitudinal Interval Follow-up Evaluation, HAMD, Hamilton Rating Scale of depression, RDC, Research Diagnostic Criteria, SADS, Schedule for Affective Disorders and Schizophrenia, SCID, Structured Clinical Interview for DSM-IV, SCAN, Schedules for Clinical Assessment in Neuropsychiatry

Table 2 Percentage of patients with a recurrence of MDD during follow up

	Setting	Author				
Follow-up (years)			**1**	**5**	**10**	**15**
Percentage (%)	Specialised mental health care	Holma et al. 2008	-	70.7	-	-
		Kanai et al. 2003	21	42	-	-
		Maj et al. 1992	37[i]	75	-	-
		Mueller et al. 1999	25	60	-	85
		Melartin et al. 2004	38[ii]	-	-	-
		Ramana et al. 1985	40[iii]	-	-	-
		Solomon et al. 2000	-	-	67	-
	Primary care	Gopinath et al. 2007	31	-	-	-
	General population	Eaton et al. 1997	-	-	-	35

[i] Percentage of recurrence after 6 months is 24%.
[ii] Percentage of recurrence after 1.5 years.
[iii] Percentage of recurrence after 15 months.

Primary care and general population

Only one primary care study was included. In this study, which included 386 patients, a percentage of recurrence of 31% after a follow-up of one year was found (Gopinath et al., 2007). This percentage is comparable with results from the abovementioned studies in specialised mental health care. We also included only one prospective population-based study. This is the Baltimore Epidemiologic Catchment Area follow-up (ECA) (Eaton et al., 1997; Eaton et al., 2008) which included 78 patients at risk for a recurrence of MDD. After a follow-up of 15 years, the percentage of recurrence after recovery was 35%.

Predictors

Demographic factors

Many studies reported on the association between demographic factors and the risk of recurrence. These studies were mainly performed in specialised mental health care. Demographic factors such as gender, age, social economic status (SES) and marital status were not found to be related to the recurrence of MDD (Table 3). However, there are exceptions. Mueller et al. (1999) and Winokur et al. (1993), both part of the earlier mentioned CDS study, found a greater risk of recurrence among women. Mueller et al. (1999) observed a higher risk of recurrence among those who have never been married. And lastly, Holma et al. (2008) and Eaton et al. (1997) reported that a younger age was related to recurrence.

Table 3 Percentage of patients with a recurrence of MDD during follow up

		Significant association between recurrence of MDD present	Significant association between recurrence of MDD absent
Demographic factors	Age	48,76	58,87,93,109,115,120, 128,153
	Female	125,201	44,48,49,76,87,93,109, 115,120,128,153,166
	Marital status	125	44,48,49,76,87,93,115, 120,128,140,153
	Low social economic status/educational level	-	44,48,49,58,76,87,93, 115,120,128,153
Life events, social support, psychosocial impairment, and personality factors	Severe life event before depressive episode	-	76,120,140
	Lack of social support	-	49,76,120,140
	Decreased psychosocial functioning	58,169	-
	Comorbid personality disorder	81	76,120,153
	Neuroticism	58	76,120
	Coping skills	58,44	-
Clinical factors	Number of previous episodes	44,58,83,109,115,125, 142,168,201	76,81,87,93,120,128,153
	Subclinical residual symptoms	83,84,87,139,141,142	81,94,120
	Age of onset	49,142,201	76,94,109,115,120,153
	Severity of the last episode	58,76,81,93,120,142,153	48,115,153,166
	Duration of last episode	109,125	76,87,115,120,153
	Comorbid psychiatric disorder	76,91,115,120	81,87,109
	Family history of MDD	115	49,87,93,128,153,201

Each row represents the studies that performed research on the specific predictor in relation to recurrence of MDD. The figures refer to the literature in the reference list.

Life events, social support, impairment of psychosocial functioning and personality factors

The included studies (Holma et al., 2008; Melartin et al., 2004; Paykel et al., 1996) reported that a severe life event and lack of social support were not related to recurrence. Patients with impaired functioning in areas such as work, relationships, and leisure after (complete) remission appear to have a higher risk for recurrence of a MDD (Gopinath et al., 2007; Solomon et al., 2004). A personality disorder can be a predictor for recurrence (Ilardi et al., 1997). In a study with 50 patients who were followed 33 to 84 months, both cluster B and C personality characteristics were related to a higher risk for recurrence. There are, however, also studies which observed no such association (Holma et al., 2008; Melartin et al., 2004; Ramana et al., 1995). Patients with a high neuroticism score could also have a high risk for recurrence (Gopinath et al., 2007). However, Holma et al. (2008) observed no such association. Furthermore, it is possible that coping skills are associated with risk for a recurrence of MDD. In a study among 110 patients in a primary care population, patients with moderate coping skills had a shorter time to recurrence in comparison to those with better skills (Conradi et al., 2008). In agreement with this result, patients with lower self-efficacy had a higher risk for recurrence (Gopinath et al., 2007).

Clinical factors

Numerous clinical variables have been studied in relation to the recurrence of MDD (Table 3). The main variables are age of onset of the first depressive episode, duration and severity of the last episode, the number of previous episodes, the presence of comorbid axis I disorders, subclinical residual symptoms and a family history of MDD. One of the variables that seems associated with the recurrence of MDD is the number of previous episodes. A larger number of included studies (Kanai et al., 2003; Mueller et al., 1999; Gopinath et al., 2007; Winokur et al., 1993; Conradi et al., 2008; Judd et al., 1998; Lavori et al., 1994; Pintor et al., 2004; Solomon et al., 2000), mainly performed in specialised mental health care, found an association between the number of previous episodes and the risk of recurrence. Within these studies are CDS studies (Mueller et al., 1999; Winokur et al., 1993; Judd et al., 1998; Lavori et al., 1994; Solomon et al., 2000) which included a high number of patients with a long follow-up using the life chart method. There are, however, also some studies that did not find an association (Kanai et al., 2003; Holma et al., 2008; Melartin et al., 2004; Ilardi et al., 1997; Ramana et al., 1995; Kennedy et al., 2003; Naz et al., 2007), but most of these studies included smaller numbers of patients at risk (Kanai et al., 2003; Ilardi et al., 1997; Ramana et al., 1995; Kennedy et al., 2003; Naz et al., 2007) or did not use the life chart method (Ramana et al., 1995; Naz et al., 2007). The association between number of previous episodes and recurrence of MDD seems strong, the odds ratio is estimated at 1.64 (Judd et al., 1998). Another strong predictor for recurrence of MDD seems to be the presence of subclinical residual symptoms. Also, a larger number of included studies found an association between this predictor and the risk of recurrence (Kanai et al., 2003; Judd et al.,

1998; Pintor et al., 2004; Judd et al., 2000; Paykel et al., 1995; Pintor et al., 2003) and the included studies had a long follow-up using the life chart method (Judd et al., 1998; Judd et al., 2000). The included studies suggest that this is the strongest predictor for a recurrence. Judd et al. (1998) described that patients with residual subclinical symptoms after recovery of MDD relapsed three times faster than an asymptomatic group (median 68 vs. 23 weeks) and found an odds ratio of 3.65 for residual symptoms. Three included studies did not find an association. However, the study by Iliadi et al. (1997) included a relatively small number of patients (n=50) and Melartin et al. (2004) did find a bivariate association with an high odds ratio of 2.12 but in the multivariate models it was not significant anymore (Melartin et al., 2004).

Nonetheless, although there is strong evidence that subclinical residual symptoms are a predictor for a shorter time to recurrence, this does not imply that in the long run the overall risk of recurrence necessarily differs. Kennedy et al. (2004) reported in a study population of 60 patients with recurrent depression and residual symptoms a percentage of recurrence of 42% after one year and 56% after two years in comparison with respectively 20% and 42% in the group without residual symptoms. After a follow-up of 8-10 years, the percentage of recurrence between the groups was no longer significantly different (74% in the group with subclinical residual symptoms and 70% in the group without residual symptoms). One of the major limitations in this study was the use of a single longitudinal interview to cover the long follow-up period of 8-10 years. Studies that assessed the association between age of onset of the first depressive episode and the risk of recurrence are inconsistent. For example, Eaton et al. (2008) observed that a younger age of onset was a significant predictor of time to recurrence, with each additional year of age at onset lowering the risk for recurrence by 0.96 (95% confidence interval 0.93-0.99), but this result was not corroborated in other studies (Maj et al., 1992; Lavori et al., 1994). There is also inconclusive data that severity or duration of the last episode is a risk factor for recurrence. A high number of included studies found an association between severity and risk of recurrence of MDD (Gopiath et al., 2007; Holma et al., 2008; Melartin et al., 2004; Ilardi et al., 1997; Ramana et al., 1995; Pintor et al., 2004; Kennedy et al., 2003) but the studies that did not find an association also included CDS studies (Mueller et al., 1999; Lavori et al., 1994). The opposite seems true for duration of the last episode; a high number of these studies did not find an association (Maj et al., 1992; Kanai et al., 2003; Holma et al., 2008; Melartin et al., 2004; Ramana et al., 1995), but the CDS studies did (Mueller et al., 1999; Lavori et al., 1994). Comorbid axis I disorders seems to increase the risk for recurrence (Melartin et al., 2004). This is shown for dysthymia (Maj et al., 1992, Keller et al., 1983) and for social phobia (Holma et al., 2008). A family history of MDD did have an association with recurrence in one study (Maj et al., 1992) but this could not be corroborated in a number of other studies (Kanai et al., 2003; Eaton et al., 2008;Winokur et al., 1993; Ramana et al., 1995; Kennedy et al., 2003; Naz et al., 2007).

2.4. Discussion

To our knowledge, this is the first systematic review which outlines the prevalence and predictors of recurrence after remission of an episode of MDD. Several conclusions can be drawn from the selected studies. i) The percentage of recurrence in the specialised mental health care is very high (up to 85% after 15 years) and in this population it is better to ask *when* instead of *whether* the patient will have a recurrence. ii) The included study suggest that the percentage of recurrence in the primary care population is similar. iii) The percentage of recurrence in the general population is lower (up to 35% after 15 years). iv) Two main predictors of recurrence can be identified: the number of previous episodes and subclinical residual symptoms after recovery for the last episode. Demographic factors such as gender, SES, and civil status, which are risk factors for the onset of the first depressive episode (Anthony et al., 1991; De Graaf et al., 2002), do not appear to predict recurrence after recovery. The age of the index episode also does not seem to predict recurrence. The evidence is (still) inconclusive for the following predictors: neuroticism, lack of social support, severe life event, the presence of a comorbid axis I and II disorder, the severity and duration of the previous episode, a younger age of onset, a family history of MDD and psychosocial impairment after a depressive episode. The severity of the previous episode and psychosocial impairment after a depressive episode seem most likely associated, whereas a family history of MDD, lack of social support and duration of the previous episode seem less likely predictors of recurrence.

Our review has several limitations. Firstly, despite the use of strict selection criteria, the included studies remain difficult to compare. This is also the reason why we did not perform a formal meta-analysis, pooling the results. The studies used different diagnostic and course instruments and the duration of follow-up varied between the studies. Our conclusions are therefore not based on a strong evidence based method but merely on number of studies with a significant association and design of the study (number of patient included, course instrument). However, other not included but well performed studies show similar results (Kessing et al., 2000; Kessing et al., 2004). These studies were not included because the data did relate to readmissions because of MDD and not to recurrence. Furthermore, in a number of studies the difference between a relapse and a recurrence of MDD could not be fully specified because these studies also included patients with partial remission. Subclinical residual symptoms can also be seen as a limited prolongation of an active disease process and is therefore a difficult predictor to interpret in relation to recurrence. Moreover, selection of specific patient samples probably influenced the outcome. For instance, in the CDS study patients were all referrals to a tertiary care centre (Mueller et al., 1999; Solomon et al., 2000), while in other studies only patients with already recurrent MDD were included (Maj et al., 1992; Gopinath et al., 2007). It is likely that this would lead to a higher risk of recurrence. Furthermore, this review only included naturalistic studies, thus treatment is a factor that was not controlled for. Patients

receiving more vigorous or more extended treatment would be less likely to recur. As more vigorous or extended treatment is more likely in tertiary care centers, this would offset the previous effect of selection. Finally, the number of well carried out studies in primary care and in the general population is limited. Therefore, no clear conclusions can be drawn on the prevalence and predictors of recurrence in these settings; the conclusion that prevalence of recurrence of MDD in the general population is 35% is only based on one study (Eaton et al., 1997). Most studies in primary care and in the general population did not use clear defined criteria for remission and recurrence and did not use a diagnostic instrument in commencement of the study. The results suggest that the percentage of recurrence of MDD in primary care is comparable with the specialised mental health care. However, the study of Gopinath et al. (2007) only included patients that experienced at least three depressive episodes, so this is not a representative sample. In other (not included) studies in primary care a lower percentage of recurrence was found. For example, a highly cited study is a Dutch study among 222 patients with a follow-up of ten years (Van Weel-Baumgarten et al., 1998). In this study a percentage of recurrence of 40% was found after ten years. This study was not included because the diagnosis was not made with a standardised instrument and the course was measured retrospectively with a registration system.

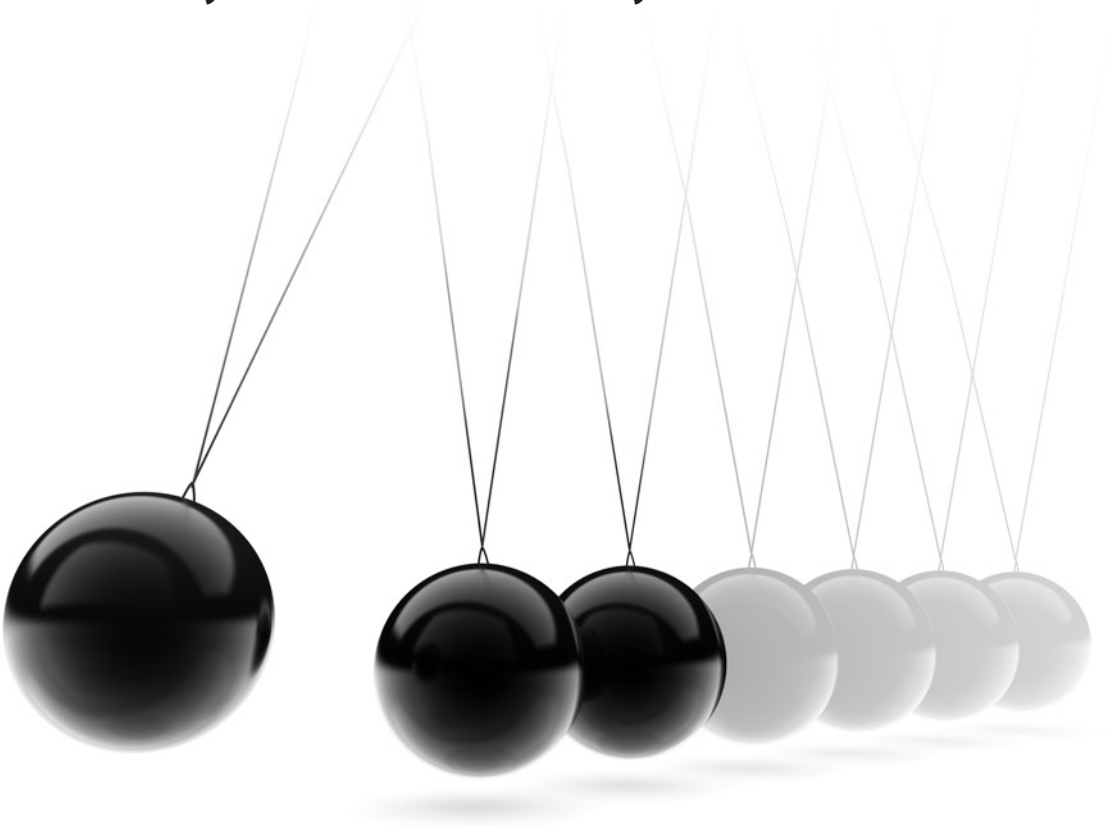
In conclusion, it becomes increasingly clear that MDD (especially in the specialised mental health care) is often a chronic and/or recurrent disorder with consequences over the entire lifespan. Demographic determinants play a role in the onset of the first depressive episode but seem not important during the course. The risk factors for recurrency and chronicity of MDD seem to have similarities. For both, clinical factors seem most important. The knowledge that clinical variables are significant risk factors could be taken into account during the initial phase of the treatment. Moreover, it is possible that chronicity and recurrency are both expressions of the same dimension: everything what predicts chronicity (subclinical residual symptoms, number of previous episodes) predicts recurrences. With the increasing knowledge on genetic and neurobiological determinants of MDD it may be possible to identify better predictors of its course (Robinson et al., 2008). Future research should pay attention to this area.

What are the consequences for clinical practice? Knowledge of predictors of recurrence is essential for making treatment decisions. Most patients with MDD in specialised mental health care will have a recurrence whereas clinical variables probably determine the time to recurrence. It is important to closely monitor and treat patients with subclinical residual symptoms because these patients have a high risk of recurrence. Patients with multiple recurrences should receive maintenance treatment with antidepressants, with special attention to treatment adherence. The risk of relapse or recurrence by maintenance treatment with antidepressants can be reduced by 25% when compared with placebo (Geddes et al., 2003; Kaymaz et al., 2008). However, we do not know the efficacy of anti-

depressants on the recurrence rate over a long period. In addition, preventive interventions should be considered in patients with multiple recurrences, focusing on residual symptomatology and specific coping styles (Bockting et al., 2006). Nonetheless, knowledge about predictors of recurrence is still incomplete and prospective research, particularly in the general population, is necessary to give better-founded conclusions which predictors play a role in recurrences. It could also be useful to take along different outcome variables (severity, time between recurrences, number of recurrences) because different factors could predict different outcome variables (Conradi et al., 2008). If we know which predictors play a role in recurrences and which interventions could help to prevent recurrences there is enough knowledge available to develop well-founded guidelines for treatment and recurrence prevention for the major depressive disorder.

3

Recurrence of major depressive disorder and its predictors in the General population: Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS)



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Abstract

Background: Knowledge of the risk of recurrence after recovery from major depressive disorder (MDD) in the general population is scarce.

Methods: Data were derived from 687 subjects in the general population with a lifetime DSM-III-R diagnosis of MDD but without a current major depressive episode (MDE) or dysthymia. Participants had to be at least 6 months in remission and were recruited from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), using the Composite International Diagnostic interview (CIDI). Recency and severity of the last MDE were assessed retrospectively at baseline. Recurrence of MDD was measured prospectively during the 3-year follow-up. Kaplan-Meier survival curves were used to measure time to recurrence. Determinants of time to recurrence were analyzed using proportional hazard models.

Results: The estimated cumulative recurrence percentage of MDD was 13.2% at 5 years, 23.2% at 10 years and 42.0% at 20 years. In bivariate analysis, the following variables predicted a shorter time to recurrence: younger age, younger age of onset, higher number of previous episodes, a severe last depressive episode, negative youth experiences, ongoing difficulties before recurrence and high neuroticism. Multivariably, younger age, higher number of previous episodes, a severe last depressive episode, negative youth experiences and ongoing difficulties remained significant.

Conclusions: In this community sample, the long-term risk of recurrence was high, but lower than that found in clinical samples. Subjects who have had a MDE have a long-term vulnerability for recurrence. Factors predicting recurrence included illness- and stress-related factors.

3.1. Introduction

Major depressive disorder (MDD) is often a chronic and/or recurrent disorder that can have major consequences over the entire lifespan. For clinical practice, it is important to be able to predict the risk of recurrence. In patients with a high risk of recurrence, it would seem reasonable to treat the depression as a chronic disorder (Andrews, 2001), for example with antidepressants as maintenance treatment (Geddes et al., 2003; Kaymaz et al., 2008); while treatment of those with a low risk of recurrence may be limited to the index episode. If the most important risk factors for recurrence are known, subgroups might be selected that need more intensive or long-term treatment.

Over the past 20-30 years, several studies have been able to assess putative risk factors for recurrence of MDD. The factors that have been considered include sociodemographic data (e.g. age, gender, and level of education), psychosocial characteristics (e.g. personality and social support) and clinical characteristics of the depressive disorder (e.g. the number, duration and the severity of the previous episodes). Clinical factors, such as subclinical residual symptoms and the number of previous episodes, have been found to be the most important predictors, whereas sociodemographic factors did not seem to predict recurrence of MDD (Hardeveld et al., 2010). However, the prediction of recurrence is complex; it is likely that multiple predictors can be identified and that predictors interact with one another producing an aversive cascade of synergetic events resulting in the recurrence of a depressive state. Consequently, it may be possible to identify a combination of risk factors that have a high overall predictive value.

A major limitation of the current knowledge is that majority of previous studies on risk factors for recurrence were performed in specialized mental health care (with more severe, complex, recurrent and long-lasting disorders) whereas the natural course of depressive disorder and the risk factors for recurrence are best studied using a general population sample without any selection bias (Eaton et al., 2008). Moreover, as most depressed patients are treated in primary care, it could be that risk factors for recurrence in specialized mental health care are different from those in primary care.

Large-scale general population-based follow-up studies addressing the recurrence of MDD are scarce. The best-known studies are the Zurich cohort (Merikangas et al., 2003), the Lundby study (Mattison et al., 2007) and the Baltimore Epidemiologic Catchment Area (ECA) follow-up (Eaton et al., 1997; Eaton et al., 2008).These studies focused mainly on the risk of recurrence of MDD and not on the determinants of recurrence. Therefore, knowledge about the predictors of recurrence is still incomplete.

The aim of this study is to determine the incidence and risk factors for the recurrence of MDD among people who had recovered from their last episode of MDD, using data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a large prospective naturalistic psychiatric survey (N=7076) among the general population.

3.2. Method

Study sample

Data were derived from the NEMESIS (Bijl et al. 1998b), which surveyed the Dutch adult general population (aged 18-64). Data were recorded at three waves: at baseline in 1996, at the 12-month follow-up in 1997 and after 3 years (1999). The methodology is described in detail elsewhere (Bijl et al. 1998b). In brief, NEMESIS is based on a multistage, stratified, random sampling procedure. The first step of this study was to draw a sample from 90 Dutch municipalities. The stratification criteria were urbanicity (five categories as classified by Statistics Netherlands) and adequate distribution over the 12 provinces. The second step was to draw a sample of private households (addresses) from post office registers. The number of households selected in each municipality was governed by the size of its population. The third step was to choose which individuals to interview. The selected households were sent a letter of introduction signed by the Minister of Public Health requesting their participation. Shortly thereafter, they were contacted by telephone by the interviewers. Households with no telephone or with ex-directory numbers (18%) were visited in person. A respondent was randomly selected in each household: the member with the most recent birthday, on the condition that they were between 18 and 64 years of age and sufficiently fluent in Dutch to be interviewed. Persons who were not immediately available (owing to circumstances such as hospitalization, travel or imprisonment) were contacted later in the year. If necessary, the interviewers made a maximum of ten phone calls or visits to an address at different times and on different days. Respondents received no remuneration, but only a token of appreciation at the end of the interview. At baseline (T0), 7076 persons were eligible for inclusion, with a response rate of 69.7% (Bijl et al. 1998a). After 12 months (T1), 1458 respondents (20.6%) were lost to attrition and, after three years (T2), a further 822 (14.6%) were lost. 4796 respondents (67.8%) were interviewed at all three waves.

Cohort

We aimed to study the time to recurrence of a major depressive episode (MDE) and associated risk factors, in respondents who had recovered from a MDE. The design relied on both retrospective and prospective data. The recency and severity of the last depressive episode was assessed retrospectively at baseline (T0) using the Composite International Diagnostic Interview (CIDI); respondents were asked at what age the last period of MDD ended. The time to recurrence was assessed prospectively between T0 and T2. To prevent contaminating the risk factor data with current levels of depression, we only included respondents without a current MDD and/or dysthymia at baseline (T0). Dysthymia was defined according to DSM-III-R criteria but we could not assess whether dysthymia was also present before the onset of MDD. An advantage of including people with remitted depression at baseline was that the measurement of the predictors was not influenced by

the presence of a MDE. Furthermore, respondents had to be free of these diagnoses for six months. As a consequence, a duration of partial or full remission of at least six consecutive months was chosen. This term was based on a 10-year follow-up study (Furukawa el al. 2008) which concluded that the best duration to declare remission is probably 4 or 6 months. Therefore, recurrence of MDD was operationalized as a return of symptoms after (partial or complete) remission of at least 6 months and symptoms that were sufficiently severe to satisfy criteria for MDD according to DSM-III-R. It is important to note that respondents with partial remission were also included because this is a well known risk factor for recurrence (Hardeveld et al. 2010). Respondents with lifetime diagnoses of bipolar disorder or schizophrenia or for whom the diagnosis had changed during the follow up period from unipolar to bipolar disorder or schizophrenia were excluded, as these subjects are likely to have a different recurrence risk. To contribute to the prospective data, respondents had to be reinterviewed at least once during follow-up.

Consequently, the study sample was assembled by first identifying all respondents with a lifetime diagnosis of MDD (first or recurrent cases) at T0 (N=1153). Three cases had missing data on the variable 'age of the last depressive episode'. Of the 1150 cases identified, 289 respondents had an ongoing episode of MDD at T0 (6-month prevalence) and 17 had dysthymia at T0 (6-month prevalence), and were excluded from further evaluation. For eight respondents, the diagnosis had changed during the follow up period from unipolar to bipolar disorder or schizophrenia, and they were also excluded. Thus, 836 respondents were at risk for a recurrent episode of MDD. Of the 836 eligible subjects, 687 (82.2%) were re-interviewed at T1 and 590 (70.1%) at T2. Hence, 687 (82.2%) respondents were reinterviewed at least once and constitute the study sample (Table 1). Drop-out (30.0%) of the eligible subjects was lower than that in the total sample (35.2%) and was not associated with demographic factors (age, gender), severity of the last episode of MDD (X^2= 2.53, df=2, p=0.28) or number of previous episodes (X^2=0.63, df=1, p=0.43).

The sociodemographic and clinical characteristics of the study sample (n=687) were as follows (Table 1): 68.0% (N=467) were female; median age was 40.7 years; 73.6% (N=506) were married or cohabiting; 70.3% (N=483) were employed; mean age of onset was 29.9 years (s.d.=10.5); 47.0% (N=323) had experienced a single MDE and 53.0% (N=364) had two or more episodes; in 31.6% (N=217) the last MDE was severe, in 31.4% (N=216) moderate and in 24.3% (N=167) mild; 40.0% (N=275) had a lifetime anxiety disorder at T0; 7.6% (N=52) had a lifetime alcohol dependence; and 2.0% (N=14) had a lifetime drug dependence.

Measurements

Diagnostic instrument

Diagnoses of psychiatric disorders according to DSM-III-R (APA, 1987) were based on the Composite International Diagnostic Interview (CIDI), version 1.1 (computerized version) (Smeets & Dingemans, 1993). The CIDI is a structured interview developed by the World

Table 1 Characteristics of 687 included subjects

			Number	Percentage (%)
Socio-demographic factors	Gender	Female	467	68.0
		Male	220	32.0
	Age	18-24	28	4.1
		25-34	187	27.2
		35-44	236	34.4
		45-54	162	23.6
		55-64	74	10.8
	Education	Low	281	40.9
		Medium	209	30.4
		High	197	28.7
	Cohabitation status	Married or cohabiting	506	73.6
	Employment	Employed	483	70.3
Clinical factors	Severity index MDD episode	Mild	167	24.3
		Moderate	216	31.4
		Severe	217	31.6
	Family history	Family history in first degree members present	317	46.1
	Number of previous episodes	Single	323	47.1
		Recurrent	364	53.0
	Comorbidity (lifetime)	Prevalence of anxiety disorder (any) present	275	40.0
		Prevalence of alcohol dependence present	52	7.6
		Prevalence of alcohol abuse present	74	10.8
		Somatic illness (12 months)	331	48.2
Psychosocial factors	Trauma before age 16	Present	192	27.9

Health Organization (WHO,1990) and has been found to have high inter-rater reliability and high test-retest reliability for most diagnoses (Wittchen, 1994). The following DSM-III-R diagnoses were recorded in NEMESIS: mood disorders (bipolar disorder, major depression, dysthymia), anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder), psychoactive substance use

disorders (alcohol or drug abuse and dependence, including sedatives, hypnotics and anxiolytics), eating disorders, schizophrenia and other non-affective psychotic disorders. Prevalence rates were calculated using the hierarchical rules of the DSM, thus excluding MDEs occurring in schizophrenic and other psychotic disorders or in bipolar disorders.

Time to recurrence

A mentioned previously, the time to recurrence was assessed retrospectively at baseline and prospectively between T0 and T2. Using the prevalence rates (1-month, 6-month, 1-year and 2-year) at T1 or T2, a period could be defined in which the recurrence of an MDE occurred and the average time of this period was calculated. For example, if a respondent had a 6-month prevalence of MDD at T1 but no 1-month prevalence at T1 and reported the last MDE 36 months before T0, it was estimated that the time to recurrence was 45 months (36 months before T0 plus 9 months between T0 and T1).

Potential predictors for time to recurrence

Sociodemographic, clinical and psychosocial factors were assessed, along with personality characteristics.

Sociodemographic factors. These included gender, age, cohabitation status (categorized into living alone or not), educational attainment (categorized into low, medium and high) and employment status (categorized into paid employment or not).

Clinical factors. With the CIDI, information was obtained on age of onset, severity of the last MDE (categorized into mild, moderate, and severe, with or without psychotic features), number of MDEs (categorized into single or recurrent) history of MDD in first-degree family members (categorized into yes or no) and lifetime comorbidity with other mental disorders. The co-morbid disorders we deemed relevant were anxiety disorders, alcohol dependence and abuse. Co-morbidity with somatic illnesses was assessed with a questionnaire listing 31 mostly chronic somatic conditions.

Psychosocial factors. Several psychosocial factors were measured at T1. Life events and ongoing difficulties were recorded with a semi-structured interview-based questionnaire (De Graaf et al. 2002; Spijker et al. 2004) based on information about life events and difficulties in the manual of the Life Events and Difficulties Schedule (LEDS) (Brown & Harris, 1987). The occurrence of the following nine negative life events in the 12 months preceding T1 were recorded: adverse change in health status, adverse change in health status of a significant other, adverse change in important domains (such as loss of employment, divorce), adverse change in important domains of a significant other, adverse change in living conditions, expected adverse changes in the future, failure to attain an important goal, another important self-reported distressing event (like physical threat or assault, sexual violence, discrimination), or another important distressing event of a significant other. The presence of three distressing ongoing conflicts or difficulties in the 12 months preceding T1 were recorded: relationship problems, conflicts at work or school,

private or occupational problems (like noise exposure, financial difficulties). These are persisting situations which usually develop gradually and form a continuous source of daily problems and concerns. Because the impact of specific events can vary, depending on their context or their meaning for the individual, we questioned respondents on their subjective perception of the effects that each event had had on their own mental health. Furthermore, the recency of life event and ongoing difficulties was assessed. Only ongoing difficulties or life events experienced as 'a significant influence' preceding recurrence were included. The outcome was categorized into 'yes' or 'no'. The subjective experience of social support between T0 and T1 was measured by the Social Support Questionnaire for Satisfaction with the supportive transactions (SSQS) (Doeglas et al. 1996; Suurmeijer et al. 1996) with 23 items. The internal reliability of the SSQS in the research cohort was high (Cronbach's $\alpha = 0.88$). Childhood experiences of emotional neglect, emotional or physical abuse or sexual abuse before age 16 were recorded. The answers for neglect and for emotional and physical abuse were categorized into 'once to sometimes' versus 'regular to frequent' and the answers for sexual abuse into 'never' versus 'once or more'. Negative youth experiences were present if the respondent confirmed emotional or physical abuse on a regular to frequent basis or if the respondent had experienced sexual abuse once or more.

Personality characteristics: Neuroticism was assessed with the Groningen Neuroticism Questionnaire containing 14 items (Ormel, 1980).The internal reliability of the questionnaire in our research cohort (Cronbach's $\alpha = 0.75$) was satisfactory. Locus of control was assessed with the 5-item Mastery Scale (Pearlin & Schooler, 1978), with high scores on mastery corresponding to an internal locus of control. The internal reliability of this questionnaire in our research cohort (Cronbach's $\alpha = 0.78$) was satisfactory.

Statistical methods

We used Kaplan-Meier survival curves to estimate the time to recurrence of MDD during the follow-up period. The primary outcome variable was the recurrence of MDD (yes/no) during the 3-year follow-up period. Hazard ratios and their 95% confidence intervals (95% CI) were calculated using Cox regression analyses in SPSS for Windows Version 17.0 (SPSS Inc., USA). Predictors that had a p-value ≤ 0.1 in the bivariate analyses were included in multivariate analyses. The stepwise backward method (Pin ≤ 0.05 and Pout ≥ 0.10) was used. In these analyses, censored data included subjects who had not met the criteria for the endpoint event of analysis, either by the end of the follow-up period or by the time they left the study.

3.3. Results

Time to recurrence

Because we could assess the timing of the last MDE retrospectively, it was possible to assess the occurrence of recurrence over a long period of time. A total of 135 respondents had a MDE during follow-up (Fig. 1). The median time to recurrence was 6 years (s.d.=5.5). The estimated cumulative recurrence percentage of MDD, after a duration of remission of at least 6 months, was 2.5% after 1 year, 4.5% after 2 years, 13.2% at 5 years, 23.2% at 10 years and 42.0% at 20 years .

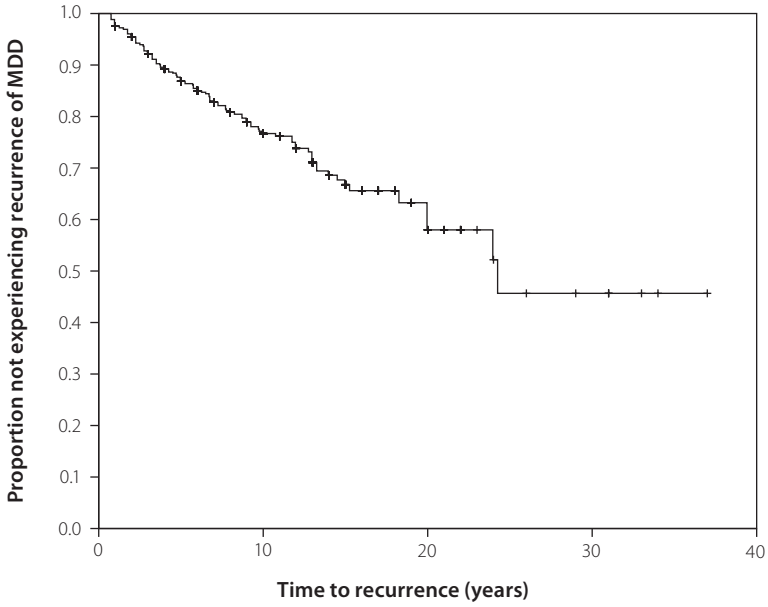


Figure 1 Survival curve of time to recurrence of MDE in a cohort from NEMESIS, + censored

Predictors

Table 2 shows the potential risk factors, corrected for age and gender, of time to recurrence of MDD using bivariate and multivariate Cox proportional regression analyses respectively. In bivariate analyses of the sociodemographic factors, age was found to be associated with recurrence of MDD, with each additional year of age lowering the risk for recurrence by 0.04 (95% CI 0.94-0.98, p<0.001). The younger age group (18-30 years) had a HR of 3.8 in comparison with the older age group (50-65 years). In addition, a younger age of onset

Table 2 Bivariate and multivariate analyses of potential predictors of time to recurrence of MDE in a cohort from NEMESIS

Determinants			Time to recurrence					
			Bivariate*			Multivariate*		
			HR	95% CI	p	HR	95% CI	P
Sociodemographic	Female		1.05	0.72-1.54	0.80			
	Age (years)		0.96	0.94-0.98	**<0.01**	0.96	0.94-0.98	**<0.001**
	Living alone		1.19	0.80-1.75	0.39			
	Education	Low	1	-	-			
		Medium	1.08	0.71-1.64	0.71			
		High	1.08	0.70-1.65	0.74			
	Employed		0.98	0.66-1.45	0.91			
Clinical	Age of onset		0.98	0.96-0.99	**0.03**			
	Severity of depression	Low	1	-	-			
		Medium	0.82	0.49-1.38	0.46			
		Severe	2.04	1.30-3.20	**<0.01**	1.91	1.22-3.00	**<0.01**
	Recurrent MDD		1.79	1.26-2.54	**<0.001**	1.68	1.15-2.46	**<0.01**
	Family history of MDD	Present	1.34	0.96-1.89	0.09			
	Co-morbidity (lifetime)	Anxiety disorders	1.36	0.97-1.91	0.08			
		Dysthymia	1.18	0.81-1.72	0.38			
		Alcohol dependence	1.26	0.69-2.32	0.45			
		Alcohol abuse	1.07	0.62-1.86	0.81			
	Somatic illnesses present		1.24	0.88-1.74	0.23			
Psychosocial	Life events (negative)	Present	1.41	0.95-2.10	0.09			
	Ongoing difficulties	Present	2.19	1.55-3.08	**<0.001**	2.19	1.51-3.16	**<0.001**
	Social support	Low	1.00	0.98-1.02	0.94			
	Negative youth experiences	Present	1.82	1.29-2.56	**<0.001**	1.59	1.10-2.29	**0.01**
Personality characteristics	Neuroticism	High	**1.09**	**1.05-1.12**	**<0.001**			
	Mastery	Low	1.04	0.99-1.09	0.12			

* Corrected for age and gender. Bold type indicates, p<0.05

was also related to a faster recurrence. Because there was a correlation between age of onset and age (Pearson correlation 0.68, p<0.001), this variable was not analyzed in the multivariate Cox proportional hazards model. Among the clinical factors, a history of recurrent episodes and severity of the last depressive episode were significant predictors for a shorter time to recurrence. However, the percentage of missing data was high in the variable 'severity of the last depressive episode' (12.8%, N=88). We analyzed the missing data and found that this was more common in women (x^2=5.16, df=1, p=0.02) and respondents who had (only) experienced a single episode of MDD (X^2=5.01, df=1, p=0.03). High neuroticism also was associated with a shorter time to recurrence of MDD. Of the psychosocial factors, negative youth experiences and ongoing difficulties were significant predictors. In multivariate Cox proportional hazards analyses (adjusted for gender), the missing data of the variable 'severity of the last MDE' were excluded. Younger age, a high number of previous episodes, a severe last depressive episode, negative youth experiences and the presence of ongoing difficulties before recurrence remained significant predictors of time to recurrence.

Furthermore, we assessed the cumulative recurrence percentage of MDD (posteriori hypotheses) of the respondents who had zero, one, two, three, or more than four of the predictors found in multivariate Cox proportional hazards analyses (Fig. 2). The number of respondents with five predictors was too small to analyze (n=5). The predictor 'age' was dichotomized into younger or older than 30 years. We found that the risk of recurrence depended on the number of predictors the respondents had; after 10 years the cumulative recurrence percentage of MDD was 3.4% for respondents with no predictors (N=78), 19.0% for respondents with one predictor (N=175), 26.6% for those with two predictors (N=197), 56.5% for those with three predictors (N=97) and 65.0% for those with more than four predictors (N=49) (log rank, X^2=63.77, df=4, p<0.001).

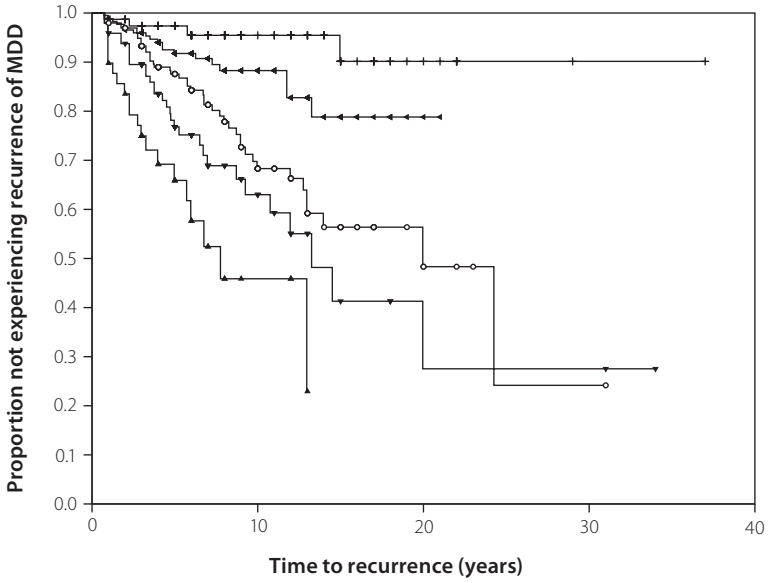


Figure 2 Survival curve of time to recurrence of MDE in a cohort from NEMESIS

Divided into respondents with 0 (N=78), 1 (N=175), 2 (N=197), 3 (N=97) or more than 4 (N=49) predictors respectively (age under 30 years, ongoing difficulties present, traumatic youth experiences present, severe last depressive episode, recurrent MDD). Number of predictors: 0 (+), 1 (◀), 2 (○), 3 (▼), 4 (▲).

3.4. Discussion

This is one of the few studies, using a large general population cohort, on the incidence and predictors for recurrence of MDD among people who had recovered from their last episode of MDD. Several conclusions can be drawn. First, the cumulative incidence of recurrence after 20 years was found to be 42.0%. This percentage is higher than that which has been found in previous research (Eaton et al., 2008; Mattison et al., 2007) but it is difficult to compare these studies because of differences in duration of remission, follow-up, diagnosis and population. The study by Eaton et al. (2008) is the most similar to ours with a percentage of recurrence of 35% over 23 years. However, one of the major differences with this study was that their cohort contained exclusively first incidence cases; the inclusion criteria of remission was different, at least 1 year in their study compared with 6 months in ours. As a consequence, our cohort contained more respondents, with a shorter time to recurrence, as well as respondents with multiple recurrences. Mattison et al. (2007) observed a lifetime recurrence percentage of 40% but

used a broader definition of depression, also including dysthymia. Our percentage for recurrence of MDD is, however, still lower than that which has been found in a specialized mental health care setting (85% in 15 years) (Mueller et al., 1999). Evidently, the discrepancy in recurrence risk of MDD between settings (general population versus specialized mental health care) is considerable. Second, the following variables predicted shorter time to recurrence in the bivariate models: younger age, younger age of onset, a large number of previous episodes, a more severe last depressive episode, negative youth experiences, the presence of ongoing difficulties before recurrence and high neuroticism. Multivariably, younger age, greater number of previous episodes, a severe last depressive episode, negative youth experiences and ongoing difficulties remained significant. Because previous large-scale general population-based follow-up studies have mainly focused on the risk of recurrence of MDD and not on the determinants of recurrence, it was not possible to fully compare our results with previous research. However, Eaton et al. (2008) also studied the main socio-demographic factors and found similar results; the 18 to 29-year-old group had a higher risk for recurrence, a younger age of onset was a significant predictor of time to recurrence (Eaton et al., 2008) and no other sociodemographic variables were related to a shorter time to recurrence. Third, our data suggests that the risk for recurrence of MDD depends on the number of predictors that are present. However, because this is a data-derived model, in other words we have included those risk factors which are modelled to be most strongly associated with recurrence, no firm conclusions can be drawn and these observations should be tested in future studies.

Previous research in NEMESIS (De Graaf et al., 2002) found that female gender, negative life events, ongoing difficulties, and a high level of neuroticism in multivariate analysis were associated with first incidence of MDD. By contrast, our study did not find that female gender was related to recurrence. However, both studies found that stress-related factors seem to play a role, and additional clinical factors related to past MDD episodes (number of previous episodes, severity of the last episode) emerged.

Our study has a number of strengths. It was performed in a large cohort from the general population, thereby avoiding selection bias. In addition, as all respondents were in remission from a MDE at baseline, the measurement of the predictors was not influenced by the presence of MDE, apart from the psychosocial predictors (life events, social support, ongoing difficulties) which were measured at follow up (T1).

In interpreting the results of this study, its limitations should be noted. First, we assessed cases with a lifetime diagnosis of MDD, and assessed the last depressive episode in retrospect using the CIDI. As a consequence, the assessment of the age of onset and recency of the last depressive episode may not have been measured exactly, and therefore the risk of recurrence may have been selectively underestimated in subjects who experienced a MDD at an earlier point in time. This would lead to an overestimation of the time to recurrence and an underestimation of the number of recurrences a respondent had. In addition, the severity of MDD may not be measured accurately, especially among

respondents who had a MDE at an earlier point in time. Furthermore, the difference in time between the end of the last MDE and the measurement of predictors may have led to an overestimation of the effect of the predictor on recurrence. Second, only respondents were included who had a duration of remission of at least 6 months, implying that respondents with a shorter time to recurrence were not included. As the literature on this subject is still scarce, we also analyzed the recurrence rate of MDD in respondents with a duration of remission of at least one month. 764 respondents were included in this analysis, of whom 155 had a MDE during follow-up. The number of respondents included was higher in this analysis because fewer respondents were excluded at baseline. As expected, the incidence of recurrence was slightly higher: 3.9% after 1 year, 5.9% after 2 years, 15.1 % after 5 years, 25% after 10 years, and 43.3% after 20 years. Third, despite the inclusion of a large number of predictors, subclinical residual symptoms, which is an important predictor of recurrence of MDD (Hardeveld et al. 2010), could not be assessed. It was also not possible to study dysthymia (as an equivalent) because the number of respondents with a 6-month prevalence of dysthymia at T0 was small (N=17) and we could not assess whether the dysthymia had occurred before or after the MDD. Fourth, the resulting HRs were an average of the whole period but it is likely that the hazard changes over time, being greater in the beginning. Previous literature (Mueller et al., 1999) has also suggested that the risk of recurrence is greater earlier on. If the risk of recurrence declines over time, the effect of the factors determining this risk may also not be constant. Moreover, the Cox regression model is built on the assumption that predictors remain constant during follow up, which may not be true for some predictors. Furthermore, although the study is in part a prospective cohort, it is less capable of confirming causality between a predictor and recurrence of MDD. Therefore, the possibility remains that the previous depressive episode has affected the presence and the effect of potential predictors, or even that some of these risk factors are a consequence of previous episodes. The question remains, for example, as to whether ongoing difficulties contribute to recurrence of MDD, or multiple recurrences generate ongoing difficulties. Finally, our cohort contained respondents with varying numbers of previous episodes. It could be that the predictors of recurrence change over subsequent episodes. For example, previous research (Kendler et al., 2000) suggested that life events were a significant risk factor during the first episodes, but when the numbers of episodes increased, life events were no longer a relevant predictor.

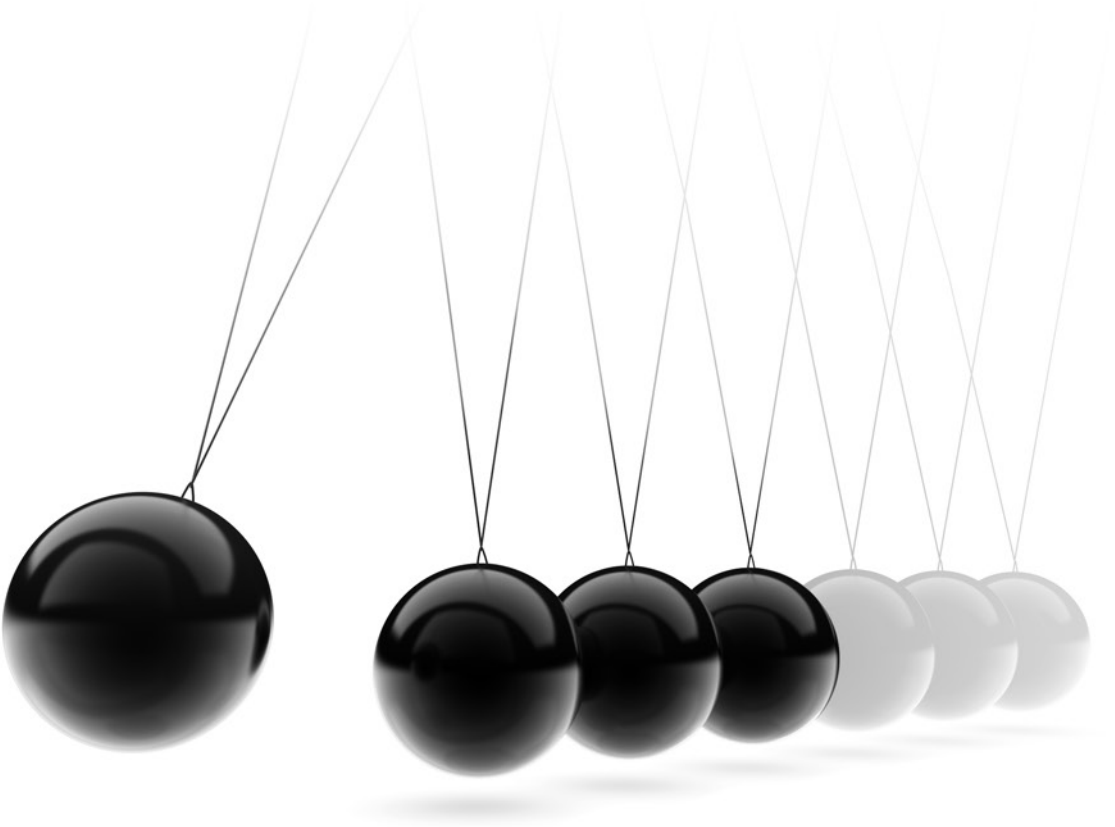
What directions does this study provide for future research? Various possible genetic and other biological predictors were not studied, but it seems likely that both genetic and environmental factors are involved and interact with one another (Caspi et al., 2003). Future research should focus on this interaction. Furthermore, ongoing difficulties preceding recurrence of an MDE seems to be an important predictor. The link between ongoing difficulties, which could cause (chronic) stress, and negative youth experiences which were also a predictor of recurrence is of particular interest. Previous research (Heim

et al., 2002) concluded that the HPA-axis could be dysregulated following traumatic childhood exposure. Subjects who have a dysregulated HPA-axis and experience ongoing difficulties might be at a higher risk for recurrence. Our data supports this association, but long-term prospective studies should further elucidate this finding.

What are the implications of our findings? Long-term naturalistic studies performed in mental health care have underscored the importance of understanding depression as a lifelong and recurrent illness, with a number of possible courses. It also seems that in the general population, subjects who have experienced a MDE have a long-term vulnerability for recurrence which could be triggered under certain circumstances. Subjects were found to have a higher risk for an earlier recurrence of MDE if they are younger, had negative youth experiences, had multiple previous episodes, experience ongoing difficulties, and had a more severe last episode. Clinicians should be aware of these risk factors and consider long-term treatment with antidepressants (Geddes et al. 2003; Kaymaz et al. 2008) or additional psychological treatment, for example preventive cognitive therapy (Bockting et al. 2009). Preventive programmes for recurrence of MDD also appear to be cost-effective (Scott et al. 2003). Moreover, not only is it important to know who will have a fast recurrence but also which group of patients will experience multiple recurrences in their lives. With this knowledge we might be better able to classify and stage the different course patterns of this disabling disorder and chose the appropriate treatment.

4

Recurrence of major depressive disorder across different treatment settings: results from the NESDA study



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Abstract

Objective: Examine time to recurrence of major depressive disorder (MDD) across different treatment settings and assess predictors of time to recurrence of MDD.

Methods: Data were from 375 subjects with a MDD diagnosis from the Netherlands Study of Depression and Anxiety (NESDA). The study sample was restricted to subjects with a remission of at least three months. These subjects were followed until recurrence or the end of the two year follow-up. DSM-IV based diagnostic interviews and Life Chart Interviews were used to assess time to recurrence of MDD across treatment settings. Predictors of time to recurrence were determined using Cox's proportional hazards analyses.

Results: Although trends indicated a slightly higher rate of and shorter time to recurrence in specialized mental health care, no significant difference in recurrence rate (26.8% versus 33.5%, p=0.23) or in time to recurrence (controlled for covariates) of MDD was found between respondents in specialized mental health care and respondents treated in primary care (average 6.6 versus 5.5 months, p=0.09). In multivariable analyses, a family history of MDD and previous major depressive episodes were associated with a shorter time to recurrence. Predictors did not differ across treatment settings.

Limitations: The study sample may not be representative of the entire population treated for MDD in specialized mental health care.

Conclusions: Health care professionals in both settings should be aware of the same risk factors since the recurrence risk and its predictors appeared to be similar across settings.

4.1. Introduction

Major depressive disorder (MDD) is among the leading causes of disability worldwide. This is largely due to its highly chronic and recurrent nature (Murray et al., 1997; Vos et al., 2004). The risk of recurrence after a first major depressive episode is 50% and increases with subsequent episodes (Post, 1992; Kupfer et al., 1996; American Psychiatric Association, 2000). Efforts to reduce the disabling effects of depression should be expanded with recurrence prevention strategies, especially in patients at high risk of recurrence (Bockting et al., 2011). Strategies to prevent recurrence of a major depressive episode can be highly effective. A meta-analysis found a number needed to treat (NNT) of five (Hansen et al., 2008). In comparison, the number needed to treat to prevent one major cerebrovascular event with aspirin over a mean follow-up of 6.9 years is 253 (Berger et al., 2011). However, knowledge of recurrence risk of MDD is incomplete (Hardeveld et al., 2010). It is still difficult to identify high risk groups, and data on MDD recurrence risk is mainly based on studies performed in specialized mental health care. It is important to understand the extent to which this information can be generalized to patients in primary care settings, where the majority of people with MDD are treated. If the risk of recurrence in MDD patients treated in primary care differs from those in specialized mental health care, different recommendations for prevention of recurrence are needed. This knowledge might facilitate further improvements in the quality and cost-effectiveness of depression management.

We expect the risk of recurrence of MDD to be higher in specialized mental health care than that in primary care since those with the most severe, complex, recurrent and long-lasting disorders are more often treated in specialized mental health care (Cooper-Patrick et al., 1994; Suh and Gallo, 1997). However, this hypothesis is not well documented, mainly because data on the risk of recurrence among MDD patients in primary care settings are scarce (Gilchrist et al., 2007; Hardeveld et al., 2010) and, in particular, prospective longitudinal studies are lacking.

Furthermore, it is important to be aware of the predictors of recurrence of MDD. This knowledge would make it possible to identify patients with a high risk for recurrence. Predictors of recurrence of MDD might be different across treatment settings. The studies available to date, which have aimed to identify risk factors for recurrence, have largely been carried out in specialized mental health care. The results suggest that subclinical residual symptoms and the number of previous episodes are the most important predictors for recurrence of MDD, whereas demographic factors are not related to recurrence of MDD (Hardeveld et al., 2010). To our knowledge, a study on risk factors for (time to) recurrence among patients treated in the specialized mental health care as well as those in primary care – also allowing a direct comparison - has not been done.

The aim of this study was therefore to examine the time to recurrence of MDD and its predictors among subjects who recovered from their last episode of MDD, and compare the findings between primary care and specialized mental health care.

4.2. Methods

Study sample

Data were from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study, which began in 2004, and examines the long-term course of depressive and anxiety disorders in different health care settings. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Centre, and subsequently by local review boards of each participating centre. All respondents provided informed consent. For the present study, data from the first two years of follow-up were used. The rationale, objectives, and methods of NESDA have been described in detail elsewhere (Penninx et al., 2008). In brief, the NESDA cohort (N=2981) consists of respondents (18-65 years) with (i) a current anxiety and/or depressive disorder, (ii) a prior history of a depressive and/or anxiety disorder and (iii) healthy controls. All respondents were administered a baseline assessment, which included evaluation of psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Respondents were recruited in primary care through a screening procedure, in specialized mental health care when newly enrolled, and in the community. Respondents with a primary diagnosis of a psychotic disorder, obsessive-compulsive disorder, bipolar disorder, a severe addiction disorder, or who were not fluent in Dutch were excluded.

For our study sample, the classification of treatment settings (primary care versus specialized mental health care) was based on the recruitment setting but this was also confirmed with data from the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P) (Hakkaart-van Roijen, 2002). The TIC-P is a fully structured interview that assesses loss of productivity, health care utilization, and costs. Respondents were asked whether they had sought help for mental problems within the past six months. Those who had not sought help were not included because we wanted to compare respondents treated in specialized mental health care with those treated in primary care. Respondents were considered to be under treatment in specialized mental health care or primary care if they had at least two contacts in the six months prior to the baseline interview. The sources of care included primary care (general practitioner, first line psychologist, social worker, social psychiatric nurse) and specialized mental health care (ambulatory mental health care including a psychiatrist/psychotherapist working in private practice and residential mental health care).

Diagnoses of MDD were based on the Composite International Diagnostic Interview (CIDI), Lifetime Version 2.1 (WHO Lifetime Version 2.1). The CIDI is a structured interview developed by the World Health Organization and has been found to have high inter-rater reliability (Wittchen et al., 1994), high test-retest reliability (Wacker et al., 2006), and satisfactory validity for depressive and anxiety disorders (Wittchen et al., 1989; Wittchen, 1994).

The study sample was restricted to subjects with a MDD diagnosis in the six months prior to baseline assessment, who were symptomatic in the month prior to baseline, and achieved remission during the two-year follow-up. In this way we tried to select a large sample of respondents who also had a MDD at baseline. Accordingly, the sample was limited to 706 subjects with a MDD diagnosis who confirmed symptoms in the month prior to baseline either through the CIDI recency questions or the Life Chart Interview (LCI) (Lyketsos, 1994) and who sought help for their MDD. Of these subjects, 566 (80.2%) participated in the two-year follow-up, of which a further six respondents were excluded because they did not have a (complete) LCI during follow-up. Drop-out was associated with lower educational attainment (p=.01), but not with gender, age, severity of the last major depressive episode (MDE) or number of previous episodes of MDD. A further 142 respondents were excluded because they did not achieve remission from MDD within the two-year follow-up. Remission was defined as a reduction of symptoms to no or minimal severity for at least three consecutive months using the LCI. This three-month criterion is in line previous research (Spijker et al., 2002). During follow-up the percentage of respondents achieving remission was not statistically significant (19.0% in primary care versus 24.0% in specialized mental health care, chi-square=1.33, df=1, p=0.25). Finally, 43 respondents were excluded because the diagnosis was changed to bipolar disorder during follow-up. So, the sample 'at risk' for a recurrence of MDD consisted of 375 respondents. Of those recruited from the community, 21 respondents were treated in specialized mental health care and twelve in primary care after checking data from the TIC-P. Furthermore, 29 respondents which were recruited in primary care were treated in specialized mental health care. As a consequence, 97 were treated in primary care (25.9%) and 278 (74.1%) were treated in specialized mental health care. A flow-chart is displayed in Fig. 1.

Time to recurrence

Time to recurrence was assessed prospectively during the two-year follow-up using the LCI. For each month with reported symptoms, severity was assessed (no or minimal severity, mild, moderate, severe, or very severe). Recurrence was operationalized as a return of symptoms after remission to at least mild severity level persisting for at least one month with the additional criterion that a CIDI-confirmed MDD diagnosis was present during follow-up.

Determinants of time to recurrence

The following variables that we considered relevant as determinant of time to recurrence or as covariate and were assessed at baseline with several semi-structured questionnaires:

Socio-demographic factors. Gender, age, and level of educational attainment (in years of education).

Clinical factors: Using the CIDI, the following information was obtained: age of onset of MDD, severity of the MDE in the month preceding baseline assessment (based on number

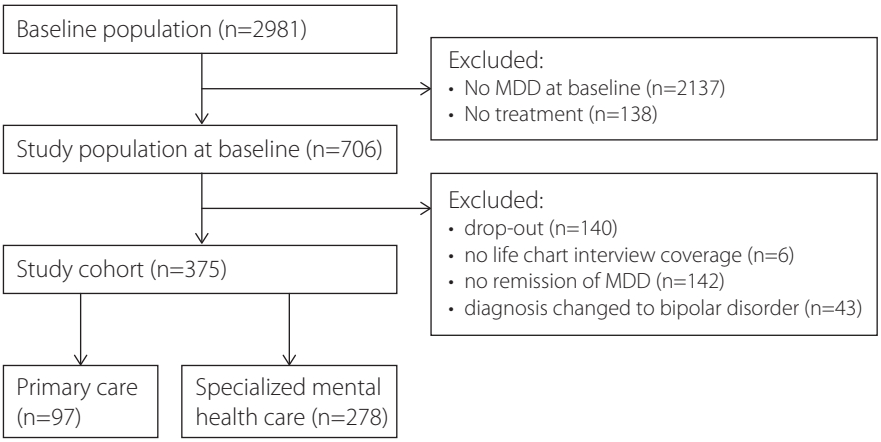


Figure 1 Flow chart of selection process for study population

of DSM-criteria and categorized into mild, moderate and severe), and lifetime number of MDEs categorized into single or recurrent. Information on the duration of symptoms prior to baseline was derived from the baseline LCI that assessed the percentage of time the respondent spent with depressive symptoms in the previous year. History of depression in first-degree family members was assessed using a family tree inventory (Fyer & Weissman, 1999), categorized into yes or no. The comorbid disorders that we deemed relevant were lifetime alcohol abuse/dependence or any anxiety disorder (panic disorder, social phobia, generalized anxiety disorder, agoraphobia) within the six months before baseline. Comorbidity with somatic illnesses was assessed by means of a questionnaire listing twenty mostly chronic disorders for which the respondent was treated.

Psychosocial factors: Neuroticism was measured with the twelve-item subscale of the NEO Five-Factor Inventory (NEO-FFI) Questionnaire ranging from 0 (low neuroticism) to 48 (high neuroticism) (Costa & McGrae, 1995). Negative life events in the last year were determined with the Brugha questionnaire ranging from 0 to 5 (Brugha et al., 1985) and included 12 specific events and one 'other' category asking about other serious negative life events. In order to examine the role of childhood trauma, a cumulative childhood index using the NEMESIS childhood trauma interview was constructed (De Graaf et al., 2004; Wiersma, 2009; Hovens et al., 2010). Participants were asked four questions regarding childhood experiences of emotional neglect, or emotional, physical, or sexual abuse. The cumulative index was calculated for each participant as the sum of the number and frequency of the four types of abuse (range, 0-8).

Treatment: Respondents were asked about the type of treatment they had received for their MDD, subdivided into pharmacological treatment and psychological treatment. Pharmacological treatment was assessed based on inspection of the medication boxes

used in the past month and coded using the WHO Anatomical Therapeutic Chemical (ATC) classification (REF to URL). Use of antidepressants was taken into account when the medication was taken at least 50% of the time and included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) or other antidepressants (N06AF/N06AX). The receipt of psychological treatment (psychotherapy, counselling, and skills training) was based on self-report.

Statistical methods

For the analyses, SPSS for Windows Version 17.0 (SPSS Inc., USA) was used. Descriptives across treatment setting (primary care, specialized mental health care) were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. A two-tailed $p \leq .05$ was considered statistically significant. We used Kaplan-Meier survival curves to estimate the time to recurrence of MDD during follow-up across treatment settings. Subjects who - at the end of the follow-up period - did not meet the criteria for the endpoint event (recurrence) were censored. Subsequently, we studied possible predictors of recurrence of MDD (including treatment setting) using Cox's proportional hazards analyses. Predictors that had a p-value $\leq .20$ in the univariable analyses were included in multivariable analyses in which the forced entry method was used. Time to recurrence of MDD (yes/no) during the two-year follow-up was the main outcome measure. Because the number of subjects treated in primary care was relatively small (n=97) we could not make a separate comparison of the predictors of recurrence between settings. Instead, we added a setting by predictor interaction term to check whether possible differences in recurrence risk between treatment settings were explained by differences in predictors.

4.3. Results

Characteristics

The mean age of the study sample was 40.3 years, and 66.9% were female. The socio-demographic, clinical and treatment variables are shown by setting in Table 1.

Respondents treated in specialized mental health care were younger, had a younger age of onset, had a higher neuroticism score and a higher percentage had psychological treatment and/or medication ($p<.05$). Table 2 describes the course characteristics of MDD during follow-up. Percentage of recurrence, mean and average time to recurrence and average duration of follow-up did not differ significantly between treatment settings.

Recurrence risk

During the two-year follow-up, 26.8% (n=26) of respondents in primary care and 33.5% (n=93) treated in specialized mental health care experienced a recurrence of MDD after

Table 1 Characteristics of 375 subjects at risk for a recurrence of MDD from the NESDA study by treatment setting

		Primary care (n=97)	Specialized mental health care (n=278)	p*
Socio-demographic factors				
Gender (% female)		70.1	65.8	0.44
Age (mean yrs, sd)		43.9 (12.1)	39.1 (11.7)	**<0.01**
Educational attainment (mean yrs, sd)		11.5 (3.1)	11.4 (3.0)	0.75
Clinical factors				
Age of onset (mean yrs, sd)		30.4 (14.0)	27.1 (12.5)	**0.03**
Family history of depression (%)		87.6	85.6	0.62
Severity of the last MDE (CIDI)	Mild	38.1	27.3	0.13
	Moderate	28.9	31.7	
	Severe	33.0	41.0	
Recurrent MDD (%)		53.8	51.1	0.66
Percentage months with symptoms of MDD in past year (mean, sd)		0.6 (0.4)	0.7 (0.3)	0.08
Anxiety disorder (any, 6 months)		59.8	68.0	0.14
Alcohol abuse/dependence (lifetime)		37.1	29.5	0.16
Number chronic somatic illness (mean number, sd)		0.8 (1.2)	0.6 (0.9)	0.12
Psychosocial factors				
Trauma before age 16 (mean score, sd)		1.0 (1.2)	1.3 (1.2)	0.07
Negative life events (mean, sd)		1.2 (1.36)	0.9 (1.09)	0.06
Neuroticism (mean score, sd)		29.0 (6.6)	31.1 (6.5)	**<0.01**
Treatment				
Pharmacological treatment (% yes)		49.5	65.1	**<0.01**
Psychological treatment (% yes)		45.4	63.3	**<0.01**

* P-value based on chi-square statistics for categorical variables and independent t-test for continuous variables in bold: statistically significant

having achieved remission for at least three months (chi-square=1.47, df=1, p=0.23) (see inclusion criteria). Fig. 2 shows the survival curve of MDD recurrence across different settings. The slope of the survival curve suggests that the risk of recurrence is highest in the first months after recovery, regardless of treatment setting. There was no significant

Table 2 Course characteristics of 375 respondents at risk for a recurrence of MDD from NESDA by setting

	Primary care	Specialized mental health care	p*
Percentage of recurrence (%)	26.8	33.5	0.23
Average time to recurrence (months)	6.6	5.6	0.30
Median time to recurrence (months)	5.5	5.0	0.30
Average duration of follow-up (months)	15.3	14.1	0.21

* Pearson Chi-square and Mann-Whitney U test used, uncontrolled for covariates

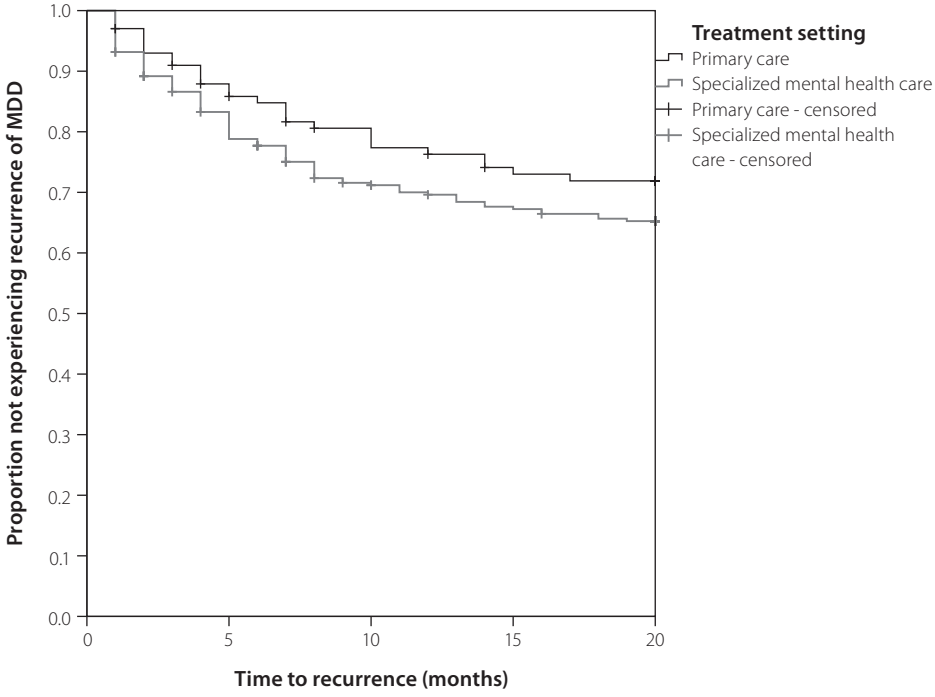


Figure 2 Survival curve of time to recurrence of MDE across different settings in a cohort from NESDA

Log-rank (Mantel-Cox): X^2=1.66, df=1, p=0.20

Table 3 Univariable and multivariable analyses of potential predictors of time to recurrence of MDE in a cohort from NESDA (n=375)

		Time to recurrence					
		Univariable analyses			Multivariable analyses*		
		HR	95% CI	p	HR	95% CI	p
Socio-demographic factors							
Gender, female		1.43	0.95-2.16	0.09	1.42	0.92-2.20	0.11
Age (yrs)		0.99	0.97-1.00	0.13	0.99	0.97-1.01	0.33
Educational attainment (yrs)		1.03	0.97-1.10	0.29			
Clinical factors							
Age of onset (yrs)		0.99	0.98-1.0	0.11	1.00	0.98-1.02	0.80
Family history of depression	Yes	**2.16**	**1.09-4.26**	**0.03**	**2.12**	**1.07-4.22**	**0.03**
Severity of the last MDE	Mild	1	-	-			
	Moderate	0.95	0.60-1.52	0.84			
	Severe	1.11	0.72-1.72	0.63			
Recurrent MDD (% recurrent)		**1.61**	**1.10-2.35**	**0.01**	**1.59**	**1.08-2.35**	**0.02**
Percentage months with symptoms of MDD in past year		0.87	0.53-1.50	0.60			
Anxiety disorder (any)	Yes	0.90	0.62-1.31	0.60			
Alcohol abuse/dependence	Yes	0.88	0.59-1.30	0.51			
Number chronic somatic illnesses	High	1.05	0.88-1.24	0.61			
Psychosocial							
Trauma before age 16	High	1.10	0.95-1.26	0.22			
Life events	Low	1.02	0.87-1.19	0.81			
Neuroticism	High	1.00	0.97-1.03	0.93			
Treatment							
Pharmacological treatment	No	1.29	0.90-1.86	0.16	1.16	0.80-1.68	0.43
Psychological treatment	No	1.64	0.81-1.67	0.41			
Setting							
Specialized mental health care		1.32	0.86-2.05	0.21			

* forced entry method used if in univariable analyses p≤.20.
in bold: statistically significant

difference in time to recurrence of MDD between respondents in specialized mental health care in comparison with respondents treated in primary care (HR 1.32, CI 0.86-2.05, p=0.21). When controlled for socio-demographic, clinical, psychosocial and treatment factors, time to recurrence did not differ significantly, but a trend was found towards a shorter time to recurrence in specialized mental health care (HR=1.52, 95% CI=0.93-2.48, p=0.09).

Table 3 shows the potential risk factors of time to recurrence of MDD using both univariable and multivariable Cox proportional regression analyses. Analyses showed that the presence of a family history of depression and having a previous MDE were associated with a shorter time to recurrence of MDD. In multivariable analyses, the presence of a family history of depression (HR= 2.12, 95%CI=1.07-4.22, p=0.03) and having a previous MDE (HR=1.59, 95% CI=1.08-2.35, p=0.02) remained significant predictors of time to recurrence. Finally, no significant interaction terms were found for treatment setting by predictor, implying that predictors of time to recurrence did not differ across treatment settings.

4.4. Discussion

To our knowledge, this is the first prospective naturalistic cohort study to directly compare the recurrence risk and predictors of time to recurrence in subjects with a MDD diagnosis across different treatment settings. The results indicate that the time to recurrence during the two-year follow-up did not differ between patients treated in primary care and in specialized mental health care. Given the presence of more severe, more treatment resistant, chronic and more complex patients in specialized mental health care, one might expect that the risk of recurrence would be higher in this care setting. However, our findings are in line with previous studies carried out in primary care (Lin et al., 1998; Gopinath et al., 2007; Vuorilehto et al., 2009; Suija et al., 2011). In a study performed in primary care among 386 respondents (Gopinath et al., 2007), 31.1% of patients had a recurrence after one year. Similar results were found in a study by Lin et al. (1998) (37.1% after one year), Vuorilehto et al. (2009) (27% after 15 months) and Suija et al. (2011) who observed a recurrence percentage of 28% after one year. In comparison, in specialized mental health care the percentage of MDD recurrence after one year ranges from 21% to 37% (Kanai et al., 2003; Maj et al., 1992; Hardeveld et al., 2010). Although remaining non-significant, a trend towards a shorter time to recurrence in specialized mental health care was noticeable (HR=1.52, 95% CI=0.93-2.48, p=.09) and the hazard ratio increased from 1.32 to 1.52 when corrected for all covariates, suggesting that the risk of recurrence increases in secondary care in comparison with primary care and was confounded by these variables. A possible explanation for the similar recurrence risk found across treatment settings is

that the distribution of risk factors for MDD recurrence does not differ much between treatment settings. Previous research, also performed with NESDA data (Piek et al., 2011), found that patients were more likely to be referred to secondary care if they were younger, reported suicidal symptoms, had chronic depression, or were referred for psychotherapy. It seems that factors related to referral to specialized mental health care, in general, differ from predictors of recurrence. It could be that the decision to refer to specialized mental health care is determined to a greater exent by the need for acute treatment of MDD or the preferences of the patient than by expectations of a protracted course. When we excluded those who did not recover from a MDE during follow-up, respondents who were younger, had an earlier age of onset and a higher neuroticism score were most likely to be referred and treated in specialized mental health care. Although these could be risk factors for recurrence, our study found that the risk factors predicting a shorter time to recurrence were a history of recurrent MDEs and the presence of a family history of depression. These factors did not differ across treatment settings. An alternative explanation may be that those referred to specialized care receive more intensive treatment for recurrence prevention and that this reduced recurrence rate to a similar level as was found in primary care.

As mentioned earlier, our study found that a history of recurrent MDD and the presence of a family history of depression predicted a shorter time to recurrence. Previous research also found these predictors to be related to recurrence of MDD (Maj et al., 1992; Mueller et al., 1999; Solomon et al., 2000). Family history of MDD, which had the highest hazard ratio for recurrence, is of special interest, because this might indicate an important genetic vulnerability for (the recurrence of) MDD. Further studies should examine this genetic basis, preferably prospectively, and should focus on predictors of recurrence early in the lifetime course. These studies should also take into account the interactions between genetic, biological, environmental, and clinical factors in concert, since causation of recurrence seems to be multifactorial with multiple putative causal factors that interact over time.

The strengths of our study are that we were able to examine a comprehensive set of predictors in a large representative sample and used standardized instruments to determine diagnosis and course. However, in interpreting the results of this study, one should also be aware of its limitations. First, the respondents treated in specialized mental health care were recently referred and, as a consequence, this sample is not representative of the entire population treated for MDD in specialized mental health care, since patients with more severe, chronic or frequent recurring MDD are probably underrepresented in the study. Consequently, the difference in recurrence risk between primary care and specialized mental health care could have been underestimated. On the other hand, the percentage of remission between respondents treated in primary care versus specialized mental health care was not statistically different in our study which suggests that the researched treatment cohorts are comparable in this way. Secondly, subclinical residual symptoms, which are a strong predictor of recurrence risk (Judd et al., 1998), could not be

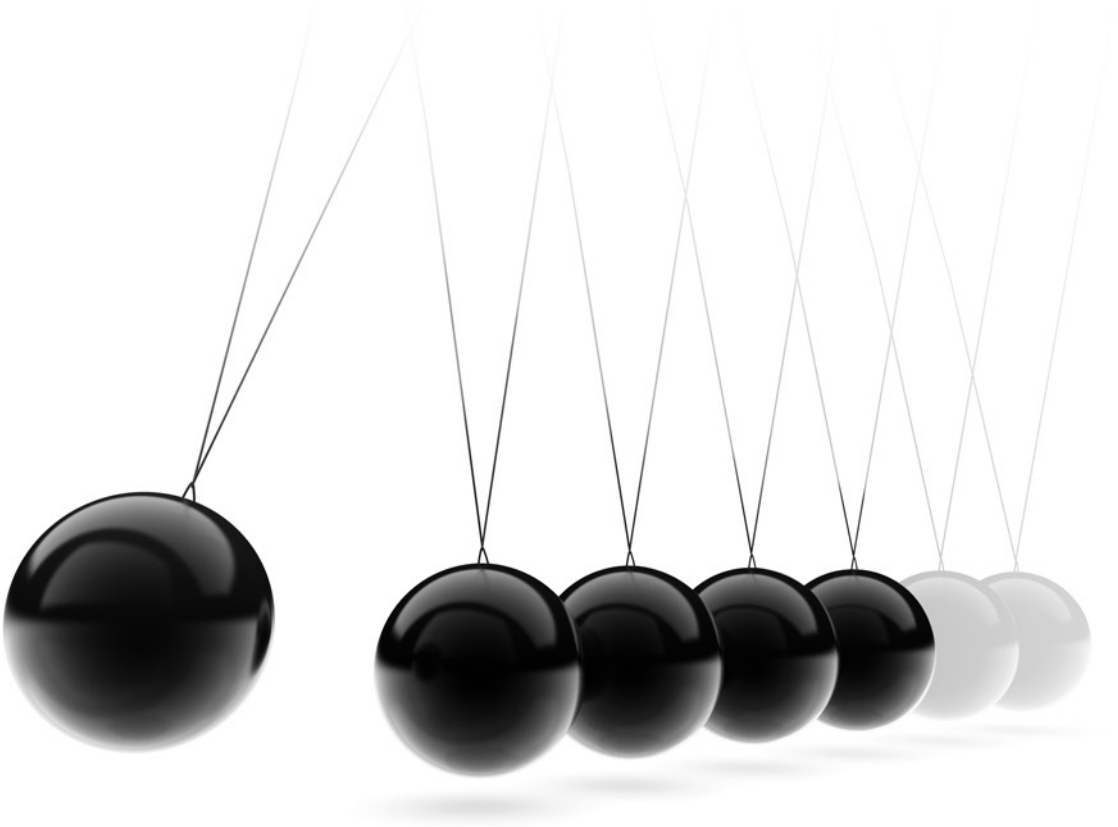
included in the analysis because the data did not allow for such precision. It is reasonable to assume that residual symptoms are more common in respondents treated in specialized mental health care than in respondents treated in primary care. Thirdly, the follow-up duration of two years was relatively short if one takes into account that respondents had to have been in remission first. Although the average duration of follow-up was modest at approximately fifteen months, it is important to realise that the risk of relapse is greatest in the first year after recovery, and declines rapidly thereafter. Therefore, it is unlikely that the conclusions of the current paper would change if a longer follow-up period had been available. Finally, our results may have been influenced by the referral behaviour of general practitioners and may not be generalizable to health systems that are very different from the system in the Netherlands. However, the structure of the Dutch health care system is comparable to that of several other European countries in which the general practitioner serves as the gatekeeper and referrals are needed for access to specialized mental health care, and also the proportion of diagnosed persons receiving mental health treatment, as well as the quality of care received, is comparable to that in other high income countries (US, UK, Spain, Belgium) (Alonso et al., 2004; Wang et al., 2007).

4.5. Conclusion

In conclusion, the recurrence risk of MDD appeared to be similar in specialized mental health care and primary care meaning that the risk of recurrence in primary care is also considerable. Respondents with a history of recurrent MDD and a family history of MDD in first-degree relatives had a shorter time to recurrence. Patients with these risk factors should be closely monitored and treatment strategies to prevent recurrence should be considered. Our results also imply that prevention of recurrence of MDD is advised for high-risk groups, not only in specialized mental health care, but also in primary care. However, aside from pharmacological treatment (Kaymaz et al., 2008), other programmes to prevent recurrence, e.g. mindfulness-based cognitive therapy (Piet et al., 2011) and cognitive therapy (Beshai et al., 2011) are mainly carried out in specialized mental health care. Therefore, general practitioners should refer patients, not only for specialized treatment of depression, but also for prevention of recurrence. Another possibility is to expand these programmes beyond specialized mental health care. To improve the management of recurrence prevention of MDD, collaborative care models (Katon et al., 2011), in which long term management and communication between primary- and specialized mental health care professionals are optimized across psychiatric services, may be helpful.

5

Increased cortisol awakening response was associated with time to recurrence of major depressive disorder



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Abstract

Introduction: Although HPA-axis activity has been studied extensively in relation to depression, there is no consensus whether HPA-axis parameters predicts major depressive disorder (MDD) recurrence. We investigated whether HPA-axis parameters (cortisol awakening response (CAR), the dexamethasone suppression test (DST) and evening cortisol) predict time to recurrence in remitted subjects with a history of MDD and whether childhood trauma and life events interact with HPA-axis parameters in increasing the risk for recurrence.
Method: Data were derived from 549 subjects with a lifetime diagnosis of MDD in remission for at least six months preceding the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA). Subjects were followed up with two interviews over the course of four years to assess recurrence. DSM-IV based diagnostic interviews were used to assess time to recurrence of MDD. Seven salivary cortisol samples were collected at baseline with information on CAR, evening cortisol and the DST. Hazard ratios were calculated using Cox regression analysis, adjusted for covariates.
Results: A higher CAR was associated with time to recurrence of MDD (HR=1.03, 95%CI 1.003-1.060, p=0.03) whereas evening cortisol and DST were not. No interactions between HPA-axis parameters and stress-related factors were found.
Conclusions: Our data support previous studies reporting that subjects with a higher CAR are more vulnerable to recurrence of MDD.

5.1. Introduction

Major depressive disorder (MDD) is often a chronic or recurrent disorder (Judd, 1997) and is one of the most disabling disorders worldwide (World Health Organization, 2008). Prevention of recurrence is therefore an important goal in the management of major depression. To that end, further knowledge on pathogenic mechanisms underlying recurrence of major depression is needed. The hypothalamic pituitary adrenal (HPA) axis is one of the main neuroendocrine systems activated under stress. Hyperactivity of the HPA-axis among depressed patients is a rather consistent research finding (Stetler & Miller, 2011) and alterations of the HPA-axis generally normalizes after full remission of depressive symptoms (Holsboer et al. 2000; Kaestner et al., 2005; Aihara et al., 2007; Pariante et al., 2009; McKay & Zakzanis, 2010 et al., 2010). However, inconsistent findings have been observed (Bhagwagar et al., 2003; Mannie et al., 2007; Vreeburg et al., 2009(b); Lok et al., 2012). Hyperactivity of the HPA-axis often results in hypercortisolism, which is associated with the pathophysiological pathway leading to MDD known as the glucocorticoid cascade hypothesis (Holsboer, 2000). A number of alterations in the HPA-axis found in major depression indicate hyperactivity of the HPA-axis. These are (i) hypercortisolism, resulting in a high evening cortisol (Kirschbaum & Hellhammer, 1989), (ii) an impaired circadian rhythm in terms of cortisol secretion in the first hour after awakening as reflected by an elevated cortisol awakening response (CAR) (Pruessner et al., 1997; Clow et al., 2010), (iii) a reduced negative feedback response to a dexamethasone suppression test (DST) (Ribeiro et al., 1993) and (iv) increased release of adrenocorticotrophic hormone (ACTH) and cortisol in response to corticotrophin-releasing hormone (CRH) after administration of 1.5 mg of dexamethasone, known as the combined dexamethasone/corticotrophin releasing hormone test (DEX/CRH test) (Nemeroff, 1996; Holsboer, 2000).

Although HPA-axis activity has been studied extensively in relation to depression (Stetler & Miller, 2011), there is no consensus on whether HPA-axis parameters have predictive value for recurrence of MDD. HPA-axis alterations may represent an underlying active disease process in depression and may predict risk for recurrence. Although a number of studies have examined this issue (Ribeiro et al., 1993; Zobel et al., 1999; Harris et al., 2000; Zobel et al., 2001; Hatzinger et al., 2002; Appelhof et al., 2006; Aubry et al., 2007; Bhagwagar & Cohen, 2008; Pintor et al., 2009; Rao et al., 2010; Bockting et al., 2012; Vrshek-Schallhorn et al., 2013), different HPA-axis measurements were used. Of the above mentioned studies, one study found that higher evening cortisol levels predicted recurrence (Rao et al., 2010), a literature review suggested that non suppression on the DST was related to relapse/recurrence (Ribiero et al., 1993), and five studies found an association between non-response on the DEX/CRH test and recurrence (Zobel et al., 1999; Zobel et al., 2001; Hatzinger et al., 2002; Appelhof et al., 2006; Pintor et al., 2009). However, also inconsistent findings have been reported, e.g. a higher CAR predicted MDD recurrence in two studies (Harris et al., 2000; Vrshek et al., 2013) whereas a lower CAR was found to do so in another study (Bockting et al., 2012).

It has also been suggested that early-life stress can induce persistent changes in the response of the HPA axis, which becomes especially visible when persons are exposed to psychosocial stressors in adulthood (Baes et al., 2012). A possible mechanism is reduction of glucocorticoid receptor function leading to a decrease in inhibitory feedback resulting in hypercortisolism. Rao et al. (2010) observed that the risk for recurrence was higher among those with elevated cortisol levels and recent life events. Therefore, when investigating the predictive value of HPA-axis parameters on recurrence of MDD, it is important to take a potential interaction effect of recent stressors and childhood trauma into account (Adam et al 2010). However, the literature is inconsistent, e.g. two other studies did not find any interactions (Bockting et al., 2012; Vrshek-Schallborn et al., 2013).

Since results are inconsistent and different HPA-axis parameters were measured, which makes previous studies difficult to compare, there is a need for further research. To our knowledge, large-scale prospective studies that examine different HPA-axis parameters simultaneously along with the interaction of HPA axis parameters with childhood trauma and life events are scarce and some of these studies only targeted adolescents (Rao et al., 2010, Vrshek-Schallborn et al., 2013). We assessed whether HPA axis parameters predict recurrence in remitted adult MDD subjects and whether stress-related factors (childhood trauma, life events) interact with HPA-axis parameters in predicting recurrence. Since hyperactivity as well as hypo-activity have been found to be associated with recurrence of MDD, we will examine potential non-linear associations with recurrence.

5.2. Methods

Study sample

Data were drawn from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study on the long-term course of depressive and anxiety disorders in different health care settings and illness phases. For the present study, we used the baseline assessment and follow-up assessments at two and four years. The study protocol was approved by the Ethical Review Board of the VU University Medical Centre Amsterdam and subsequently by the local review boards of each participating institute. All subjects provided informed consent. The rationale, objectives, and methods of the NESDA have been described in detail elsewhere (Penninx et al., 2008). In brief, the NESDA cohort (N=2981) consists of subjects (18-65 years) with (i) a current anxiety and/or depressive disorder, (ii) a prior history of a depressive and/or anxiety disorder and (iii) healthy controls. Subjects were recruited in primary care through a screening procedure, in specialized mental health care upon registration and in the community. All 2981 subjects were administered a baseline assessment, which lasted on average 4h and included assessment of psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Based on clinical judgment and if necessary

screening of the medical records, subjects with a primary diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder, severe addiction disorder, and those not fluent in Dutch were excluded.

For the present study, we selected subjects with a lifetime history of major depressive disorder who did not fulfill the criteria for major depressive disorder in the six months preceding the baseline assessment, as recommended in a previous study (Furukawa et al., 2008). An advantage of including people with remitted depression at baseline was that the measurement of life events, childhood trauma and cortisol levels was not influenced by the presence of a major depressive episode. This definition of MDD was based on the DSM-IV based Composite International Diagnostic Interview (CIDI), Lifetime Version 2.1 (World Health Organization Lifetime Version 2.1, 1997). 810 participants met the criteria for a remitted MDD diagnosis. We excluded pregnant and breastfeeding women (n=6) as they may have altered cortisol levels. We did not take into account the timing of the menstrual cycle because in a previous study performed with NESDA data (Vreeburg et al., 2009(a)) this was shown not to be associated to cortisol levels. None of the subjects used corticosteroid derivates. Furthermore, 34 subjects were excluded because their diagnosis was changed to bipolar disorder at follow-up, which puts them at a different recurrence risk level. Of the 770 subjects who met the criteria, 702 were re-interviewed at least once, either at the two- or four-year follow-up assessment. After attrition, the sample 'at risk' for recurrence of MDD consisted of 702 subjects. Of these, 549 (78.2%) subjects had usable saliva samples to contribute to at least one of the saliva cortisol analyses and they constitute the present study sample.

These 549 subjects were older in comparison with the 261 subjects who were excluded from the present study sample (mean age 45.0 versus 40.5, $p<0.001$), but they did not differ in sex, educational attainment or number of previous episodes of MDD.

Time to recurrence of MDD

Recurrence of MDD was assessed prospectively at two and four year follow-up using the CIDI, which measured the 1-month, 6-month, 1-year and 2-year prevalence of depression. To assess time to recurrence, the average within a certain period of prevalence was taken. Time from baseline to recurrence was calculated on the basis of this data. So, eight time intervals were made (12, 18, 21, 23.5, 36, 42, 45, 47.5 months). For example, if the respondent had a 1-month prevalence of MDD after two years, it was estimated that the time to recurrence from baseline was 23.5 months (24 minus 0.5 months). This represents the time to the first new major depressive episode (MDE). If the respondent had multiple episodes during follow-up the time from baseline to the first recurrence was taken.

Cortisol assessments

Cortisol measurements have been described previously (Vreeburg et al., 2009a). In short, cortisol was measured through saliva sampling, reflecting the active unbound form of

cortisol (Kirschbaum & Hellhammer, 1989). Subjects were instructed to collect saliva samples at home shortly after the interview. Saliva samples were obtained using cotton salivettes (Sarstedt, Germany) seven times during the day. The cortisol awakening response includes four sampling points; upon awakening (t1), and 30 (t2), 45 (t3) and 60 (t4) minutes thereafter. Evening cortisol values were collected at 2200h (t5) and 2300h (t6). Dexamethasone suppression was measured using cortisol sampling the next morning upon awakening (t7) after ingestion of 0.5 mg dexamethasone directly after the saliva sample of 2300h (t6). Samples were centrifuged at 2000*g* for 10 minutes, aliquoted and stored at -80°C. The analysis of cortisol was performed using competitive eletrochemiluminescence immunoassay (E170; Roche, Basel, Switzerland) as described by van Aken et al. (2003). The functional detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. Assays were repeated if cortisol levels were very high (>80 nmol/l) or very low (<1 nmol/l). Data cleaning was performed by excluding cortisol values higher than two standard deviations (SD) from the mean (47 of 3813 values). Additionally for CAR analysis, morning cortisol samples were excluded which were collected more than 5 minutes before or after the right protocol time (132 of 2170 values).

Three cortisol indicators were calculated: the CAR, the evening cortisol level, and the DST. The CAR was assessed by calculating the area under the curve with reference to the increase (AUCi) and the ground/zero (AUCg) using Pruessner's formulas (Pruessner et al., 2003). The AUCg measures total cortisol secretion during the first hour after awakening and estimates total body exposure to cortisol. The AUCi measures cortisol increase with respect to awakening and is therefore a measure of the dynamics of the CAR, related to the sensitivity of the system and change in cortisol exposure over time (Clow et al., 2010). As the two evening cortisol values are strongly correlated (Spearman's rho = 0.71, $p<0.001$), we used the mean of both cortisol levels as a measure of evening cortisol, which reflects basal activity. The DST provides information on the negative feedback system of the HPA-axis, since dexamethasone reduces cortisol levels by acting on the pituitary (Carroll et al., 1981). We calculated a cortisol suppression ratio by dividing the cortisol value at T1 by the value at T7 the following morning.

Covariates

Based on previous studies (Burcusa & Iacono, 2007; Vreeburg et al., 2009a; Hardeveld et al., 2010), various factors with the potential to predict MDD recurrence and salivary cortisol levels were assessed at baseline.

Socio-demographic factors: Sex; age.

Clinical factors: Number of previous episodes (MDEs), categorized into single versus recurrent episodes. Anxiety disorders (social phobia, panic disorder with/without agoraphobia, agoraphobia, and generalized anxiety disorder) in the six months preceding baseline assessment were deemed to constitute relevant comorbid disorders. Severity of residual

symptoms of depression was measured with the inventory of depressive symptoms (IDS) (Rush et al., 1996); because cortisol levels could be state dependent (Stetler & Miller, 2011), we adjusted for residual depressive symptoms. History of depression in first-degree family members was assessed using a family tree inventory (Fyer & Weissman, 1999), categorized into 'yes' and ''no'.

Stress related factors: Negative life events over the past year were assessed with the Brugha questionnaire (Brugha et al., 1985) which included 12 specific events and one 'other' category asking about other serious negative life events (sum score ranging from 0 to 5). The number of life events in the past year was calculated. In order to examine the role of childhood trauma, a cumulative childhood index using the NEMESIS childhood trauma interview was constructed (De Graaf et al., 2004; Wiersma, 2009; Hovens et al., 2010). Participants were asked four questions regarding childhood experiences of emotional neglect, and emotional, physical and sexual abuse. A cumulative index was calculated as the sum of the number and frequency of the four types of abuse for each participant (sum score ranging from 0 to 8) in line with earlier studies (Wiersma, 2009; Hovens et al., 2010).

Sampling factors associated with cortisol levels: Vreeburg et al. (2009a) established sampling factors relevant for HPA-axis indicators in our study: smoking (current or nonsmoker); awakening time; working day (yes, no). Presence of cardiovascular disease was established with an algorithm based on self-report and medication use, categorized into 'yes' and ''no'.

Treatment: Pharmacological treatment was assessed based on inspection of the medication boxes used in the past month and coded using the WHO Anatomical Therapeutic Chemical (ATC) classification (REF to URL). Regular use of antidepressants was categorized into selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (ATC-code N06AA) or other antidepressants (ATC-code N06AF/N06AX).

Sociodemographic, clinical, sampling factors and use of antidepressants were set as potential confounders. The stress related factors (childhood trauma and number of life events in past year) were set as potential effect modifiers (Shea et al., 2005; Rao et al., 2010; Morris et al., 2012). In a previous study performed with NESDA data (Holleman et al., 2012) stress related factors were found not to be associated to HPA-axis parameters and they were therefore not further considered potential confounders in our study.

Statistical analyses

T-tests and X^2- square tests were performed to compare recurrent and non-recurrent subjects on baseline characteristics. The associations between HPA-axis parameters and risk for MDD recurrence over the course of the four year follow-up were analyzed using Cox regression analyses. The independent variables were the HPA-axis parameters, time to recurrence of depression was the dependent variable which was expressed in months and based on the CIDI. Hazard ratios and their 95% confidence intervals (95% CI) were

calculated, adjusted for covariates. The covariates were entered in blocks; sociodemographic factors, sampling factors and treatment with antidepressants in the first block, and clinical factors in the second block. As previous studies identified both hyperactivity and hypoactivity as predictors of MDD recurrence, we checked for potential non-linear associations by dividing the HPA axis parameters into quintiles. Linear mixed model analyses (LMM) were performed for the four morning cortisol measurements. LMM analyses can accommodate for incomplete cases and takes correlations between repeated measurements into account (Gueorguieva & Krystal, 2004). Therefore, LMM analysis included all subjects with at least two valid CAR values. In this analysis, recurrence of MDD, morning cortisol moments and all covariates were entered as fixed factors. Recurrence of MDD during follow-up was operationalized dichotomously (yes/no). Subjects were treated as a random effect and a random intercept was estimated. Recurrence of depression was the independent variable and the various morning cortisol levels were entered as the dependent variables. This analysis was used as a confirmation of the results of the Cox regression analysis. Furthermore, we checked whether interactions between stress-related factors (childhood trauma, number of life events in past year) and the HPA-axis parameters (CAR, DST, evening cortisol) were associated with the risk for MDD recurrence. Interaction terms were calculated by multiplying the stress-related factors by the different HPA-axis parameters which were centered because they were continuous. So, eight interaction terms were assessed. p Values ≤0.05 were deemed to be statistically significant for main effects and p values ≤0.10 for interaction terms.

5.3. Results

Characteristics of the 549 subjects are presented in Table 1.

Of these, 392 subjects (71.4%) were female and the mean age was 45.0 years. The mean number of previous episodes of MDD was 2.9; 484 subjects (88.2%) remitted more than 12 months ago and 227 (41.3%) had no depressive symptoms in the five years preceding baseline which was assessed with the life chart interview (Lyketsos et al., 1994). During the four year follow-up, 131 subjects (23.9%) experienced a recurrence of MDD over the first two years, and 193 (35.2%) over the course of the four year follow-up. Mean time to recurrence was 27.4 months (sd=12.1). Subjects who experienced a recurrence (n=193) during the 4-year follow-up were more often younger, more likely to have a history of more than one episode of depression at baseline, more often had a 6-month comorbid anxiety disorder at baseline, had more severe depressive symptoms at baseline, a higher number of traumatic youth experiences, used antidepressants more frequently, and had a higher AUCi. There were no differences between recurrent and non-recurrent subjects in sex, number of negative life events in the past year, family history of depression and covariates related to cortisol levels.

Table 1 Characteristics of 549 subjects divided in recurrence versus non recurrence of MDD during follow-up

	No recurrence (n=356)	Recurrence (n=193)	p
Socio-demographic factors			
Gender, n (% female)	248 (69.7)	144 (74.6)	0.22
Age, mean yrs (sd)	45.9 (12.6)	43.4 (12.0)	0.03
Clinical factors			
History of MDEs, n (%)	158 (44.4)	109 (56.5)	<0.01
6-Month anxiety disorder, n (%)	98 (27.5)	86 (44.6)	<0.001
Severity of depressive symptoms (IDS), mean (sd)	15.0 (9.5)	21.2 (9.5)	<0.001
Family history of depression, n (%)	287 (80.6)	164 (85.0)	0.20
Stress related factors			
Trauma before age 16, n (%)	167 (60.3)	110 (39.6)	0.02
Trauma before age 16 index, mean score (sd)	0.8 (1.1)	1.1(1.2)	0.01
Number of negative life events, mean (sd)	0.5 (0.8)	0.5 (0.8)	0.62
Covariates related to cortisol levels			
Smoking, n (%)	125 (35.1)	68 (35.2)	0.98
Time of awakening, mean hour (sd)	7:29 (1:04)	7:28 (1:05)	0.82
Cardiovascular disease, n (%)	14 (3.9)	6 (4.1)	0.90
Working on day of sampling, n (%)	230 (64.6)	119 (61.7)	0.49
Treatment			
Use of antidepressants, n (%)	63 (17.7)	59 (30.6)	0.001
Cortisol			
AUCi (n=399), nmol/l/h (sd)	2.3 (6.3)	3.9 (6.5)	0.02
AUCg (n=399), nmol/l/h (sd)	19.0 (6.5)	19.7 (7.5)	0.34
DST (n=345), mean (sd)[1]	2.72 (1.37)	2.54 (1.09)	0.22
Mean evening cortisol (n=546), nmol/l (sd)[2]	5.6 (4.4)	5.6 (4.0)	0.93

Abbreviations: MDEs=major depressive episodes, IDS=inventory of depressive symptoms, AUCi/AUCg=area under the curve with respect to the curve with respect to the increase/ground, DST= dexamethasone suppression test, mean evening cortisol.

[1] DST= salivary cortisol at T1/cortisol level at T7 after 0.5 mg of dexamethasone ingestion.

[2] mean evening cortisol=mean cortisol at T5 and T6.

A Cox regression analysis was performed, adjusted for covariates. Fully adjusted results illustrate that a higher AUCi is associated with time to recurrence of MDD (HR 1.03, 95%CI 1.003-1.060, p=0.03) (Table 2). These results were also confirmed by LMM analyses (direct effect: p=0.10, interaction with time: p=0.05; Fig. 1).

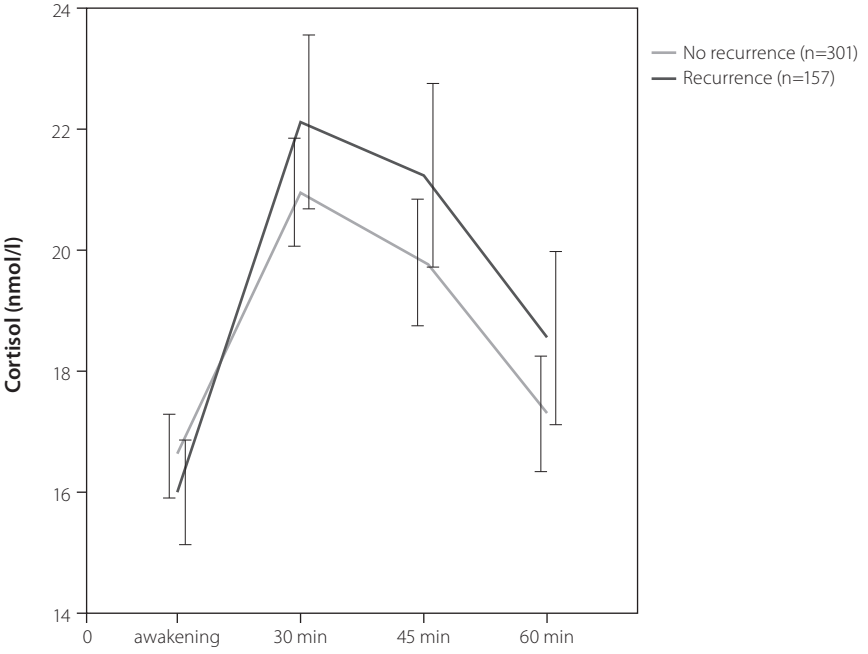


Figure 1 Baseline 1-hour cortisol awakening levels for subjects with and without a recurrence of depression after four years based on linear mixed model analyses

Error bars illustrate 95% CI. Analyses are adjusted for gender, age, smoking, time of awakening, cardiovascular disease, working day, use of antidepressants, history of major depressive episodes, 6-month prevalence of anxiety disorder, severity of depressive symptoms and family history of depression.

Evening cortisol levels and cortisol suppression after dexamethasone ingestion were not related to time to recurrence. The hazard ratios were constant over time. This was checked by calculating the different interaction terms (HPA-axis parameter x time) which were not statistically significant.

To analyze whether higher as well as lower cortisol levels were related to time to recurrence, we divided the HPA-axis parameters into quintiles, resulting into five categories. The middle quintile was the reference category. Table 2 shows that the highest AUCi, fully

Table 2 Recurrence of MDD across various salivary cortisol indicators adjusted for covariates

	HR (95% CI)*	p	HR (95% CI)**	p
AUCg (nmol/l/hour) (n=399)				
Continuous	1.02 (1.00-1.05)	0.08	1.03 (1.00-1.05)	0.08
<13.68	1.19 (0.68-2.09)	0.55	1.27 (0.72-2.26)	0.41
13.68-16.63	0.94 (0.51-1.70)	0.85	0.90 (0.50-1.62)	0.72
16.64-19.73	ref	ref	ref	ref
19.74-24.30	1.52 (0.88-2.63)	0.13	1.49 (0.86-2.58)	0.15
>24.30	1.46 (0.80-2.47)	0.24	1.40 (0.79-2.47)	0.25
AUCi (nmol/l/hour) (n=399)				
Continuous	1.03 (1.003-1.060)	**0.03**	1.03 (1.004-1.059)	**0.03**
<-2.15	1.14 (0.61-2.20)	0.69	1.03 (0.55-1.92)	0.94
-2.15-0.95	1.34 (0.75-2.40)	0.32	1.38 (0.76-2.50)	0.29
0.96-3.84	ref	ref	ref	ref
3.85-7.00	1.33 (0.75-2.36)	0.34	1.27 (0.71-2.27)	0.43
>7.00	1.90 (1.08-3.33)	**0.03**	1.81 (1.02-3.21)	**0.04**
DST[1] (n=345)				
Continuous	0.92 (0.79-1.07)	0.28	0.93 (0.80-1.08)	0.32
<1.69	1.19 (0.68-2.08)	0.54	1.18 (0.67-2.08)	0.56
1.69-2.21	0.67 (0.37-1.24)	0.20	0.79 (0.43-1.46)	0.45
2.22-2.65	ref	ref	ref	ref
2.66-3.27	1.19 (0.69-2.05)	0.54	1.24 (0.72-2.16)	0.44
>3.27	0.71 (0.39-1.30)	0.27	0.79 (0.43-1.44)	0.43
Mean evening cortisol[2] (n=546)				
Continuous	0.99 (0.96-1.03)	0.67	0.99 (0.96-1.02)	0.46
<3.10	0.82 (0.52-1.29)	0.39	0.81 (0.52-1.27)	0.35
3.10-4.42	0.78 (0.50-1.23)	0.29	0.73 (0.46-1.16)	0.19
4.43-5.57	ref	ref	ref	ref
5.58-7.11	0.95 (0.61-1.47)	0.81	0.94 (0.60-1.47)	0.78
>7.11	0.88 (0.56-1.39)	0.59	0.83 (0.52-1.31)	0.42

Abbreviations: HR=hazard ratio, CI= confidence interval, AUCi/AUCg area under de curve with respect to the increase/ground, DST=dexamethasone suppression test, ref=reference category.
In bold: statistically significant.
* Based on Cox's survival analyses and adjusted for gender, age, smoking, time of awakening, cardiovascular disease, working day, use of antidepressants. ** Based on Cox's survival analyses and adjusted for gender, age, smoking, time of awakening, cardiovascular disease, working day, use of antidepressants, history of major depressive episodes, 6-month prevalence of anxiety disorder, severity of depressive symptoms and family history of depression.
[1] DST= salivary cortisol at T1/cortisol level at T7 after 0.5 mg of dexamethasone ingestion
[2] mean evening cortisol=mean cortisol at T5 and T6.

adjusted for covariates, was associated with recurrence (HR 1.81, 95% CI 1.02-3.21, p=0.04). AUCg, evening cortisol and DST were also divided into quintiles. No difference in risk for MDD between low and high cortisol levels was found for these HPA-axis parameters. In the fully adjusted Cox regression model, we checked whether the stress related factors (childhood trauma and number of life events in past year) and the HPA axis parameters (AUCi, AUCg, DST, mean evening cortisol) interacted by entering the interaction term separately into the model (8 interactions). However, no statistically significant interaction terms were found (p interaction>0.10).

5.4. Discussion

The aim of this study was to examine whether HPA-axis parameters are related to risk for MDD recurrence among subjects who had recovered from a previous episode of MDD. We found that a higher cortisol awakening response was associated with time to recurrence of MDD. Hypocortisolism was not related to recurrence and we did not find any associations with other HPA-axis parameters (DST and evening cortisol). Furthermore, no significant interactions between HPA axis parameters and stress related factors were found. This indicates that the increased risk for a recurrence of depression due to a high CAR is not dependent on recent life events or childhood trauma.

Our study supports the predictive role of a higher CAR in recurrence of depression, in line with previous studies which also found that hyperactivity was related to recurrence of MDD (Ribeiro et al., 1993; Zobel et al., 1999; Harris et al., 2000; Zobel et al., 2001; Hatzinger et al., 2002; Appelhof et al., 2006; Aubry et al., 2007; Bhagwagar et al., 2008; Pintor et al., 2009; Vrshek-Schallhorn et al., 2013). The study by Vrshek-Schallborn et al. (2013) is the most similar to our study and also found a higher CAR to be related to recurrence. One study (Bockting et al., 2012) found decreased mean morning cortisol levels to be predictive of recurrence. In line with Bocking et al. (2012) a recent NESDA study (Vreeburg et al., 2013) found that a lower CAR in persons with a current depressive and/or anxiety disorder was associated with an unfavorable prognosis for cases without remission longer than 3 months. Such discrepancies may be explained by the fact that we did not study subjects with multiple episodes in the recent past but those who had an major depressive episode further in the past. Bockting et al. (2012) included subjects with at least two major depressive episodes in the last five years. In our study sample, 41.3% had no depressive symptoms in the five years preceding baseline and only 51.4% of the subjects had one MDE in the past, indicating that subjects in our study sample did not have a chronic recurrent course in the recent past. Thus, while our data suggest that a higher CAR is associated with MDD recurrence in remitted depressed patients, previous studies also based on NESDA data postulate that a lower CAR is associated with chronicity of MDD in currently depressed patients data (Vreeburg et al., 2013). A possible explanation for such

discrepancies is that chronic stress or duration of symptoms of depression may lead initially to HPA axis hyperactivity and over time to down-regulation of glucocorticoid and mineralocorticoid receptors, resulting in hypocortisolism (Buchanan et al., 2004; Pruessner et al., 2007). It has been argued that a higher CAR represents a 'trait' marker for recurrence of depression whereas a lower CAR can be identified as a 'scar' marker for current depression (Vreeburg et al., 2013). Thus, a high AUCi may also represent a trait marker for recurrence of depression. This is in line with previous studies. A recent study (Vrshek-Schallborn et al., 2013) concluded that a higher CAR also predicted first onset. Furthermore, the CAR is higher in young people who have not been depressed themselves but have a family history of depression (Mannie et al., 2007; Vreeburg et al., 2010) and a recent study also using data of NESDA did suggest that cortisol levels were not convincingly associated with childhood trauma (Holleman et al., 2012). Besides, Lok et al. (2012) found that remitted highly recurrent MDD patients had higher cortisol concentrations than controls which was not influenced by MDD-episodes during follow-up and HPA axis activity had no association with daily hassles or childhood life events. These data could suggest a genetic vulnerability trait. A previous study (Wüst et al., 2000) also concluded that there is a significant genetic influence on the CAR. It could be that in those in remission for a long time who are not exposed to high stress levels the HPA-axis activity returns to the original level prior to the depression. Hyperactivity of the HPA-axis could function as a risk factor as before a first episode. Interestingly, the study by Vrshek-Schallhorn et al. (2013) found that the CAR was a time-limited risk factor and predicted recurrences of depression with greater strength than it predicted a first episode. However, in our study the number of prior major depressive episodes experienced did not interact with CAR to predict time to recurrence.

Despite a large number of studies on the CAR, the exact function of the sharp cortisol increase after awakening is still unknown. Fries et al. (2009) hypothesized that "the cortisol rise after awakening may accompany an activation of prospective memory representations at awakening enabling individual's orientation about the self in time and space as well as anticipation of demands of the upcoming day, with an important role for the hippocampus". In our study, the AUCi was associated with recurrence of depression which is a measure of the dynamics of the CAR, related to the sensitivity of the system (Clow et al., 2010). Therefore, our data provides some indications that the sensitivity of the HPA-axis could play a role in the risk for recurrence, whereas the total amount of cortisol during the day or the negative feedback mechanism as evening cortisol and DST were not related to recurrence. An alternative hypothesis is that the CAR is more sensitive to moderate degrees of depression than the DST, e.g. failure to suppress to dexamethasone is associated with more severe depression such as melancholia and inpatient status (Nelson & Davis, 1997). Although there is no use of the CAR as a diagnostic tool or biomarker in a clinical setting so far, it is a valuable instrument in research on stress-related disorders such as MDD. It remains to be seen whether a higher AUCi is an epiphenomenon or plays a

substantial role in the onset or course of a depressive episode. A hypothesis could be that a higher CAR reflects a marker for increased sensitivity for (psychosocial) stress which is associated with an increased risk for a recurrence. Though, our analyses did not support this assumption as the CAR did not interact with stressful life events in increasing the risk for a recurrence. However, it is important to note that the stressful life events measures were assessed for the time period prior to baseline assessment.

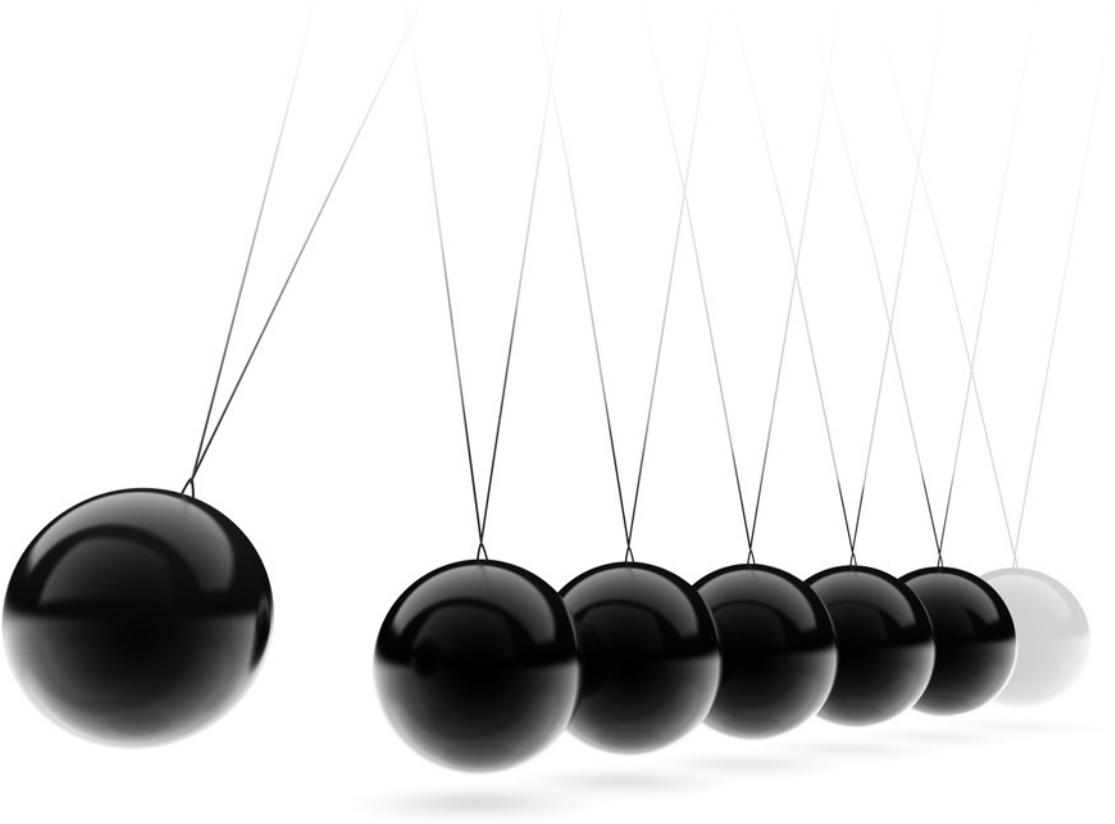
The strengths of our study are that we were able to examine several HPA axis parameters and take into account important covariates in a large representative sample using standardized instruments to determine diagnosis and course. It should be mentioned that our results are restricted to those without a chronic recurrent course of depression in the recent past as 41.3% of our study sample had no depressive symptoms in the five years preceding baseline. Furthermore, the HPA-axis has an diurnal rhythm, and although we took the morning awakening response into account, by creating the area under curve to the ground and to the increase and measured evening cortisol levels we could not determine a more precise diurnal rhythm during the day since we did not collect mid-day cortisol levels. We could have created diurnal rhythm, by extracting the evening curve levels from the morning curve levels. However, the resulting diurnal variable is highly correlated to the morning curve levels. This is due to the fact that the evening levels are generally much lower than the morning curve levels, causing the height of the morning curve levels to heavily determine the diurnal rhythm variable. We also had missing data in our study sample largely because we had no information on cortisol values at baseline of these subjects. Selection was not at random as the study sample was older in comparison with the subjects who were excluded from the study (mean age 45.0 versus 40.5, $p<0.001$). They did however not differ in sex, educational attainment or number of previous episodes of MDD. Nevertheless, our sample seems representative for an outpatient treated group. When interpreting the results of this study, its limitations should also be taken into account. First, time to recurrence of depression was measured during follow-up with the use of the prevalence rates at 2- and 4 years. The estimated time to recurrence was measured with the averages of these prevalence rates (see method section) which may not be completely accurate to assess time to recurrence. Time to recurrence could therefore be overestimated. Also, lifetime diagnoses of depression were assessed retrospectively and could be affected by recall bias. Second, the subjects' state of depressive symptoms may lead to unreliable results of HPA-axis values. Although they were all in remission for at least six months some subjects may be in a recurrence for a rather short period, others for a more extended period of time. Although subjects were in remission as confirmed by the CIDI psychiatric interview, subjects could experience residual symptoms at baseline. The mean IDS score in our study sample was 17.2 (s.d.=9.9). The IDS could affect HPA-axis parameters. We, however, adjusted for the IDS score in the final model which did change the results only slightly and examined possible interaction effects of IDS with HPA-axis parameters which were not found. Also, physical diseases

could affect the HPA-axis values which we did not exclude specifically. We, however, excluded pregnant and breastfeeding women, those who used corticosteroid derivates and adjusted for health indicators which in a previous NESDA study (Vreeburg et al., 2009a) have been found to be associated with HPA-axis parameters. We also excluded those with cortisol values two standard deviations above the mean. Furthermore, we did not measure current stress levels or state effects (such as variations in mood, sleep, etc.) on the exact day of saliva sampling. Although we instructed subjects to collect the samples on a representative day without unusual amounts of stress, state effects could have played a role. Sampling on multiple days would have increased the reliability of the measurements (Hellhammer et al., 2007). However, the large sample size of our study may have partly of fully compensated for this. Finally, our study was based on observational data, so no causal association between cortisol levels and recurrence of MDD can be drawn.

In conclusion, this study shows that a higher cortisol awakening response, related to the sensitivity of the HPA-axis, increases vulnerability to new depression episodes, even if a subject has been in remission for a long period. Neither the DST or evening cortisol levels were associated with recurrence and the higher risk for recurrence related to a high CAR was not dependent on stressful life events. Further research should investigate the CAR in association with the course of depression over time to distinguish possible depression trajectories in association with the HPA-axis.

6

Glucocorticoid and mineralocorticoid receptor polymorphisms and recurrence of major depressive disorder



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Abstract

Objective: Previous research found that variants of the glucocorticoid receptor (GR) (9ß, ER22/23EK, *Bcl*I, *TthIII*I, NR3C1-1 and N363S) and mineralocorticoid receptor (MR) gene polymorphism (-2C/G and I180V) are associated with both glucocorticoid (GC) sensitivity and major depressive disorder (MDD). There are no data which investigated prospectively whether these variants are associated with recurrence of MDD.

Methods: Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) which used the Composite International Diagnostic Interview (CIDI) to determine MDD. Polymorphisms in the GR and MR gene were determined and haplotypes were characterized. We analysed in retrospect whether recurrent MDD (n=951) in comparison with first onset MDD (n=919) was associated with polymorphisms in the GR and MR gene. Furthermore, we analysed prospectively for four years the time to recurrence amongst 683 subjects with a remitted MDD diagnosis. Time to recurrence of MDD was assessed using the CIDI and a life chart interview. Additionally, we analysed interactions of the investigated polymorphisms with childhood trauma and recent negative life events.

Results: GR and MR gene polymorphisms and derived haplotypes were not associated with recurrence of depression in both retrospective and prospective analyses. In addition, no consistent interactions between GR and MR polymorphisms and childhood trauma or life events were found.

Conclusion: This study did not find consistent associations between GR and MR gene polymorphisms, interactions between GR and MR haplotypes and stressful conditions and recurrence of MDD.

6.1. Introduction

Major depressive disorder (MDD) is one of the disorders with the highest morbidity worldwide (World Health Organisation, 2008) and long term strategies aimed at reducing recurrence could be an effective way to reduce the population burden of MDD (Vos et al., 2004). However, knowledge of the predictors of recurrence is still sparse. MDD is a complex disorder that does not result from either genetic or environmental influences alone but rather from both.

A possible link between environmental influences, e.g. stressful conditions, genetic risk factors and the risk for a recurrence of MDD could be an altered function of the hypothalamic-pituitary-adrenal (HPA) axis. In reaction to stressful conditions, glucocorticoids coordinate metabolic, endocrine, immune and nervous system responses. Recurrences of MDD are associated with childhood trauma (Hardeveld et al., 2013), recent life events (Monroe et al., 2014) and HPA-axis alterations (Ribeiro et al., 1993; Zobel et al., 1999; Harris et al., 2000; Zobel et al., 2001; Hatzinger et al., 2002; Bhagwagar et al., 2003; Appelhof et al., 2006; Aubry et al., 2007; Bhagwagar and Cohen, 2008; Pintor et al., 2009; Rao et al., 2010; Bockting et al., 2012; Vrshek-Schallhorn et al., 2013). It has been postulated that childhood trauma can induce persistent changes in the response of the HPA axis, which can become apparent when persons are exposed to psychosocial stressors in adulthood (Von Werne Baes et al., 2012; Juruena, 2014). A recent study (Hardeveld et al., 2014) published in this Journal concluded that the cortisol awakening response was associated with time to recurrence of MDD and it was postulated that an increased cortisol awakening response could also be a genetic vulnerability trait. The effects of glucocorticoids are mediated by the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) and altered sensitivity to glucocorticoids of both receptors could lead to reduced negative feedback of cortisol, an increased production of corticotrophin releasing factor and consequently hypercortisolism which has been associated with the pathophysiology of MDD (glucocorticoid cascade hypothesis) (Nemeroff, 1996; Holsboer, 2000; Pariante, 2009). Sensitivity to glucocorticoids varies between individuals (Stevens et al., 2004) and various common single nucleotide polymorphisms (SNPs) are associated with glucocorticoid sensitivity (Spijker and van Rossum, 2012). For the MR gene these are: -2 G/C and I180V (De Rijk et al., 2006; van Leeuwen et al., 2011) and for the GR gene these are: 22/23 EK, 9β, N363S, *Tth*III*l*, NR3C1-1, and *Bcl*I (Huizinga et al., 1998; van Rossum et al., 2002; van Rossum et al., 2003; Wüst et al., 2004; Spijker et al., 2012). Studies also found that these polymorphisms were associated with onset and presence of major depression (van Rossum et al., 2006; van West et al., 2006; Kuningas et al., 2007; Zobel et al., 2008; Krishamurthy et al., 2008; Bet et al.,2009; Otte et al., 2009; Klok et al., 2011; Spijker and van Rossum, 2012; Szczepankiewicz et al., 2011; Galecka et al., 2013). Three studies examined recurrent MDD versus controls in retrospect (van West et al., 2006; Zobel et al, 2008; Galecka et al., 2013) and found that N363s, *Bcl*I and 22/23 EK were associated with recurrent MDD. Only one study (Bet et al.,

2009) investigated interactions and found that an interaction between the GR polymorphisms 22/23 EK and 9β and childhood trauma resulted in an increased risk for developing depressive symptoms at old age. To the best of our knowledge, there is no research which investigated prospectively whether these variants are associated with recurrence of MDD.

We aimed to investigate retrospectively as well as prospectively whether the SNPs located on the GR and MR which are associated with glucocorticoid sensitivity and MDD are also associated with recurrence of MDD. Furthermore, we investigated whether these SNPs interact with stressful conditions (childhood trauma, life events). Our hypothesis was that polymorphisms of the GR and MR gene associated with glucocorticoid sensitivity and depression increase the risk of a recurrent course of depression or a faster time to recurrence. Moreover, we hypothesized that these polymorphisms interact with stressful conditions (childhood trauma, recent life events), increasing the risk for a recurrence.

6.2. Methods

Study sample

Data were from the Netherlands Study of Depression and Anxiety (NESDA), a prospective cohort study investigating the long-term course of depressive and anxiety disorders. At baseline, 2981 subjects (18-65 years) were recruited in primary care, in specialized mental health care and in the community. The study protocol was approved by the Ethical Committee of participating universities. All subjects provided written informed consent. The rationale, objectives, and methods of NESDA have been described in detail elsewhere (Penninx et al., 2008). In brief, the NESDA cohort (N=2981) consists of subjects (18-65 years) with (i) a current anxiety and/or depressive disorder, (ii) a prior history of a depressive and/or anxiety disorder and (iii) healthy controls. Subjects were recruited in primary care through a screening procedure, in specialized mental health care upon registration and in the community. All 2981 subjects were administered a baseline assessment, which lasted on average 4h and included assessment of psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Based on clinical judgment and if necessary screening of the medical records, subjects with a primary diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder, severe addiction disorder, and those not fluent in Dutch were excluded. All subjects were from Northern-European ancestry.

For our present study, the first four years were used. We selected subjects with a lifetime history of MDD (n=1925). The diagnosis was assessed at baseline and based on the DSM-IV based Composite International Diagnostic Interview (CIDI), lifetime version 2.1. Of these, 55 subjects were excluded because they did not have DNA data or that the samples of these subjects did not pass basic quality control (see GR and MR variants section).

Subjects with or without DNA data did not differ in age, sex or history of recurrent MDD. We applied two different analytic approaches. First, we analysed in retrospect whether subjects with GR and MR polymorphisms associated with glucocorticoid sensitivity more often had a recurrent MDD (n=951) as compared to those having a single episode (n=919). Second, in a more stricter approach we selected those who were in remission of MDD for at least six months preceding the baseline assessment and assessed time to recurrence prospectively during four years using the life chart interview (LCI) (Lyketsos et al., 1994). The LCI uses age- and calendar-linked personal landmarks to describe time sequence of symptoms of MDD. In this way, it was possible to assess time to recurrence of MDD per month follow-up. Recurrence was defined as recurrence of symptoms after remission to at least mild severity level persisting for at least one month with the additional criterion that a CIDI-confirmed MDD diagnosis was present during follow-up. 810 subjects fulfilled the definition of a remitted MDD diagnosis. Of these, 18 subjects were excluded because these subjects did not collect DNA data or the DNA samples did not pass basic quality control. 80 subjects (10.1%) were excluded because they did not have a (complete) LCI during follow-up or were lost to follow-up. Drop-out was associated with lower educational attainment (F=1.99, p=0.05), but not with sex or age. Finally, 29 subjects were excluded because the diagnosis changed to bipolar disorder during follow-up. Consequently, in 683 subjects GR and MR polymorphisms could be analysed prospectively for recurrence of MDD.

GR and MR variants

For the present study, MR and GR SNPs were selected which in previous research were associated with glucocorticoid sensitivity (Spijker et al., 2012). For the GR gene these are: 22/23 EK (rs6189/rs6190, GAGAGG>GAAAGG), 9ß (rs6198, A>G), N363S (rs56149945, previously coded rs6195, AAT>AGT), *TthIII*I (rs10052957, C>T) NR3C1-1 (rs10482605, T>C) and *Bcl*I (rs41423247, C>G). For the MR gene these are: – 2 G/C (rs2070951, G>C) and I180V (rs5522, A>G). Genotyping of the SNPs was performed on two platforms: OpenArray® Real timePCR System (Life Technologies, Carlabad, USA) and Affymetrix 6.0 (Santa Clara CA; Perfegen 5.0, Mountain View, CA USA) which was imputed against the 1000 genomes (1KG Phase reference panel l release version 3 2012-03-14). Subjects were excluded based on a SNP genotype missing rate of > 10%, heterozygosity -0.1 < F < 0.1 or when the X chromosome status did not match phenotype sex. Best guess genotype data was used based on a cut-off of 0.90. Allele frequencies lower than 1% were excluded. For the data retrieved from OpenArray® Real timePCR System, also samples with a call rate < 95% were removed. The retrieved SNP data were highly correlated (Pearson square>0.95). Because the number of usable DNA samples was larger in the Affymetrix 6.0 dataset, this dataset was used. An exception was -2 G/C which could only be retrieved through OpenArray® Real timePCR System.

Stress related factors

We determined two types of stress related factors: negative life events in the last year and childhood trauma. Number of negative life events were determined with the Brugha questionnaire (Brugha et al., 1985) which included 12 specific events and one 'other' category asking about serious other negative life events. The number of life events in the past year was calculated. For childhood trauma a cumulative childhood index was constructed (Wiersma et al., 2009; Hovens et al., 2010) by asking four questions regarding the occurrence and frequency of childhood experiences of emotional neglect, or emotional, physical, or sexual abuse. A cumulative index was calculated as the sum of the number and frequency of the four types of abuse for each subject in line with earlier studies (Wiersma et al., 2009; Hovens et al., 2010).

Covariates

Besides age and sex, pharmacological treatment was also considered a covariate based on previous studies (Brouwer et al., 2006; Anacker et al., 2011). This was assessed based on inspection of the medication boxes used in the past month and coded using the WHO Anatomical Therapeutic Chemical (ATC) classification (REF to URL). Regular use of anti-depressants was categorized into selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (ATC-code N06AA) or other antidepressants (ATC-code N06AF/N06AX). Use of antidepressants was dichotomized into yes or no. Furthermore, we took into account possible genetic variation in the Dutch population. An earlier study performed in NESDA (Abdellaoui et al., 2013) identified three principal components which showed significant correlations with geography, distinguishing between: North and South, East and West, and the middle-band and the rest of the Netherlands.

Statistical Analyses

SNPs were tested for Hardy-Weinberg equilibrium. Haplotypes were created with Phase (http://stephenslab.uchicago.edu/software.html) (Stephens et al., 2001). For each haplotype three genotype combinations were distinguished carrying 0, 1, or 2 copies of the haplotype allele. Power calculations for the cross sectional (logistic regression) analyses were performed with Quanto version 1.2.4 (http://www.mybiosoftware.com/population-genetics/5931), and indicated that for the SNP with the highest minor allele frequency (rs2070951) we could detect an OR of 1.13 with 80% power, this was OR=1.92 for the SNP with the lowest minor allele frequency (rs6189) (calculation of gene-effect only, unmatched case control ratio 1:1 and assuming a log additive model of inheritance). As recommended by Owzar et al. 2012, for the prospective (Cox proportional hazards model) analysis the software program R version 3.1.2 was used. Calculations indicated that for the SNP highest minor allele frequency (rs2070951) we could detect an HR of 1.29 with 80% power, this was HR=3.00 for the SNP with the lowest minor allele frequency (rs6189) (event rate=36.6%, landmark time=24 months, probability that time to event is greater than landmark time=19.2%,

and assuming a log additive model). All other analyses were performed with SPSS version 20.0. Subsequently, associations between GR and MR polymorphisms, its haplotypes and recurrence (recurrent versus single episode, time to recurrence) were analysed using multinomial logistic regression analyses and Cox regression analyses, adjusted for age, sex, principal components and treatment. Finally, we checked for interactions between GR and MR haplotypes and stress related factors. Interaction terms were calculated by multiplying the GR and MR haplotypes by the stress-related factors. So, nine different haplotypes were analysed with two different stress related factors (18 tests), in retrospect as well as prospectively. Bonferoni correction for multiple testing was performed for GR/MR polymorphism analyses (16 tests, $p<0.003$), haplotype analyses (18 tests, $p<0.003$) and interaction terms (18 tests <0.003).

6.3. Results

Characteristics

As mentioned previously, we applied two different analytic approaches to assess recurrence. The characteristics are presented in Table 1.

Of the subjects (n=1870) which were analysed in retrospect 68.4% were female and the mean number of episodes of MDD was 3.4 (sd=3.9). 919 subjects (49.1%) had a first MDD and 50.9% had a recurrent MDD lifetime. As expected, the average age of the subjects was higher in those with a recurrent course (41.2 versus 42.8 years, $p<0.01$). In the longitudinal analyses (n=683) 48.8% (n=333) of the included subjects had a lifetime recurrent MDD and 36.6% (n=250) had a recurrence of MDD during follow-up. The mean time to recurrence was 11.8 months (sd=12.6). Subjects with a recurrence of MDD during follow-up more often had a childhood trauma (48.3% versus 57.3%, $p=0.03$) and used more often an antidepressant (17.3% versus 31.6%, $p<0.001$). Age and sex distributions did not differ among the GR and MR genotypes besides SNP -2 G/C of which less females had a GG genotype in comparison with GC or CC (62.8 versus resp. 69.0 and 70.7, $p=0.03$).

MR- and GR genotypes and haplotypes

Genotype distributions for all polymorphisms were in Hardy Weinberg equilibrium (Pearson square >0.05). The frequencies of the GR and MR SNPs are described in Table 2.

Notable, there were no individuals in our study sample carrying homozygote SNPs of rs6189/6190 TT and rs56149945 CC. Concordant with previous studies (van Winsen et al., 2009; Spijker et al., 2011; Klok et al., 2011), six main haplotypes were found for GR and three for MR. Frequencies are displayed in Table 3. Both haplotypes of GR and MR (haplotypes 1) with the highest frequencies consisted of the major alleles of the measured SNPs. After post hoc Bonferroni correction for multiple testing ($p<0.003$), no associations between the GR and MR SNPs, its haplotypes and recurrence of depression were found (Table 2 and 3).

Table 1 Characteristics of the subjects in the retrospective and prospective cohort

	Life time MDD (n=1870)			Recurrence during follow-up (n=683)		
	First (n=919)	Recurrent (n=951)	p	No recurrence (n=433)	Recurrence (n=250)	p
Socio-demographic factors						
Female, n (%)	616 (67.0)	664 (69.8)	0.19	300 (69.3)	190 (76.0)	0.06
Age, mean yrs (sd)	41.2 (12.9)	42.8 (11.8)	<0.01	44.4 (12.8)	42.6 (12.0)	0.07
Stress related factors						
Childhood trauma, n (%)	513 (55.9)	558 (59.0)	0.18	210 (48.6)	142 (57.3)	0.03
Childhood trauma, mean (sd)	1.12 (1.23)	1.11 (1.17)	0.87	0.85 (1.07)	1.11 (1.22)	0.003
Life events in past year present, n (%)	403 (43.9)	379 (39.9)	0.08	144 (33.3)	96 (38.4)	0.18
Life events in past year, mean (sd)	0.75 (1.09)	0.64 (0.94)	0.02	0.50 (0.83)	0.54 (0.80)	0.50
Treatment						
Use of anti-depressants, n (%)	336 (36.3)	309 (32.5)	0.08	75 (17.3)	79 (31.6)	<0.001

Also no consistent interaction terms (p<0.003) between stress related factor and GR/MR haplotypes were found (Table 4). Although non-significant after Bonferoni correction, there are results worth mentioning. Two copies of the haplotype characterized by the minor allele of -2 C/G of the MR were associated with time to recurrence (HR=0.53, 95% CI=0.29-0.94, p=0.03) indicating a protective effect (Table 3). Subjects with two copies of the haplotype TCTCCAA (BclI,TthIII) of the GR had more often a recurrent course in comparison with those with one or zero copies (OR=2.75, 95% CI 1.07-7.03, p=0.04) (Table 3). Two copies of this haplotype was, on the other hand, also associated with a longer time to recurrence (33.5 months versus 11.9 and 11.3, p=0.002). It should be noted that in this later analyses the number of subjects who had two copies of the haplotype 4 was only four. Also two interactions need to be addressed, GR haplotype CGTCCGA (9ß,NR3C1-1,T-thIII) with childhood trauma (HR=0.74, 95%CI=0.60-0.92, p=0.01) and GR haplotype TGCCCAG (N363S) with recent life events (HR= 7.75, 95% CI, 1.07-56.10, p=0.04) because of the low p-values (see Table 4). However, considering the number of tests conducted and the inconsistency of the findings with contrasting findings in the retrospective and prospective analyses, we consider these chance findings.

Table 2 Association of GR and MR gene polymorphisms with recurrence of MDD*

SNP genotype (%)			Female (n=1870)		Age (n=1870)		First (n=919, 49.1%), versus recurrent (n=951, 50.9%) MDD at baseline					Time to recurrence during follow-up (n=683)	
			%	p	Mean	p	First[a] n (%)	Recurrent n (%)	p	OR[b] (95% CI)	p	HR[c] (95% CI)	p
Glucocorticoid receptor gene													
ER22/ 23EK	CC	84.1	68.6	0.54	42.1	0.56	792 (98.4)	826 (98.0)	0.54	-	-	-	-
	CT	1.6	63.3		42.6		13 (1.6)	17 (2.0)		1.31 (0.63-2.71)	0.54	1.36 (0.64-2.93)	0.43
N363S	TT	80.2	68.3	0.30	42.0	0.52	765 (97.2)	778 (96.6)	0.52	-	-	-	-
	TC	2.5	61.2		43.2		22 (2.8)	27 (3.4)		0.83 (0.46-1.47)	0.52	0.92 (0.34-2.50)	0.88
BclI	GG	39.5	68.5	0.94	42.2	0.96	360 (43.5)	401 (46.4)	0.31	-	-	-	-
	CG	30.6	68.0		42.1		379 (45.8)	364 (42.1)		0.87 (0.71-1.06)	0.17	0.92 (0.70-1.20)	0.52
	CC	9.8	67.2		41.9		89 (10.7)	100 (11.6)		1.02 (0.74-1.40)	0.89	1.04 (0.68-1.58)	0.86
9ß	TT	61.0	67.1	0.82	42.1	0.37	579 (68.0)	596 (66.9)	0.89	-	-	-	-
	TC	26.5	68.7		42.3		246 (28.9)	265 (29.7)		1.04 (0.85-1.29)	0.68	1.07 (0.81-1.41)	0.62
	CC	3.0	71.9		39.8		27 (3.2)	30 (3.4)		1.10 (0.64-1.87)	0.74	0.71 (0.31-1.60)	0.41
TthIII	CC	40.7	68.5	0.96	42.6	0.39	386 (49.2)	398 (47.6)	0.70	-	-	-	-
	TC	35.0	68.1		42.8		324 (41.3)	350 (41.9)		1.04 (0.84-1.27)	0.74	0.85 (0.64-1.23)	0.27
	TT	8.4	67.6		41.9		74 (9.4)	88 (10.5)		1.14 (0.82-1.63)	0.40	0.92 (0.60-1.42	0.72

Table 2 Continued

SNP genotype (%)			Female (n=1870)		Age (n=1870)		First (n=919, 49.1%), versus recurrent (n=951, 50.9%) MDD at baseline					Time to recurrence during follow-up (n=683)	
			%	p	Mean	p	First[a] n (%)	Recurrent n (%)	p	OR[b] (95% CI)	p	HR[c] (95% CI)	p
Glucocorticoid receptor gene													
NR-C3C1-1	AA	54.7	68.4	0.85	42.4	0.51	512 (67.3)	541 (66.5)	0.93	-	-	-	-
	AG	24.2	67.7		42.4		223 (29.3)	242 (29.8)		1.03 (0.83-1.28)	0.78	1.14 (0.86-1.51)	0.37
	GG	2.9	71.4		40.4		26 (3.4)	30 (3.7)		1.11 (0.65-1.91)	0.71	0.52 (0.21-1.27)	0.15
Mineralocorticoid receptor gene													
-2G/C	CC	16.4	69.0	0.03	42.2	0.80	140 (21.3)	176 (25.7)	0.16	1.23 (0.89-1.71)	0.20	1.29 (0.80-2.06)	0.29
	GC	35.4	70.7		41.7		341 (52.0)	339 (49.6)		0.97 (0.74-1.28)	0.85	1.21 (0.79-1.85)	0.37
	GG	17.9	62.8		42.0		175 (26.7)	169 (24.7)		-	-	-	-
I180V	CC	1.5	68.3	0.38	41.0	0.56	17 (2.0)	12 (1.3)	0.30	0.67 (0.32-1.40)	0.29	1.12 (0.28-4.46)	0.87
	TC	18.9	67.1		41.5		187 (21.7)	177 (19.7)		0.89 (0.70-1.12)	0.30	1.15 (0.84-1.56)	0.39
	TT	71.2	61.9		42.2		658 (76.3)	712 (79.0)		-	-	-	-

* GR data was completed for ER22/23EK in 1648 (85.7%) subjects, for N363S in 1592 subjects (82.7%), for *Bcl*I in 1693 subjects (87.9%), for 9β in 1743 subjects (90.5%), for *Tth*III*I* in 1620 (84.4%) subjects and for NRC3C1-1 in 1574 (81.8) subjects. In 1340 subjects (69.6%) MR genotyping was completed for -2 G/C and in 1763 subjects (91.6%) for I180V. Abbreviations: SNP= single nucleotide polymorphism, OR=odds ratio, HR=hazard ratio. [a] Pearson chi-square. [b] Logistic regression, adjusted for age, sex and principal components. Reference category is the major allele. [c] Associations were tested with Cox regression analyses adjusted for age, sex, principal components and treatment with antidepressants. Reference category is the major allele.

Table 3 Associations of GR and MR haplotypes with recurrence of MDD

Haplotype[a]			First (n=919, 49.1%), versus recurrent (n=951, 50.9%) MDD at baseline[c]			Time to recurrence during follow-up (n=683)[d]			Mean time to recurrence (months)[e]	
	%	n[b]	n (%)	OR (95% CI)	p	n (%)	HR (95% CI)	p	Mean (sd)	p
Glucocorticoid receptor gene										
1. TGTCCAG (wildtype)	47.2	0	478 (25.6)	-	-	184 (26.9)	-	-	14.1 (13.2)	0.17
		1	1005 (53.7)	0.97 (0.78-1.21)	0.79	354 (51.8)	0.96 (0.71-1.29)	0.77	11.3 (12.6)	
		2	387 (20.7)	0.99 (0.76-1.30	0.95	145 (21.2)	1.13 (0.80-1.60)	0.49	10.0 (11.4)	
2. TCTCCAG (BclI)	20.2	0	1189 (63.6)	-	-	428 (62.7)	-	-	11.6 (13.3)	0.60
		1	618 (33.0)	0.87 (0.72-1.06)	0.18	229 (33.5)	1.05 (0.80-1.37)	0.75	12.5 (11.6)	
		2	63 (3.4)	0.94 (0.57-1.57)	0.82	26 (3.8)	0.90 (0.46-1.77)	0.76	8.2 (9.1)	
3. CGTCCGA (9ß,NR3C1-1,TthIIII)	16.7	0	1324 (70.8)	-	-	484 (70.9)	-	-	11.0 (12.2)	0.29
		1	492 (26.3)	1.03 (0.83-1.27)	0.80	177 (25.9)	0.99 (0.74-1.31)	0.93	13.8 (13.7)	
		2	54 (2.9)	1.14 (0.66-1.97)	0.64	22 (3.2)	0.69 (0.31-1.56)	0.37	11.5 (8.8)	
4.TCTCCAA (BclI,TthIIII)	12.8	0	1473 (78.8)	-	-	531 (77.7)	-	-	11.3 (12.0)	0.002
		1	374 (20.0)	0.96 (0.76-1.21)	0.74	144 (21.1)	0.86 (0.63-1.19)	0.37	11.9 (13.4)	
		2	23 (1.2)	2.75 (1.07-7.03)	0.04	8 (1.2)	1.21 (0.45-3.27)	0.71	33.5 (17.9)	
5.TGCCCAG (N363S)	1.5	0	1823(97.5%)	-	-	668 (97.8)	-	-	11.9 (12.6)	0.17
		1	47 (2.5%)	1.18 (0.66-2.13)	0.58	15 (2.2)	0.89 (0.33-2.39)	0.81	3.25 (2.6)	
		2	0	-	-		-	-	-	

Table 3 Continued

Haplotype[a]			First (n=919, 49.1%), versus recurrent (n=951, 50.9%) MDD at baseline[c]			Time to recurrence during follow-up (n=683)[d]			Mean time to recurrence (months)[e]	
	%	n[b]	n (%)	OR (95% CI)	p	n (%)	HR (95% CI)	p	Mean (sd)	p
Glucocorticoid receptor gene										
6. CGTTTGA (9ß,ER22/23EK, NR3C1-1, TthIIII)	1.1	0	1840 (98.4)	-	-		-	-	11.9 (12.6)	0.30
		1	30 (1.6)	1.23 (0.63-2.72)	0.48	668 (97.8)	1.33 (0.62-2.86)	0.46	6.9 (10.4)	
		2	0	-	-	15 (2.2)	-	-		
Mineralocorticoid receptor gene										
1. GA (Wildtype)	49.2	0	358 (19.1)	-	-	111 (16.3)	-	-	14.2 (14.8)	0.47
		1	1196 (64.0)	1.00 (0.78-1.28)	0.91	451 (66.0)	1.27 (0.86-1.87)	0.24	11.6 (12.1)	
		2	316 (16.9)	1.25 (0.91-1.72)	0.18	121 (17.7)	1.30 (0.82-2.07)	0.27	10.8 (12.7)	
2. CA (-2 G/C)	38.8	0	596 (31.9)	-	-	218 (31.9)	-	-	12.1 (12.9)	0.33
		1	1056 (56.5)	0.95 (0.77-1.17)	0.63	397 (58.1)	0.95 (0.73-1.24)	0.82	11.1 (12.3)	
		2	217 (11.6)	1.00 (0.72-1.41)	0.99	68 (10.0)	0.53 (0.29-0.94)	0.03	16.0 (13.0)	
3. CG (I180V)	12.0	0	1477 (79.0)	-	-	548 (80.2)	-	-	11.3 (12.0)	0.34
		1	364 (19.5)	0.89 (0.70-1.12)	0.30	130 (19.0)	1.17 (0.86-1.59)	0.32	13.8 (14.5)	
		2	29 (1.6)	0.67 (0.32-1.41)	0.29	5 (0.7)	1.30 (0.32-5.30)	0.71	5.5 (6.4)	

Abbreviations: OR=odds ratio, HR=hazard ratio. MDD=major depressive disorder. [a] Wildtype consisted of the major alleles of the six SNPs of GR haplotype respectively two SNPs of the MR haplotype. Haplotype were further characterized by the minor allele (in brackets) of the SNP plus the major alleles of the other SNPs. [b] Estimated number of haplotype copies. [c] Logistic regression, adjusted for age, sex, and principal components. Reference category is zero copies of the haplotype. [d] Associations were tested with Cox regression analyses, adjusted for age, sex, principal components and treatment with antidepressants. [e] Associations were tested with ANOVA.

Table 4 Interactions of stress related factors, haplotypes of the GR and MR gene on the risk for a recurrence of MDD

Haplotype[a]	Haplotype by childhood trauma (n=1870)[b]		Haplotype by childhood trauma (n=683)[c]		Haplotype by recent life events (n=1870)[b]		Haplotype by recent life events (n=683)[c]	
	OR (95% CI)	p	HR (95% CI)	p	OR (95% CI)	p	HR (95% CI)	P
Glucocortocoid receptor gene								
1. TGTCCAG (wildtype)	1.04 (0.93-1.17)	0.51	1.14 (0.98-1.33)	0.10	1.06 (0.93-1.21)	0.41	1.18 (0.94-1.48)	0.16
2. TCTCCAG (BclI)	0.91 (0.79-1.04)	0.16	1.07 (0.89-1.29)	0.48	0.97 (0.82-1.14)	0.68	0.86 (0.65-1.15)	0.30
3.CGTCCGA (9ß,NR3C1-1,TthIIII)	1.07 (0.92-1.24)	0.36	0.74 (0.60-0.92)	0.01	0.90 (0.76-1.07)	0.23	0.95 (0.68-1.33)	0.76
4.TCTCCAA (BclI,TthIIII)	1.02 (0.86-1.22)	0.80	1.02 (0.80-1.32)	0.86	1.16 (0.93-1.44)	0.19	0.82 (0.53-1.25)	0.35
5.TGCCCAG (N363S)	0.70 (0.44-1.10)	0.12	0.72 (0.27-2.00)	0.52	0.77 (0.40-1.47)	0.43	7.75 (1.07-56.10)	0.04
6.CGTTTGA (9ß,ER22/23EK, NR3C1-1, TthIIII)	0.94 (0.52-1.69)	0.83	1.36 (0.85-2.17)	0.20	0.93 (0.41-2.08)	0.86	1.00 (0.50-2.02)	0.99
Mineralocorticoid receptor gene								
1. GA (Wildtype)	0.94 (0.82-1.08)	0.40	1.00 (0.82-1.21)	0.98	0.96 (0.82-1.13)	0.65	0.96 (0.71-1.28)	0.76
2. CA (-2 G/C)	1.00 (0.87-1.13)	0.93	1.10 (0.92-1.32)	0.31	1.05 (0.91-1.21)	0.53	1.16 (0.89-1.50)	0.28
3. CG (I180V)	1.11 (0.93-1.32)	0.22	0.84 (0.65-1.09)	0.20	0.98 (0.82-1.20)	0.81	0.77 (0.49-1.22)	0.27

Abbreviations: OR=odds ratio, HR=hazard ratio. MDD=major depressive disorder. [a] Wildtype consisted of the major alleles of the six single nucleotide polymorphisms (SNPs) of glucocorticoid gene haplotype respectively two SNPs of the mineralocorticoid gene haplotype. Haplotype were further characterized by the minor allele (in brackets) of the SNP plus the major alleles of the other SNPs representing the number of haplotype copies (0,1,or 2). [b] Risk for a life time recurrent course versus first episode. Logistic regression, adjusted for age, sex and principal components. [c] Time to recurrence. Associations were tested with Cox regression analyses, adjusted for age, sex, principal components and treatment with antidepressants.

Our recent study (Hardeveld et al., 2014) published in this Journal concluded that the cortisol awakening response was associated with time to recurrence of MDD and it was postulated that an increased cortisol awakening response (CAR) could also be a genetic vulnerability trait. Therefore, we also investigated whether the CAR was associated with GR and MR polymorphisms in our study sample. The methods of the HPA-axis parameters measurements were described in our recent study (Hardeveld et al., 2014). For this analyses we used the baseline sample (n=2981). Eventually, 1211 subjects were included, after excluding invalid CAR data or DNA data. Using ANOVA, no associations between CAR and the investigated haplotypes were found. We also analysed a possible interaction of CAR by haplotype on time to recurrence (n=490). However, no interactions were found.

6.4. Discussion

This study did not find consistent associations between GR and MR polymorphisms, interactions with childhood trauma or recent life events and recurrence of MDD. So, our results suggest that these polymorphisms may be associated with onset and presence of MDD (van Rossum et al., 2006; van West et al., 2006; Kuningas et al., 2007; Zobel et al., 2008; Krishamurthy et al., 2008; Bet et al., 2009; Otte et al., 2009; Klok et al., 2011; Spijker et al., 2012; Szczepankiewicz et al., 2011; Galecka et al., 2013) but not with recurrence of MDD. Three studies examined recurrent MDD versus healthy controls in retrospect (van West et al., 2006; Zobel et al, 2008; Galecka et al., 2013). So, these studies found that the investigated SNPs were associated with presence of recurrent MDD but these studies did not investigate recurrence of MDD versus first onset which makes a comparison with our study difficult. It should be noted that also negative results were found and none of the investigated SNPs were consistently confirmed in previous studies.

What could be explanations for our negative results? El Hage et al. (2009) postulated that gene environmental interactions in depression involves complex participation of serotonergic genes modulating responses to stress through the HPA-axis. Also modulating genes involved in the HPA-axis, for example FKPB5, may be associated with MDD risk (Spijker and van Rossum, 2012; Szczepankiewicz et al., 2014). El Hage et al. (2009) hypothesized that subjects with a low activity of 5-HTTLPR have elevated activity in the amygdala. A hyperactive amygdala enhances HPA-axis functioning which could lead to sustained hypercortisolism which is associated with recurrence of MDD (Hardeveld et al., 2014). Whether sustained hypercortisolism will be present is also dependent on MR and GR expression which is modulated by FKPB5, amongst others. In our study the CAR was not associated with GR and MR haplotypes. So, it could be that in our sample GR and MR haplotypes did not, or only slightly, contribute to hypercortisolism and hereby did not increase the risk for a recurrence of MDD. Alternatively, interactions of GR and MR haplotypes with serotonergic or modulating genes of the HPA-axis may increase the risk for a recurrence.

Although an earlier study using NESDA data (Holleman et al., 2012) did not convincingly find an association of HPA-axis parameters and childhood trauma, substantial evidence reviewed by Juruena (2014) indicate that childhood trauma can induce changes in the ability of the HPA-axis to respond to stress in adulthood by reducing the ability of cortisol to bind to GR and MR. It was postulated that an imbalance in MR and GR functioning may be a risk factor for depression. This mechanism could also lead to an increased awakening response which we found to be associated with recurrence of MDD (Hardeveld et al., 2014). The contribution of the GR and MR polymorphisms in epigenetic modification may be minor.

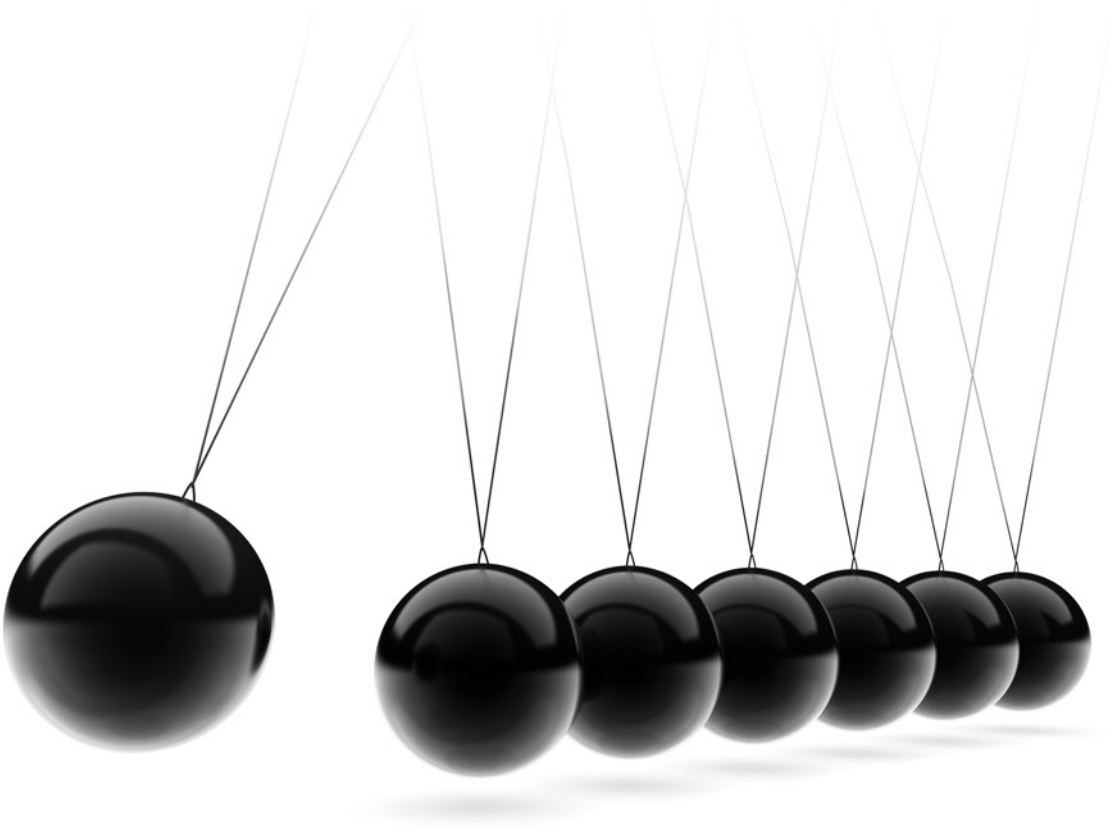
To our knowledge, this is the first study that investigated GR and MR polymorphisms and recurrence of MDD prospectively. We examined multiple GR and MR gene polymorphisms in a large sample and used standardized instruments to determine diagnosis and recurrence. However, there are a number of limitations. First, we did investigate candidate genes which were associated with glucocorticoid sensitivity and MDD but other SNPs located on the GR or MR gene could be involved in recurrence. We did not perform a whole gene-based association analysis of SNPs on the GR and MR. However, if we would have tested more SNPs, requirements for significance would have been more stringent with accompanying power issues. On the other hand, because we tested several SNPs Bonferonni correction had to be performed. If we would have tested less SNPs a significant result would have been found. Also, for some polymorphisms the sample size was small or absent limiting our power to detect small to medium effect sizes, given that we had 80% power to detect an odds ratio 1.92 for the SNP with the lowest minor allele frequency in the retrospective analyses, this was HR=3.00 for the prospective analyses.

Another concern relates to the retrospective collection of data. The assessment of a single episode MDD in retrospect may not be accurate. Though, our prospective data were not showing associations either.

In conclusion, although there is considerable evidence that these polymorphisms are associated with onset and presence of MDD no consistent associations of the GR and MR candidate gene polymorphisms with recurrence of MDD were found. To draw firmer conclusions, replication is needed preferably using a whole gene-based association analysis of SNPs on the GR and MR also including interactions with modulating and serotonergic genes. In this way, the complex pattern of interaction between environmental factors and genetic factors related to recurrence of MDD could be further unravelled.

7

Summary
General discussion



This thesis reports on several studies about the prevalence and predictors of recurrence of major depressive disorder based on data of the studies NEMESIS and NESDA. The aims of this thesis were to investigate the risk of recurrence of major depressive disorder across care settings and to study its predictors and the way these predictors interact. In this chapter, the main findings are summarized and discussed, and also methodological considerations and suggestions for future research are set out.

7.1. Summary

Major depressive disorder is highly prevalent and morbid. The high burden of MDD is in part due to its course, since chronicity and recurrence are frequent features of the condition. Major depressive disorder is a heterogeneous disorder and its aetiology involves a complex interplay between genetic and environmental factors which is not yet understood. Knowledge of predictors of recurrence of major depressive disorder recurrence predictors is essential for the development of prevention and treatment decisions. Over the past 20-30 years, a number of studies have investigated predictors of recurrence of major depressive disorder. However, no systematic literature review is available on prevalence and predictors, comparing patients in specialized care with those in primary care and community settings. In **Chapter 2**, a systematic literature review is presented. The overall conclusion is that the percentage of recurrence in specialized mental health care is very high (up to 85% after 15 years). Therefore, in this population it is more appropriate to ask *when* rather than *whether* the patient will experience a recurrence. The studies found that the percentage of recurrence in the primary care population is similar to that in specialized mental health care and is lower again in the general population (up to 35% after 15 years). Clinical factors (number of previous episodes and subclinical residual symptoms) appear to be the most important predictors of time to recurrence, whereas sociodemographic factors do not seem to play a role. It was concluded that data from studies performed in the general population and primary care on the recurrent course of major depressive disorder are scarce and prospective studies are lacking. Data on genetic risk factors and dysregulated neuro-endocrine parameters (HPA-axis) were not included in this review. In **Chapter 3**, the main predictors of recurrence of a major depressive disorder in the general population were investigated. It was concluded that the estimated cumulative percentage of recurrence of MDD was 42.0% by 20 years. Multivariably, younger age, higher number of previous episodes, a severe last depressive episode, negative youth experiences and ongoing difficulties are significant predictors of recurrence. Although the long-term risk of recurrence was high, the recurrence risk was lower than that found in clinical samples. Thus, subjects in the general population who have experienced a major depressive episode have a long-term vulnerability for recurrence. Factors predicting recurrence include illness-related and stress-related factors.

It was found that the risk of recurrence depended on the number of predictors present: after 10 years the cumulative recurrence percentage of MDD was 3.4% for respondents with no predictors, 19.0% for respondents with one predictor, 26.6% for those with two predictors, 56.5% for those with three predictors and 65.0% for those with four or more predictors. In **Chapter 4**, the time to recurrence of MDD and its predictors were studied in primary care and specialized mental health care. The main findings were that there was no significant difference in time to recurrence of MDD between subjects in specialized mental health care and those in primary care. In multivariable analyses, a family history of MDD and previous major depressive episodes were associated with a shorter time to recurrence. The predictors did not differ across treatment settings. In **Chapter 5**, it was investigated whether HPA-parameters were associated with time to recurrence of major depressive disorder. The study confirmed previous findings that a higher cortisol awakening response (CAR), related to the sensitivity of the HPA-axis, increased vulnerability to recurrence of MDD even if a subject had been in remission for a long period. Neither the dexamethasone test nor evening cortisol levels were associated with recurrence and the higher risk for recurrence related to a high CAR was not dependent on stressful life events. Finally in **Chapter 6**, the research focused on the association between polymorphisms of the glucocorticoid and mineralocorticoid receptor and the risk for recurrence. Recurrence of MDD was not associated with these polymorphisms and no interaction effects were found with stressful conditions.

7.2. Discussion

Recurrence risk

In Chapter 2, it was concluded that MDD is often a recurrent disorder with consequences over the entire lifespan. The risk of recurrence among subjects treated in general practice and specialized care settings seems to be comparable; at two-year follow-up 26.8% of subjects treated in primary care and 33.5% treated in specialized mental health care experienced recurrence of MDD after achieving remission for at least three months (Chapter 4). These percentages are in line with previous studies (Lin et al., 1998; Gopinath et al., 2007; Vuorilehto et al., 2009; Suija et al., 2011). It also appears that in the general population, subjects who have experienced an MDE have a long-term vulnerability for recurrence which could be triggered under certain circumstances (Chapter 3). A cumulative incidence of MDD recurrence of 42% was found. This percentage is higher in comparison with previous studies. This result is difficult to compare with other studies due to differences in duration of remission, follow-up, diagnosis and population. The study by Eaton et al. (2008) is the most similar to this study but included first incident cases only. This study found a recurrence rate of 35% after 23 years.

Predictors of recurrence of MDD: comparison with first episode and chronic course

In this thesis, several predictors of time to recurrence of MDD were found. In the general population (Chapter 3), younger age, higher number of previous episodes, a severe last depressive episode, negative youth experiences and ongoing difficulties were significant predictors of recurrence. The risk for recurrence was also higher in subjects with multiple risk factors. In patients treated for MDD in general practice and specialized mental health care (Chapter 4), family history was also a predictor of time to recurrence. These predictors have also been found in other studies (Solomon et al., 2000; Melartin et al., 2004; Gophinah et al., 2008) and did not differ across treatment settings (Chapter 4). Subclinical residual symptoms could not be taken into account in these studies because the data did not allow for such precision. However, in Chapter 2 (review) subclinical residual symptoms were one of the main risk factors. Moreover, in Chapter 5 was found that the cortisol awakening response was a predictor of recurrence. This result was also in line with previous studies (Ribeiro et al., 1993; Zobel et al., 1999; Harris et al., 2000; Zobel et al., 2001; Hatzinger et al., 2002; Appelhof et al., 2006; Aubry et al., 2007; Bhagwagar et al., 2008; Pintor et al., 2009; Vrshek-Schallhorn et al., 2013). The results of this thesis (Chapter 2, 3 and 4) indicate that demographic determinants are not clear predictors for MDD recurrence, although in other studies was found that they play a role in the onset of the first depressive episode (de Graaf et al., 2002; de Graaf et al., 2013). Previous research with data from NEMESIS and NEMESIS-2 (de Graaf et al., 2002; de Graaf et al., 2013) concluded that first incidence of mood disorder (major depression, dysthymia and bipolar disorder) is associated with

female gender, low educational status, substantial decrease in income, no longer living with partner, negative life events, ongoing difficulties and a high level of neuroticism. Thus, it can be concluded that stress-related factors play a role in both incidence and recurrence. Additionally, clinical factors related to past MDD episodes (number of previous episodes, severity of the last episode) are prominent predictors for time to recurrence. Hence, past episodes predict future episodes. The predictors for recurrence and chronicity of MDD also show similarities. Using NEMESIS data, Spijker et al. (2004) found that determinants of persistence of MDD were severity of the index episode, longer duration of previous episodes, physical illness, including chronic physical illness, and lack of social support. For both courses, illness-related factors are important. Moreover, it is possible that chronicity and recurrence are both expressions of the same dimension given that illness-related factors are prominent predictors in recurrence and in a chronic course.

Methodological considerations

Despite the use of strict selection criteria, the studies were difficult to compare in the systematic review (Chapter 2). This also explains why a formal meta-analysis was not performed. In Chapters 3 through 6, datasets from both NESDA and NEMESIS were used. Although both studies included a large sample, were prospective and included a large set of covariates, several limitations must be acknowledged. First, in NEMESIS (Chapter 3) and NESDA (Chapters 4 and 5), the last depressive episode was assessed in retrospect. It might be that the assessment for age of onset and recency of the last depressive episode have not been accurate. It is likely that this could have led to an overestimation of the time to recurrence and an underestimation of the number of recurrences. Secondly, in NESDA the recurrence risk was investigated across different treatment settings. The subjects treated in specialized mental health care were recently referred and, as a consequence, this sample is not representative of the entire population treated for MDD in specialized mental health care, since subjects with more severe, chronic or frequently recurring MDD are probably underrepresented. Therefore, the difference in recurrence risk between primary care and specialized mental health care could have been underestimated. On the other hand, there was no statistical difference in our study in the percentage of remission in primary care versus specialized mental health care. This suggests that both cohorts are comparable in this regard. Third, in both NEMESIS and NESDA, subclinical residual symptoms, which are a strong predictor of recurrence risk (Judd et al., 1998), could not be included in the analysis because the data did not allow for such precision. However, it is reasonable to assume that residual symptoms are more common in subjects treated in specialized mental health care than in those treated in primary care.

Towards a model of risk

What research is needed?

The studies in this thesis assessed recurrence risk across settings and identified several predictors of recurrence. Important predictors for inclusion in a model of risk have probably been identified, it seems unlikely that new factors with a high predictive value will emerge in the near future. Although there is no use of the CAR, the increase of cortisol upon awakening, as a predictor in a clinical setting so far, it is a valuable instrument in research on stress-related disorders such as MDD. It remains to be seen whether a higher CAR is an epiphenomenon or plays a substantial role in the onset or course of a depressive episode. It could be hypothesized that a higher CAR reflects a marker for increased sensitivity for stress, including psychosocial stress, which is associated with an increased risk for recurrence. Although genetic factors hold promise, it is believed that many genes are involved and it is likely that individual genes only contribute a small percentage of the risk for recurrence of MDD. Chapter 6 did not find GR or MR polymorphisms associated with recurrence either. Understanding how predictors interact with one another is a major challenge. There may be specific interactions that raise the risk for recurrence. For example, a recent study by Wilson et al. (2014) found that individuals with both adolescent onset and recurrent episodes of MDD represented a particularly severe group with persistent psychosocial impairment in adulthood (Wilson et al., 2014). In this way, a specific high-risk profile could be identified.

To better understand the aetiology of recurrence of MDD, it is also advisable to measure different course variables (severity, time between recurrences, number of life-time recurrences) because different factors could predict different courses (Conradi et al., 2008). The influence of past episodes on risk is a major problem. Conducting research in this field is like shooting at a moving target. Keeping the long term vulnerability for recurrence of MDD in mind, this suggests that, to better understand aetiology of recurrence, future research must move to time-sensitive modelling techniques, e.g. structural equation modelling, incorporating multiple interacting factors across long periods of time (Beard et al., 2008; Colman et al., 2010).

Predictors: scar versus trait

Given that recurrence of MDD contributes to risk for depression, it follows that either depression itself increases vulnerability to recurrence (scar-effect) or individuals at high risk for recurrence already possess certain vulnerability characteristics (trait-effect) (Burcusa & Iacono, 2007). This distinction is important because if the scar hypothesis is true, early intervention is key. It is likely that both scar and trait factors play a role. Our results (Chapter 5) suggest that a high cortisol awakening response (CAR) may constitute a 'trait' marker for recurrence, whereas a lower CAR can be identified as a 'scar' marker for current depression (Vreeburg et al., 2013). This is in line with previous studies. Vrshek-Schallborn et al. (2013) concluded that a higher CAR predicted initial onset. Furthermore, the CAR is higher in

young people who have not experienced depression but have a family history of depression (Mannie et al., 2007; Vreeburg et al., 2010) which suggests a genetic vulnerability trait. A previous study (Wüst et al., 2000) also concluded that there is a significant genetic influence on the CAR. However, no associations between GR and MR gene polymorphisms or interactions between GR and MR haplotypes, stressful conditions and recurrence of MDD were found in Chapter 6. Replication of this study using a fully gene-based association analysis of SNPs on the GR and MR is recommended. In this way, a better understanding of the complex pattern of interaction between environmental factors and genetic factors related to recurrence of MDD could be achieved.

Identifying a high risk group for recurrence

Nonetheless, with each recurrent depressive episode, the impact on symptoms and well-being appears to worsen (Roca et al., 2011). This highlights the need to intervene early to prevent future episodes. Thus, identification of high risk groups after the first episode is of particular importance (Monroe et al., 2011). Research should focus on individuals who recover after the first episode of MDD, as this could lead to the greatest health gains. Approximately 50% of those who recover after a first episode will experience a recurrence (APA, 2000). In other major psychiatric disorders, e.g. schizophrenia and bipolar disorder, early intervention is thought to prevent a protracted course (McGorry et al., 2006; Berk et al., 2010). This is also likely to be true for MDD, but research is still lacking.

Clinicians should not only classify depression into prodromal phase, first episode, residual symptoms after depression, recurrence or chronic course (Hetrick et al., 2008), but also perform a risk assessment for recurrence (short time to recurrence, multiple recurrences) after the first episode. It could be helpful to develop a short risk assessment tool for this purpose. Wang et al. (2014) was the first to develop a risk assessment tool for recurrence of MDD using a general population sample. This 19-item tool can be filled in by the individual via internet, has a reasonable predictive value (C-statistic=0.75) and is easy to use. The C-statistic was 0.59 when only the number of previous episodes was used in the model. This model has not yet been tested in treatment settings and was not developed to identify high risk groups for recurrence after the first episode, which should be the next step. As a minimum, the research model should contain the illness-related factors (severity of the MDD, subclinical residual symptoms) stress related factors (childhood trauma, life events, and ongoing difficulties), younger age and family history. Recommendations from the recent TRIPOD (transparent reporting of the multivariable prediction model for individual prognosis or diagnosis) statement (Collins et al., 2015) should be applied. Other disciplines in medicine have developed risk assessment tools. In cardiology, the application of risk assessment tools in daily practice has improved treatment of risk factors and reduced the risk for myocardial infarction substantially (Bata et al., 2000). Identification of individuals with a high risk profile and understanding of the type of interventions that are effective in preventing recurrences after the first episode

could form the basis for well-founded guidelines for treatment and recurrence prevention of MDD. Based on this knowledge, we could draw up an integrated model of risk.

Implications for treatment decisions

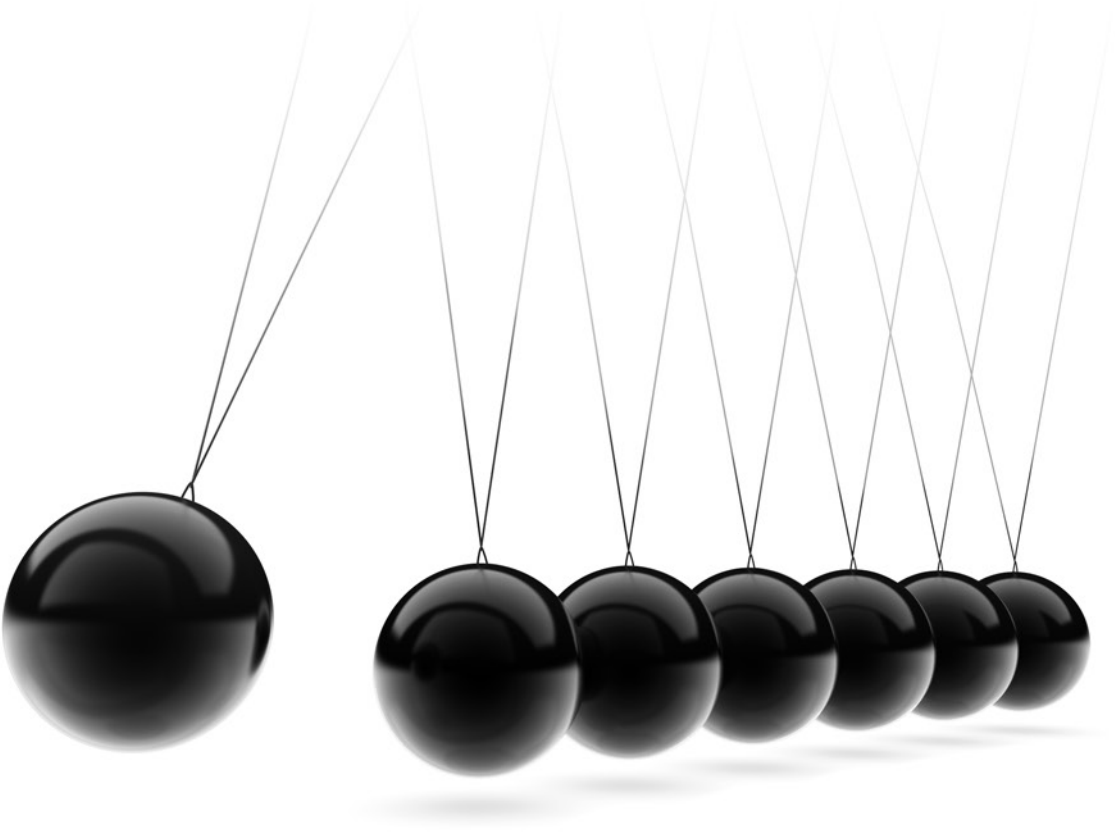
Subjects with significant and multiple predictors for recurrence should be closely monitored and treatment strategies to prevent recurrence should be considered. The knowledge that clinical variables are significant predictors could be taken into account during the initial phase of treatment for depression. It would seem reasonable to treat frequent recurrences and residual symptoms as a chronic disorder (Andrews et al., 2001), whereas treatment for patients with a low risk of recurrence may be limited to the index episode. Subjects with a high risk for recurrence should receive maintenance treatment with antidepressants, with special attention to treatment adherence. The risk of relapse or recurrence for those undergoing maintenance treatment with antidepressants can be reduced by 25% compared with a placebo (Geddes et al., 2006; Kaymaz et al., 2008). However, the efficacy of antidepressants on the recurrence rate over a long period is unknown. Preventive psychotherapeutic interventions should also be considered in subjects with multiple recurrences, focusing on residual symptomatology and specific coping styles to improve resilience to stressful circumstances (Bockting et al., 2008). For recurrence prevention, it is also important to identify which predictors are causal, which predictors might change over time or therapy and in what way they interact (Kraemer, 2001). A variable could be a proxy risk factor, a moderator, a mediator, be independent but also protective (Kraemer, 2001). As mentioned before, clinical risk factors are important predictors of recurrence, but most of these factors, apart from subclinical factors, lie in the past and cannot be changed. Programmes for depression recurrence prevention should focus on those risk factors that can be changed. For example, it is important to treat subclinical symptoms aggressively, alleviate ongoing difficulties where possible and improve coping strategies for dealing with stress.

The risk of recurrence in primary care is also considerable. Our results also imply that prevention of the recurrence of MDD is advised for high-risk groups, not only in specialized mental health care, but also in primary care. Nowadays, subjects are more likely to be referred to specialized mental health care if they are younger, report suicidal symptoms, had chronic depression or are referred for psychotherapy (Piek et al., 2011). It could be that the need for acute treatment of MDD or the preferences of the patient play a greater role in decisions to refer to specialized care than expectations of a protracted course. This latter factor should also be taken into account. To improve the management of MDD recurrence prevention, collaborative care models are desirable (Katon et al., 2011), with long term management and enhanced communication between primary and specialized mental health care professionals across psychiatric services. Both general practitioners and specialized mental health care professionals should be aware of the main risk factors and recurrence prevention should be integrated across care settings.

7.3. Concluding remarks

Kraeplin wrote more than 90 years ago that he found it impossible to predict whether depression would be limited to one episode or an individual would experience further episodes (Kraeplin, 1921). Do we have a better understanding of recurrence of MDD today? Can we inform Miss C, who was introduced in the Introduction, better? Yes, we can. We can inform her that she has, unfortunately, a high risk for a recurrence due to previous episodes of depression, along with subclinical residual symptoms and a first degree family member with depression in the past. We could also advise her to turn to psychotherapy to diminish the risk of recurrence. While the main risk factors have probably been identified, their precise interactions are unknown. Prediction of time to recurrence after a first episode is a major challenge. This is likely to be the area in which the greatest health gains can be made. To that end, a risk assessment tool for recurrence should be further developed to distinguish those with and whose without a high risk for recurrence.

References



References

1. Abdellaoui, A., Hottenga, J.J., de Knijff, P., Nivard, M.G., Xiao, X., Scheet, P., Brooks, A., Ehli., E.A., Hu, Y., Davies, G.E., Hudziak, J.J., Sullivan, P.F., van Beijsterveldt, T., Willemsen, G., de Geus, E.J., Penninx, B.W., Boomsma, D.I., 2013. Population structure, migration, and diversifying selection in the Netherlands. Eur J Hum Genet. 21, 1277-85.
2. Abou-Seif, C., Shipman, K.L., Allars, M., Norris, M.H., Chen, Y.X., Smith, R., Nicholson, R.C., 2012. Tissue specific epigenetic differences in CRH gene expression. Front Biosci. 1(17), 713-25.
3. Adam, E.K., Doane, L.D., Zinbarg, R.E., Mineka, S., Craske, M.G., Griffith, J.W.., 2010. Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. Psychoneuroendocrinology 35(6), 921-31.
4. Aihara, M., Ida, I., Yuuki, N., Oshima, A., Kumano, H., Takahashi, K., Fukuda, M., Oriuchi, N., Endo, K., Matsuda, H., Mikuni, M., 2007. HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. Psychiatry Res. 155(3), 245-56.
5. Aken van, M.O., Romijn, J.A., Miltenburg, J.A., Lentjes, E.G., 2003. Automated measurement of salivary cortisol. Clin Chem. 49(8), 1408-9.
6. Anacker, C., Zunszain, P.A., Carvalho, L.A., Pariante, C.A., 2011.The glucocorticoid receptor: Pivot of depression and of antidepressant treatment?
7. Andrews G., 2001. Should depression be managed as a chronic disease? Bmj. 322, 419-421.
8. Psychoneuroendocrinology 36, 415–425.
9. Angst, J., 2002. Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. Schizophr Res. 57(1), 5-13.
10. Anthony, J.C., Petronis, K.R., 1991. Suspected risk factors for depression among adults 18-44 years old. Epidemiology 2, 123-132.
11. American Psychiatric Association, 1987. DSM-III-R. Diagnostic and statistical Manual of Mental disorders 3rd ed. Revised. Washington DC.
12. American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders. Text Revision – Fourth, Washington, D.C.
13. Alonso, J., Angermeyer, M.C., Bernert, S., et al., 2004. Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatrica Scandinavica Suppl. 47-54.
14. Appelhof, B.C., Huyser, J., Verweij, M., Brouwer, J.P., van Dyck, R., Fliers, E., Hoogendijk, W.J., Tijssen, J.G., Wiersinga, W.M., Schene, A.H., 2006. Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). Biol Psychiatry. 59 (8), 696-701.
15. Aubry, J.M., Gervasoni, N., Osiek, C., Perret, G., Rossier, M.F., Bertschy, G., Bondolfi, G., 2007. The DEX/CRH neuroendocrine test and the prediction of depressive relapse in remitted depressed outpatients. J Psychiatr Res. 41(3-4), 290-4.
16. Baes, C.V.W., Tofoli, S.M.C., Martins, C.M.S., Juruena, M.F., 2012. Assessment of the hypothalamic–pituitary–adrenal axis activity: glucocorticoid receptor and mineralocorticoid receptor function in depression with early life stress – a systematic review. Acta Neuropsychiatrica. 24 (1), 4-15.
17. Bata, I.R., Gregor, R.D., Eastwood, B.J., Wolf, H.K., 2000. Trends in the incidence of acute myocardial infarction between 1984 and 1993 - The Halifax County MONICA project. 16, :589-95.
18. Beard, J.R., Galea, S., Vlahov, D., 2008. Longitudinal population-based studies of affective disorders: where to from here? BMC Psychiatry 8(83), 1-11.
19. Belsher, G., Costello, C.G., 1988. Relapse after recovery from unipolar depression: a critical review. Psychol Bull. 104(1), 84-96.
20. Berger, J.S., Lala, A., Krantz, M.J., et al., 2011. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. American Heart Journal 162, 115-24.
21. Berk, M., Hallam, K., Malhi, G.S., Henry, L., Hasty, M., Macneil, C., Yucel, M., Pantelis, C., Murphy, B., Vieta, E., Dodd, S., McGorry, P.D., 2010. Evidence and implications for early intervention in bipolar disorder. J Ment Health. 19, 113-26.

22. Beshai, S., Dobson, K.S., Bockting, C.L., et al., 2011. Relapse and recurrence prevention in depression: current research and future prospects. Clinical Psychological Review 31, 1349-60.
23. Bet, P.M., Penninx, B.W., Bochdanovits, Z., Uitterlinden, A.G., Beekman, A.T., van Schoor, N.M., Deeg, D.J., Hoogendijk, W.J., 2009. Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: New evidence for a gene-environment interaction. Am J Med Genet B Neuropsychiatr Genet. 5 (5), 660-9.
24. Bhagwagar, Z., Hafizi, S., Cowen, P.J., 2003. Increase in concentration of waking salivary cortisol in recovered patients with depression. Am J Psychiatry 160(10), 1890-1.
25. Bhagwagar, Z., Cowen, P.J., 2008. 'It's not over when it's over': persistent neurobiological abnormalities in recovered depressed patients. Psychol Med. 38(3), 307-13.
26. Biesheuvel-Leliefeld, K.E., Kok, G.D., Bockting, C.L., Cuijpers, P., Hollon, S.D., van Marwijk, H.W., Smit, F., 2014. Effectiveness of psychological interventions in preventing recurrence of depressive disorder: Meta-analysis and meta-regression. J Affect Disord. 13, 174C:400-410.
27. Bijl, R.V., Van Zessen, G., Ravelli, A., De Rijk, C., Langendoen, Y., 1998a. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Social Psychiatry and Psychiatric Epidemiology 33, 581-6.
28. Bijl, R.V., Ravelli, A., Van Zessen, G., 1998b. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Social Psychiatry and Psychiatric Epidemiology 33, 587-95.
29. Bockting, C.L., Spinhoven, P., Koeter, M.W., Wouters, L.F., Schene, A.H., 2006. Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: a 2-year prospective study. J Clin Psychiatry 67, 747-755.
30. Bockting, C.L., Spinhoven, P., Wouters, L.F., Koeter, M.W., Schene, A.H., 2009. DELTA Study Group. Long-term effects of preventive cognitive therapy in recurrent depression: a 5.5-year follow-up study. Journal of Clinical Psychiatry 70, 1621-88.
31. Bockting, C.L., Kok, G.D., van der Kamp, L., et al., 2011. Disrupting the rhythm of depression using Mobile Cognitive Therapy for recurrent depression: randomized controlled trial design and protocol. BMC Psychiatry 11, 12.
32. Bockting, C.L., Lok, A., Visser, I., Assies, J., Koeter, M.W., Schene, A.H.; DELTA study Group, 2012. Lower cortisol levels predict recurrence in remitted patients with recurrent depression: a 5.5 year prospective study. Psychiatry Res. 200 (2-3), 281-7.
33. Bromet, E., Andrade, L.H., Hwang, I., Sampson, N.A., Alonso, J., Girolamo de,G,. Graaf de R., Demyttenaere, K., Hu, C., Iwata, N., Kaur, J., Karam, A.N., Kostyuchenko, S., Lepine, J.P., Levinson, D., Matschinger, H., Medina More, M.E., Oakley Browne M., Posada-Villa, J., Viana, M.C., Williams, D.R., Kessler, R.C., 2011. Cross-National Epidemiology of DSM-IV Major Depressive Episode. BMC Medicine. 9, 90.
34. Brouwer, J.P., Appelhof, B.C., van Rossum, E.F., Koper, J.W., Fliers, E., Huyser, J., Schene, A.H., Tijssen, J.G., Van Dyck, R., Lamberts, S.W., Wiersinga, W.M., Hoogendijk, W.J. 2006. Prediction of treatment response by HPA-axis and glucocorticoid receptor polymorphisms in major depression. Psychoneuroendocrinology 31, 1154-63.
35. Brown, G.W., Harris, T.O., 1987. A study of psychiatric disorder in women. In Social Origins of Depression. Tavistock: London.
36. Brugha, T., Bebbington, P., Tennant, C., Hurry, J., 1985. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. Psychol Med. 15(1), 189-94.
37. Buchanan, T.W., Kern, S., Allen, J.S., Tranel, D., Kirschbaum, C., 2004. Circadian regulation of cortisol after hippocampal damage in humans. Biol Psychiatry. 56(9), 651-6.
38. Burcusa, S.L., Iacono, W.G., 2007. Risk for recurrence in depression. Clin Psychol Rev. 27(8), 959-85.
39. Carroll, B.J., Feinberg, M., Greden, J.F., Tarika, J., Albala, A.A., Haskett, R.F., James, N.M., Kronfol, Z., Lohr, N., Steiner, M., de Vigne, J.P., Young, E., 1981. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. Arch Gen Psychiatry 38(1), 15-22.
40. Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386-9.

41. Clow, A., Hucklebridge, F., Thorn, L., 2010. The cortisol awakening response in context. Int Rev Neurobiol. 93, 153-75.
42. Colman, I., Ataullahjan, A., 2010. Life course perspectives on the epidemiology of depression. Can J Psychiatry 55(10), 622-32.
43. Collins, G.S., Reitsma, J.B., Altman, D.G., Moons, K.G., 2015. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BJOG. 122(3):434-43.
44. Conradi, H.J., de Jonge, P., Ormel, J., 2008. Prediction of the three-year course of recurrent depression in primary care patients: different risk factors for different outcomes. J Affect Disord. 105, 267-271.
45. Cooper-Patrick, L., Crum, R.M., Ford, D.E., 1994. Characteristics of patients with major depression who received care in general medical and specialty mental health settings. Medical Care 32, 15-24.
46. Costa, P.T. Jr., McCrae, R.R., 1995. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. Journal of Personality Assessment 64, 21-50.
47. Doeglas, D., Suurmeijer, Th., Briancon, S., Moum, T., Krol, B., Bjelle, A., Sanderman, R., Van den Heuvel, W.J.A., 1996. An international study on measuring social support: interactions and satisfaction. Social Science and Medicine 43, 1389-1397.
48. Eaton, W.W., Anthony, J.C., Gallo, J., Cai, G., Tien, A., Romanoski, A., Lyketsos, C., Chen, L.S., 1997. Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. Archives of General Psychiatry 54, 993-9.
49. Eaton, W.W., Shao, H., Nestadt, G., Lee, H.B., Bienvenu, O.J., Zandi, P., 2008. Population-based study of first onset and chronicity in major depressive disorder. Archives of General Psychiatry 65, 513–520.
50. El Hage, W., Powell, J.F., Surguladze, S.A., 2009. Vulnerability to depression: what is the role of stress genes in gene x environment interaction? Psychol Med. 39, 1407-11.
51. Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., et al., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 48,851-855.
52. Fries, E., Dettenborn, L., Kirschbaum, C., 2009. The cortisol awakening response (CAR): facts and future directions. Int J Psychophysiol. 72(1):67-73.
53. Furukawa, T.A., Fujita, A., Harai, H., Yoshimura, R., Kitamura, T., Takahashi, K., 2008. Definitions of recovery and outcomes of major depression: results from a 10-year follow-up. Acta Psychiatrica Scandinavica 117, 35-40.
54. Fyer, A.J., Weissman, M.M., 1999. Genetic linkage study of panic: clinical methodology and description of pedigrees. American Journal of Medical Genetics 88, 173-81.
55. Gałecka, E., Szemraj, J., Bieńkiewicz, M., Majsterek, I., Przybyłowska-Sygut, K., Gałecki, P., Lewiński, A., 2013. Single nucleotide polymorphisms of NR3C1 gene and recurrent depressive disorder in population of Poland. Mol Biol Rep. 40(2), 1693-9.
56. Geddes, J.R., Carney, S.M., Davies, C., Furukawa, T.A., Kupfer, D.J., Frank, E., et al. 2003. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 361, 653-661.
57. Gilchrist, G., Gunn, J., 2007. Observational studies of depression in primary care: what do we know? BMC Fam Pract. 8, 28.
58. Gopinath, S., Katon, W.J., Russo, J.E., Ludman, E.J., 2007. Clinical factors associated with relapse in primary care patients with chronic or recurrent depression. J Affect Disord. 101, 57-63.
59. Graaf de R., Bijl, R.V., Ravelli, A., Smit, F., Vollebergh, W.A.M., 2002. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. Acta Scandinavica Psychiatrica 106, 303-313.
60. Graaf de, R., Bijl. R.V., Smit, F., et al., 2002. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. American Journal of Psychiatry. 159, 620-9.
61. Graaf de, R., Bijl, R.V., ten Have, M., Beekman, A.T., Vollebergh, W.A., 2004. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. J Affect Disord. 82(3), 461-7.
62. Graaf de, R., Have ten, M., Gool van, C. Dorsselaer van, S., 2012. Prevalence of mental disorders, and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2. Social Psychiatry and Psychiatric Epidemiology. 47, 203-213.

63. Graaf de R., Tuithof, M., Dorsselaer van, S., Have van, M., 2012. Comparing the effects on work performance of mental and physical disorders. Social Psychiatry and Psychiatric Epidemiology. 47, 1873-1883.
64. Graaf de R., Have ten, M., Tuithof, M., Dorsselaer van, S., 2013. First-incidence of DSM-IV mood, anxiety and substance use disorders and its determinants: Results from the Netherlands Mental Health Survey and Incidence Study-2. Journal of Affective Disorders. 149, 100-107.
65. Gueorguieva, R., Krystal, J.H., 2004. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry. 61(3), 310-7.
66. Hakkaart-van Roijen, L., 2002. Handleiding Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P). Edition Rotterdam: Institute for Medical Technology Assessment & Erasmus Universitair Medisch Centrum Rotterdam.
67. Hansen, R., Gaynes, B., Thieda, P., et al., 2008. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatric Services. 59, 1121-30.
68. Hardeveld, F., Spijker, J., de Graaf, R., Nolen, W.A., Beekman, A.T., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr Scand. 122(3), 184-91.
69. Hardeveld, F., Spijker J., De Graaf, R., Nolen, W.A., Beekman, A.T.F., 2013. Recurrence of major depressive disorder and its predictors in the General population: Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychol Med. 43, 39-48.
70. Hardeveld, F., Spijker, J., Vreeburg, S.A., De Graaf R., Hendriks, S.M., Licht, C.M., Nolen, W.A., Penninx. B.W., Beekman, A.T., 2014. Increased cortisol awakening response was associated with time to recurrence of major depressive disorder. Psychoneuroendocrinology 12, 62-71.
71. Harris, T.O., Borsanyi, S., Messari, S., Stanford, K., Cleary, S.E., Shiers, H.M., Brown, G.W., Herbert, J., 2000. Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. Br J Psychiatry 177, 505-10.
72. Hatzinger, M., Hemmeter, U.M., Baumann, K., Brand, S., Holsboer-Trachsler, E., 2002. The combined DEX-CRH test in treatment course and long-term outcome of major depression. J Psychiatr Res. 36(5), 287-97.
73. Heim, C., Newport, D.J., Wagner, D., Wilcox, M.M., Miller, A.H., Nemeroff, C.B. (2002). The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. Depression and Anxiety 15, 117-25.
74. Hellhammer, J., Fries, E., Schweisthal, O.W., Schlotz, W., Stone, A.A., Hagemann, D., 2007. Several daily measurements are necessary to reliably assess the cortisol rise after awakening: state- and trait components. Psychoneuroendocrinology. 32(1), 80-6.
75. Holleman, M., Vreeburg, S.A., Dekker, J.J., Penninx, B.W., 2012. The relationships of working conditions, recent stressors and childhood trauma with salivary cortisol levels. Psychoneuroendocrinology. 37(6), 801-9.
76. Holma, K.M., Holma, I.A., Melartin, T.K., Rytsala, H.J., Isometsa, E.T., 2008. Long-term outcome of major depressive disorder in psychiatric patients is variable. J Clin Psychiatry 69, 196-205.
77. Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology. 23 (5), 477-501.
78. Hovens, J.G., Wiersma, J.E., Giltay, E.J., van Oppen, P., Spinhoven, P., Penninx, B.W., Zitman, F.G., 2010. Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. Acta Psychiatr Scand. 122(1), 66-74.
79. Hovens, J.G., Giltay, E.J., Wiersma, J.E., Spinhoven, P., Penninx, B.W., Zitman, F.G., 2012. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatr Scand. 126(3), 198-207.
80. Huizenga, N.A., Koper, J.W., De Lange, P., Pols, H.A., Stolk, R.P., Burger, H., Grobbee, D.E., Brinkmann, A.O., De Jong, F.H., Lamberts, S.W., 1998. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab. 83(1), 144-51.
81. Ilardi, S.S., Craighead, W.E., Evans, D.D., 1997. Modeling relapse in unipolar depression: the effects of dysfunctional cognitions and personality disorders. J Consult Clin Psychol 65, 381-391.
82. Judd, L.L., 1997. The clinical course of unipolar major depressive disorders. Arch. Gen. Psychiatry. 54 (11), 989-91.
83. Judd, L.L., Akiskal, H.S., Maser, J.D., et al., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. Journal of Affective Disorders 50, 97-108.
84. Judd, L.L., Paulus, M.J., Schettler, P.J., Akiskal, H.S., Endicott, J., Leon, A.C., Maser, J.D., Mueller, T., Solomon, D.A., Keller, M.B., 2000. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 157, 1501-1504.

85. Juruena, M.F., 2014. Early-life stress and HPA axis trigger recurrent adulthood depression. Epilepsy Behav. 38, 148-159.
86. Kaestner, F., Hettich, M., Peters, M., Sibrowski, W., Hetzel, G., Ponath, G., Arolt, V., Cassens, U., Rothermundt, M., 2005. Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity. J Affect Disord. 87(2-3), 305-11.
87. Kanai, T., Takeuchi, H., Furukawa, T.A., Yoshimura, R., Imaizumi, T., Kitamura, T., et al., 2003. Time to recurrence after recovery from major depressive episodes and its predictors. Psychol Med. 33, 839-845.
88. Katon, W., Guico-Pabia, C.J., 2011. Improving quality of depression care using organized systems of care: a review of the literature. Primary Care Companion CNS Disorders 13.
89. Kaymaz, N., van Os, J., Loonen, A.J., Nolen, W.A., 2008. Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry 69, 1423-36.
90. Keller, M.B., Shapiro, R.W., Lavori, P.W., Wolfe, N., 1982. Relapse in major depressive disorder: analysis with the life table. Arch Gen Psychiatry 39, 911-5.
91. Keller, M.B., Lavori, P.W., Endicott, J., Coryell, W., Klerman, G.L., 1983. "Double depression": two-year follow-up. Am J Psychiatry 140:689-694.
92. Kendler, K.S., Thornton, L.M., Gardner, C.O., 2000. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. American Journal of Psychiatry 157, 1243-51.
93. Kennedy, N., Abbott, R., Paykel, E.S., 2003. Remission and recurrence of depression in the maintenance era: long-term outcome in a Cambridge cohort. Psychol Med.v 33, 827-838.
94. Kennedy, N., Paykel, E.S., 2004. Residual symptoms at remission from depression: impact on long-term outcome. J Affect Disord. 80, 135-144.
95. Kessing, L.V., Andersen, E.W., Andersen, P.K., 2000. Predictors of recurrence in affective disorder-analyses accounting for individual heterogeneity. J Affect Disord. 57:139-145.
96. Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., et al., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 3095-3105.
97. Kessing, L.V., Hansen, M.G., Andersen, P.K., Angst, J., 2004. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders- a life-long perspective. Acta Psychiatr Scand. 109, 339-344.
98. Kirschbaum, C., Hellhammer, D.H., 1989. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology. 22 (3),150-69.
99. Kloet de E.R., Vreugdenhil, E., Oitzl, M.S., Joëls, M., 1998. Brain corticosteroid receptor balance in health and disease. Endocr Rev.19(3), 269-301.
100. Kloet de E.R., Joëls, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 6(6), 463-75.
101. Klok, M.D., Giltay, E.J., Van der Does, A.J., Geleijnse, J.M., Antypa, N., Penninx, B.W., de Geus, E.J., Willemsen, G., Boomsma, D.I., van Leeuwen, N., Zitman, F.G., de Kloet, E.R., De Rijk, R.H., 2011. A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females. Transl. Psychiatry 13(1), e62.
102. Kraemer, H.C., Stice, E., Kazdin, A., Offord, D., Kupfer, D., 2001. How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. Am J Psychiatry 158(6), 848-56.
103. Kraepelin, E., 1899. Psychiatrie: ein Lehrbuch für Studirende und Aertze (6th edn). Leipzig: Barth Verlag. Reprinted (1990) as Psychiatry: A Textbook for Students and Physicians (ed. J. M. Quen; trans. H. Metoiu & S. Ayed). Canton, MA: Science History Publications.
104. Kraeplin, E., 1921. Manic-depressive insanity and paranoia. E. & S. Livingstone.
105. Krishnamurthy, P., Romagni, P., Torvik, S., Gold, P.W., Charney, D.S., Detera-Wadleigh, S., Cizza, G.; P.O.W.E.R. (Premenopausal, Osteoporosis Women, Alendronate, Depression) Study Group. 2008. Glucocorticoid receptor gene polymorphisms in premenopausal women with major depression. Horm Metab Res. 40(3), 194-8.
106. Kuningas M., de Rijk, R.H., Westendorp, R.G., Jolles, J., Slagboom, P.E., van Heemst, D., 2007. Mental performance in old age dependent on cortisol and genetic variance in the mineralocorticoid and glucocorticoid receptors. Neuropsychopharmacology 32(6), 1295-301.
107. Kupfer, D.J., Frank, E., Wamhoff, J., 1996. Mood disorders: Update on prevention of recurrence. In: Mundt C, Goldstein MJ, editors. Interpersonal factors in the origin and course of affective disorders. London, England: Gaskell/Royal College of Psychiatrists. 289–302.

108. Lavori, P.W., Keller, M.B., Klerman, G.L., 1984. Relapse in affective disorders: a reanalysis of the literature using life table methods. J Psychiatr Res. 18(1), 13-25.
109. Lavori, P.W., Keller, M.B., Mueller, T.I., Scheftner, W., Fawcett, J., 1994. Recurrence after recovery in unipolar MDD: an observational follow-up study of clinical predictors and somatic treatment as a mediating factor. Int J Methods Psychiatr Res. 4, 211-229.
110. Leeuwen van, N., Bellingrath, S., de Kloet, E.R., Zitman, F.G., de Rijk, R.H., Kudielka, B.M.,
111. Lavori, P.W., Keller, M.B., Klerman, G.L., 1984. Relapse in affective disorders: a reanalysis of the literature using life table methods. J Psychiatr Res. 18(1), 13-25.
112. Lin, E.H., Katon, W.J., Von Korff, M., et al., 1998. Relapse of depression in primary care. Rate and clinical predictors. Archives of Family Medicine 7, 443-9.
113. Lok, A., Mocking, R.J., Ruhé, H.G., Visser, I., Koeter, M.W., Assies, J., Bockting, C.L., Olff, M., Schene, A.H., 2012. Longitudinal hypothalamic-pituitary-adrenal axis trait and state effects in recurrent depression. Psychoneuro-endocrinology 37(7), 892-902.
114. Lyketsos, C.G., Nestadt, G., Cwi, J., Heithoff, K., Eaton, W.W., 1994. The life-chart method to describe the course of psychopathology. International Journal of Methods in Psychiatric Research 4, 143-155.
115. Maj, M., Veltro, F., Pirozzi, R., et al., 1992. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 149:795-800.
116. Mannie ZN, Harmer CJ, Cowen PJ., 2007. Increased waking salivary cortisol levels in young people at familial risk of depression. Am J Psychiatry 164(4), 617-21.
117. Mattison, C., Bogren, M., Horstmann, V., Munk-Jorgensen, P., Nettelbrandt, P., 2007. The long-term course of depressive disorders in the Lundby Study. Psychological Medicine 37, 883-891.
118. McGorry, P.D., Killackey, E., Yung, A., 2008. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry 7(3), 148-56.
119. McKay, M.S., Zakzanis, K.K., 2010. The impact of treatment on HPA axis activity in unipolar major depression. J Psychiatr Res. 44 (3), 183-92.
120. Melartin, T.K., Rytsala, H.J., Leskela, U.S., Lestela-Mielonen, P.S., Sokero, T.P., Isometsa, E.T., 2004. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. J Clin Psychiatry 65, 810-819.
121. Merikangas, K.R., Zhang, H., Avenevoli, S., Acharyya, S., Neuenschwander, M., Angst, J., 2003. Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study. Archives of General Psychiatry 60, 993-1000.
122. Monroe, S.M., Harkness, K.L., 2011. Recurrence in major depression: a conceptual analysis. Psychol Rev. 118(4), 655-74.
123. Monroe, S.M., Slavich, G.M., Gotlib, I.H., 2014. Life stress and family history for depression: the moderating role of past depressive episodes. J Psychiatr Res. 49, 90-5.
124. Morris M.C., Rao, U., Garber, J., 2012. Cortisol responses to psychosocial stress predict depression trajectories: social-evaluative threat and prior depressive episodes as moderators. J Affect Disord. 143(1-3), 223-30.
125. Mueller, T.I., Leon, A.C., Keller, M.B., Solomon, D.A., Endicott, J., Coryell, W., Warshaw, M., Maser, J.D., 1999. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. American Journal of Psychiatry 156, 1000-6.
126. Murray, C.J., Lopez, A.D., 1997. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 349, 1436-42.
127. Nathan, D.M., 1998. Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study. Lancet 352, 832-833.
128. Naz, B., Craig, T.J., Bromet, E.J., Finch, S.J., Fochtmann, L.J., Carlson, G.A., 2007. Remission and relapse after the first hospital admission in psychotic depression: a 4-year naturalistic follow-up. Psychol Med. 37, 1173-81.
129. Nemeroff, C.B., 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol Psychiatry. 1(4), 336-42.
130. Nelson, J.C., Davis, J.M., 1997. DST studies in psychotic depression: a meta-analysis. Am J Psychiatry 154(11), 1497-503.
131. Ormel, H., 1980. Moeite met leven of een moeilijk leven. Thesis, University of Groningen. (Dutch).

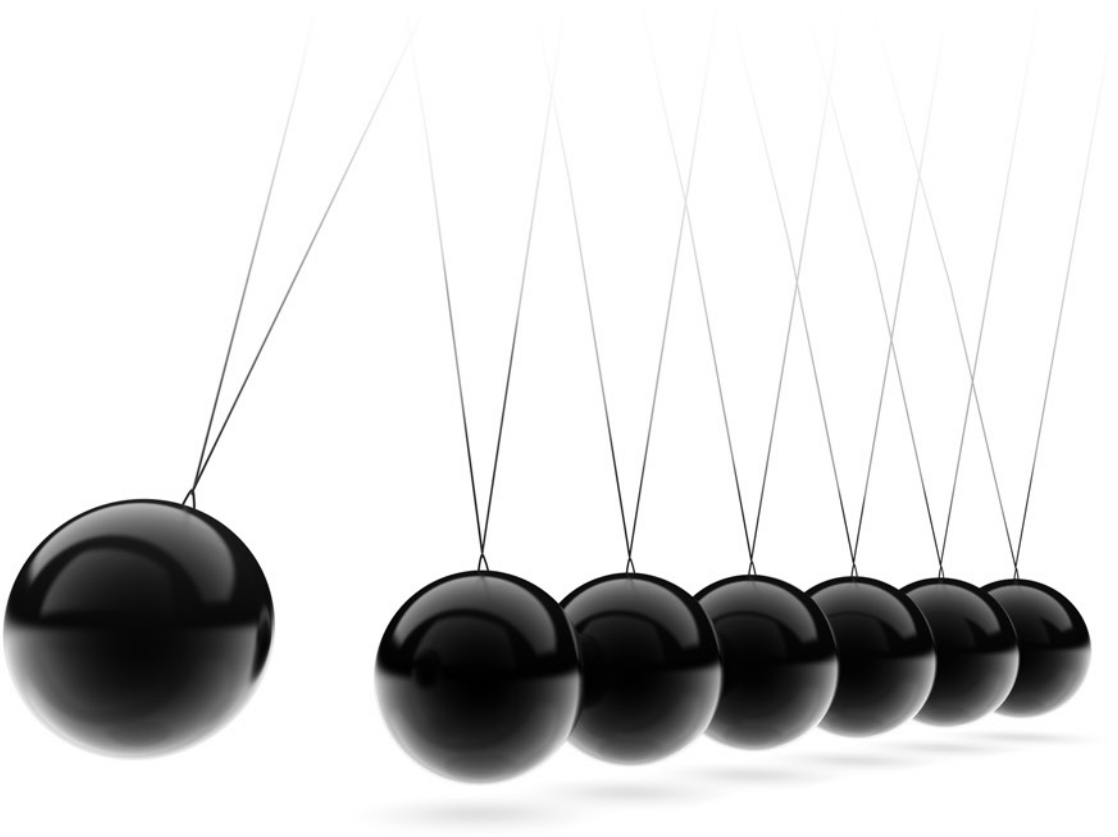
132. Ormel, J., Oldehinkel, A.J., Brilman, E.I., 2001. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. Am J Psychiatry 158(6), 885-91.
133. Otte, C., Wüst, S., Zhao, S., Pawlikowska, L., Kwok, P.Y., Whooley, M.A., 2009. Glucocorticoid receptor gene and depression in patients with coronary heart disease: the Heart and Soul Study-2009 Curt Richter Award Winner. Psychoneuroendocrinology 34(10), 1574-81.
134. Owzar, K., Li, Z., Cox, N., Jung, S., 2012. Power and sample size calculations for SNP association studies with censored time-to-event outcomes. Genet Epidemiol. 36(6), 538-548.
135. Pais, P.S., 2006. Early intervention and prevention of myocardial infarction. J Hypertens Suppl. 24, S25-30.
136. Pariante, C.M., Lightman, S.L., 2008. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 31(9):464-8.
137. Pariante, C.M., 2009. Risk factors for development of depression and psychosis. Glucocorticoid receptors and pituitary implications for treatment with antidepressant and glucocorticoids. Ann N Y Acad Sci. 1179, 144-52
138. Paykel, E.S., 1994. Historical overview of outcome of depression. Br J Psychiatry Suppl. 26, 6-8.
139. Paykel, E.S., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., Barocka, A., 1995. Residual symptoms after partial remission: an important outcome in depression. Psychol Med. 25, 1171-1180.
140. Paykel, E.S., Cooper, Z., Ramana, R., Hayhurst, H., 1996. Life events, social support and marital relationships in the outcome of severe depression. Psychol Med. 26, 121-133.
141. Pintor, L., Gastó, C., Navarro, V., Torres, X., Fañanas, L., 2003. Relapse of major depression after complete and partial remission during a 2-year follow-up. J Affect Disord. 73, 237-44.
142. Pintor, L., Torres, X., Navarro, V., Matrai, S., Gastó, C., 2004. Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up?J Affect Disord. 82, 291-6.
143. Pintor, L., Torres, X., Navarro, V., Martinez de Osaba, M.A., Matrai, S., Gastó, C., 2009. Prediction of relapse in melancholic depressive patients in a 2-year follow-up study with corticotropin releasing factor test. Prog Neuropsychopharmacol Biol Psychiatry. 33(3), 463-9.
144. Pearlin, I.P., Schooler, C., 1978. The structure of coping. Journal of Health and Social Behavior 19, 2-21.
145. Penninx, B.W., Beekman, A.T., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., de Jong, P.J., van Marwijk, H.W., Assendelft, W.J., van der Meer, K., Verhaak, P., Wensing, M., de Graaf, R., Hoogendijk, W.J., Ormel, J., van Dyck, R.; NESDA Research Consortium. 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res.17(3), 121-40.
146. Piccinelli, M., Wilkinson, G., 1994. Outcome of depression in psychiatric settings. Br J Psychiatry 164(3), 297-304.
147. Piek, E., van der Meer, K., Penninx, B.W., et al., 2011. Referral of patients with depression to mental health care by Dutch general practitioners: an observational study.BMC Family Practice 12, 41.
148. Piet, J., Hougaard, E., 2011. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. Clinical Psychological Review. 31, 1032-40.
149. Post, R.M., 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. American Journal of Psychiatry 149, 999–1010.
150. Pruessner, J.C., Wolf, O.T., Hellhammer, D.H., Buske-Kirschbaum, A., von Auer, K., Jobst, S., Kaspers, F., Kirschbaum, C., 1997. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. Life Sci. 61(26), 2539-49.
151. Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology. 28(7), 916-31.
152. Pruessner, M., Pruessner, J.C., Hellhammer, D.H., Bruce Pike, G., Lupien, S.J., 2007. The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men. Psychiatry Res. 155(1), 1-10.
153. Ramana, R., Paykel, E.S., Cooper, Z., Hayhurst, H., Saxty, M., Surtees, P.G., 1995. Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med. 25, 1161-1170.
154. Rao, U., Hammen, C.L., Poland, R.E., 2010. Longitudinal course of adolescent depression: neuroendocrine and psychosocial predictors. J Am Acad Child Adolesc Psychiatry. 49(2), 141-51.

155. Ribeiro, S.C., Tandon, R., Grunhaus, L., Greden, J.F., 1993. The DST as a predictor of outcome in depression: a meta-analysis. Am J Psychiatry. 150 (11), 1618-29.
156. Rijk de, R.H., Wüst, S., Meijer, O.C., Zennaro, M.C., Federenko, I.S., Hellhammer, D.H., Giacchetti, G., Vreugdenhil, E., Zitman, F.G., De Kloet, E.R., 2006. A common polymorphism in the mineralocorticoid receptor modulates stress responsiveness. J Clin Endocrinol Metab. 91(12), 5083-9.
157. Riso, L.P., Thase, M.E., Howland, R.H., Friedman, E.S., Simons, A.D., Tu, X.M., 1997. A prospective test of criteria for response, remission, relapse, recovery, and recurrence in depressed patients treated with cognitive behavior therapy. J Affect Disord. 43(2), 131-42.
158. Robinson, O.J., Sahakian, B.J., 2008. Recurrence in major depressive disorder: a neurocognitive perspective. Psychol Med. 38, 315-8.
159. Roca, M., Armengol, S., García-García, M., Rodriguez-Bayón, A., Ballesta, I., Serrano, M.J., Comas, A., Gili, M., 2011. Clinical differences between first and recurrent episodes in depressive patients. Compr Psychiatry 52(1), 26-32.
160. Rossum van, E.F., Koper, J.W., Huizenga, N.A., Uitterlinden, A.G., Janssen, J.A., Brinkmann, A.O., Grobbee, D.E., de Jong, F.H., van Duyn, C.M., Pols, H.A., Lamberts, S.W., 2002. A polymorphism in the glucocorticoid receptor gene, which decreases sensitivity to glucocorticoids in vivo, is associated with low insulin and cholesterol levels. Diabetes 51(10), 3128-34.
161. Rossum van, E.F., Koper, J.W., van den Beld, A.W., Uitterlinden, A.G., Arp, P., Ester, W., Janssen, J.A., Brinkmann, A.O., de Jong, F.H., Grobbee, D.E., Pols, H.A., Lamberts, S.W., 2003. Identification of the BclI polymorphism in the glucocorticoid receptor gene: association with sensitivity to glucocorticoids in vivo and body mass index. Clin Endocrinol (Oxf). 59(5), 585-92.
162. Rossum van, E.F., Binder, E.B., Majer, M., Koper, J.W., Ising, M., Modell, S., Salyakina, D., Lamberts, S.W., Holsboer, F., 2006. Polymorphisms of the glucocorticoid receptor gene and major depression. Biol Psychiatry. 59, 681-8.
163. Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med. 26(3), 477-86.
164. Scott, J., Palmer, S., Paykel, E., Teasdale, J., Hayhurst, H., 2003. Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. British Journal of Psychiatry 182, 221-7.
165. Shea, A., Walsh, C., Macmillan, H., Steiner, M., 2005. Child maltreatment and HPA axis dysregulation: relationship to major depressive disorder and post traumatic stress disorder in females. Psychoneuroendocrinology 30(2),162-78.
166. Simpson, H.B., Nee, J.C., Endicott, J., 1997. First-episode major depression. Few sex differences in course. Arch Gen Psychiatry 54, 633-639.
167. Smeets, R.M.W. & Dingemans, P.M.A.J., 1993. Composite International Diagnostic Interview (CIDI), version 1.1. World Health Organization: Amsterdam/Geneva.
168. Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Lavori, P.W., Shea, M.T., et al., 2000. Multiple recurrences of major depressive disorder. Am J Psychiatry 157, 229-233.
169. Solomon, D.A., Leon, A.C., Endicott, J., Mueller, T.I., Coryell, W., Shea, M.T., et al., 2004. Psychosocial impairment and recurrence of major depression. Compr Psychiatry 45, 423-430.
170. Spijker, J., de Graaf, R., Bijl, R.V., Beekman, A.T., Ormel, J., Nolen, W.A., 2002. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry. 181, 208-13.
171. Spijker, J., De Graaf, R., Bijl, R.V., Beekman, A.T.F., Ormel, J., Nolen, W.A., 2004. Determinants of persistence of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Journal of Affective disorders, 81, 231-240.
172. Spijker, A.T., Giltay, E.J., van Rossum, E.F., Manenschijn, L., De Rijk, R.H., Haffmans, J., Zitman, F.G., Hoencamp, E., 2011. Glucocorticoid and mineralocorticoid receptor polymorphisms and clinical characteristics in bipolar disorder patients. Psychoneuroendocrinology 36(10), 1460-9.
173. Spijker, A.T., van Rossum, E.F., 2012. Glucocorticoid sensitivity in mood disorders. Neuroendocrinology 95, 179-86.
174. Stephens, M., Smith, N.J., Donnelly, P., 2001. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet. 68(4), 978-89.
175. Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med. 73 (2), 114-26.

176. Stevens, A., Ray, D.W., Zeggini, E., John, S., Richards, H.L., Griffiths, C.E., Donn, R., 2004. Glucocorticoid sensitivity is determined by a specific glucocorticoid receptor haplotype. J Clin Endocrinol Metab. 89(2), 892-7.
177. Suh, T., Gallo, J.J., 1997. Symptom profiles of depression among general medical service users compared with specialty mental health service users. Psychological Medicine 27, 1051-63.
178. Suija, K., Aluoja, A., Kalda, R., et al., 2011. Factors associated with recurrent depression: a prospective study in family practice. Family Practice. 28, 22-8.
179. Suurmeijer, Th., Doeglas, D.M., Briancon, S., Krijnen, W.P., Krol, B., Sanderman, R., Bjelle, A., Van den Heuvel, W.J.A., 1996. The measurement of social support in the European research on incapacitating diseases and social support: the development of the social support questionnaire for transactions (SSQT). Social Science and Medicine 40, 1221-1229.
180. Szczepankiewicz, A. Leszczyńska-Rodziewicz, A., Pawlak, J., Rajewska-Rager, A., Dmitrzak-Weglarz, M., Wilkosc, M., Skibinska, M., Hauser, J., 2011. Glucocorticoid receptor polymorphism is associated with major depression and predominance of depression in the course of bipolar disorder. J Affect Disord. 134(1-3), 138-44.
181. Szczepankiewicz, A., Leszczyńska-Rodziewicz, A., Pawlak, J., Narozna, B., Rajewska-Rager, A., Wilkosc, M., Zaremba, D., Maciukiewicz, M., Twarowska-Hauser, J., 2014. FKBP5 polymorphism is associated with major depression but not with bipolar disorder. J Affect Disord. 164:33-7.
182. Ten Doesschate, M.C., Bockting, C.L., Koeter, M.W., Schene, A.H., DELTA Study Group, 2010. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. J Clin Psychiatry 71(8), 984-91.
183. Thase, M.E., 1990. Long-term nature of depression. J Clin Psychiatry 60 (Suppl 14), 3-9.
184. Vöhringer, P.A., Ghaemi, S.N., 2011. Solving the antidepressant efficacy question: effect sizes in major depressive disorder. Clin Ther. 33, B49-61.
185. Von Werne Baes, C., de Carvalho Tofoli, S. M., Martins, C. M. S. and Juruena, M. F. 2012. Assessment of the hypothalamic–pituitary–adrenal axis activity: glucocorticoid receptor and mineralocorticoid receptor function in depression with early life stress – a systematic review. Acta Neuropsychiatrica 24, 4–15.
186. Vos, T., Haby, M.M., Barendregt, J.J., Kruijshaar, M., Corry, J., Andrews, G., 2004. The burden of major depression avoidable by longer-term treatment strategies. Arch Gen Psychiatry 61, 1097-103.
187. Vreeburg, S.A., Kruijtzer, B.P., van Pelt, J., van Dyck, R., de Rijk, R.H., Hoogendijk, W.J., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009(a). Associations between sociodemographic, sampling and health factors and various salivary cortisol indicators in a large sample without psychopathology. Psychoneuroendocrinology, (8):1109-20.
188. Vreeburg S.A., Hoogendijk, W.J., van Pelt, J., Derijk, R.H., Verhagen, J.C., van Dyck, R., Smit, J.H., Zitman, F.G., Penninx, B.W., 2009(b).Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry. 66(6), 617-26.
189. Vreeburg, S.A., Hartman, C.A., Hoogendijk, W.J., van Dyck, R., Zitman, F.G., Ormel, J., Penninx, B.W., 2010. Parental history of depression or anxiety and the cortisol awakening response. Br J Psychiatry. 197(3), 180-5.
190. Vreeburg, S.A., Hoogendijk, W.J., de Rijk, R.H., van Dyck, R., Smit JH, Zitman FG, Penninx BW., 2013. Salivary cortisol levels and the 2-year course of depressive and anxiety disorders. Psychoneuroendocrinology. 38(9), 1494-502.
191. Vrshek-Schallhorn, S., Doane, L.D., Mineka, S., Zinbarg, R.E., Craske, M.G., Adam, E.K., 2013. The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. Psychol Med. 43(3), 483-93.
192. Vuorilehto, M.S., Melartin, T.K., Isometsä, E.T., 2009. Course and outcome of depressive disorders in primary care: a prospective 18-month study. Psychological Medicine 39, 1697-707.
193. Wacker, H.R., Battegay, R., Mullejans, R., et al., 2006. Using the CIDI-C in the general population. In Stefanis CN, Rabavilas AD, Soldatos CR (ed) Psychiatry: A World Perspective. Amsterdam: Elsevier Science Publishers.
194. Wang, P.S., Aguilar-Gaxiola, S., Alonso, J., et al., 2007. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. Lancet 370, 841-50.
195. Wang, J.L., Patten, S., Sareen, J., Bolton, J., Schmitz, N., MacQueen, G., 2014. Development and validation of a prediction algorithm for use by health professionals in prediction of recurrence of major depression. Depress Anxiety 31(5), 451-7.
196. Weel-Baumgarten, van E., van den Bosch, W., van den Hoogen, H., Zitman, F.G., 1998. Ten year follow-up of depression after diagnosis in general practice. Br J Gen Pract. 48, 1643-1646.

197. Weel-Baumgarten van E.M., Schers, H.J., van den Bosch, W.J., van den Hoogen, H.J., Zitman, F.G., 2000. Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. J Fam Pract. 49(12), 1113-20.
198. West van, D., Van Den Eede, F., Del-Favero, J., Souery, D., Norrback, K.F., Van Duijn, C., Sluijs, S., Adolfsson, R., Mendlewicz, J., Deboutte, D., Van Broeckhoven, C., Claes, S., 2006. Glucocorticoid receptor gene-based SNP analysis in patients with recurrent major depression. Neuropsychopharmacology 31(3), 620-7.
199. Wiersma, J.E., Hovens, J.G., van Oppen, P., Giltay, E.J., van Schaik, D.J., Beekman, A.T., Penninx, B.W., 2009. The importance of childhood trauma and childhood life events for chronicity of depression in adults. J Clin Psychiatry 70(7), 983-9.
200. Wilson, S., Hicks, B.M., Foster, K.T., McGue, M., Iacono, W.G., 2014. Age of onset and course of major depressive disorder: associations with psychosocial functioning outcomes in adulthood. Psychol Med. 10, 1-10.
201. Winokur, G., Coryell, W., Keller, M., Endicott, J., Akiskal, H., 1993. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. Arch Gen Psychiatry 50, 457-465.
202. Winsen van, L.M., Manenschijn, L., van Rossum, E.F., Crusius, J.B., Koper, J.W., Polman, C.H., Uitdehaag, B.M., 2009. A glucocorticoid receptor gene haplotype (TthIII1/ER22/23EK/9beta) is associated with a more aggressive disease course in multiple sclerosis. J Clin Endocrinol Metab. 94(6), 2110-4.
203. Wittchen, H.U., Burke, J.D., Semler, G., et al. 1989. Recall and dating of psychiatric symptoms. Test-retest reliability of time-related symptom questions in a standardized psychiatric interview. Archives of General Psychiatry. 46, 437-43.
204. Wittchen, H.U., 1994. Reliability and validity studies of the WHO-CIDI: a critical review. Journal of Psychiatric Research 28, 57-84.
205. World Health Organization, 1997. Composite International Diagnostic Interview. Core version 2.1: Interview's Manual. World Health Organisation, Sydney, Australia.
206. World Health Organization. (1990). Composite Diagnostic Interview (CIDI), version 1.0. World Health Organization: Geneva.
207. World Health Organization, 2008. The global burden of disease: 2004 update. Geneva: World Health Organisation.
208. Wüst, S., Federenko, I., Hellhammer, D.H., Kirschbaum, C., 2000. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. Psychoneuroendocrinology 25(7), 707-20.
209. Wüst, S., van Rossum, E.F., Federenko, I.S., Koper, J.W., Kumsta, R., Hellhammer, D.H., 2004. Common polymorphisms in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. J Clin Endocrinol Metab. 89, 565-73.
210. Wüst, S., 2011. Human mineralocorticoid receptor (MR) gene haplotypes modulate MR expression and trans-activation: implication for the stress response. Psychoneuroendocrinology 36, 699-709.
211. Zis, A.P., Goodwin, F.K., 1979. Major affective disorder as a recurrent illness: a critical review. Arch Gen Psychiatry 36(8), 835-9.
212. Zobel, A.W., Yassouridis, A., Frieboes, R.M., Holsboer, F., 1999. Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. Am J Psychiatry. 156(6), 949-51.
213. Zobel, A.W., Nickel, T., Sonntag, A., Uhr, M., Holsboer, F., Ising, M., 2001. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. a prospective study. J Psychiatr Res. 35(2), 83-94.
214. Zobel, A., Jessen, F., von Widdern, O., Schuhmacher, A., Höfels, S., Metten, M., Rietschel, M., Scheef, L., Block, W., Becker, T., Schild, H.H., Maier, W., Schwab, S.G., 2008. Unipolar depression and hippocampal volume: impact of DNA sequence variants of the glucocorticoid receptor gene. Am J Med Genet B Neuropsychiatr Genet. 5 (6):836-43.

Samenvatting

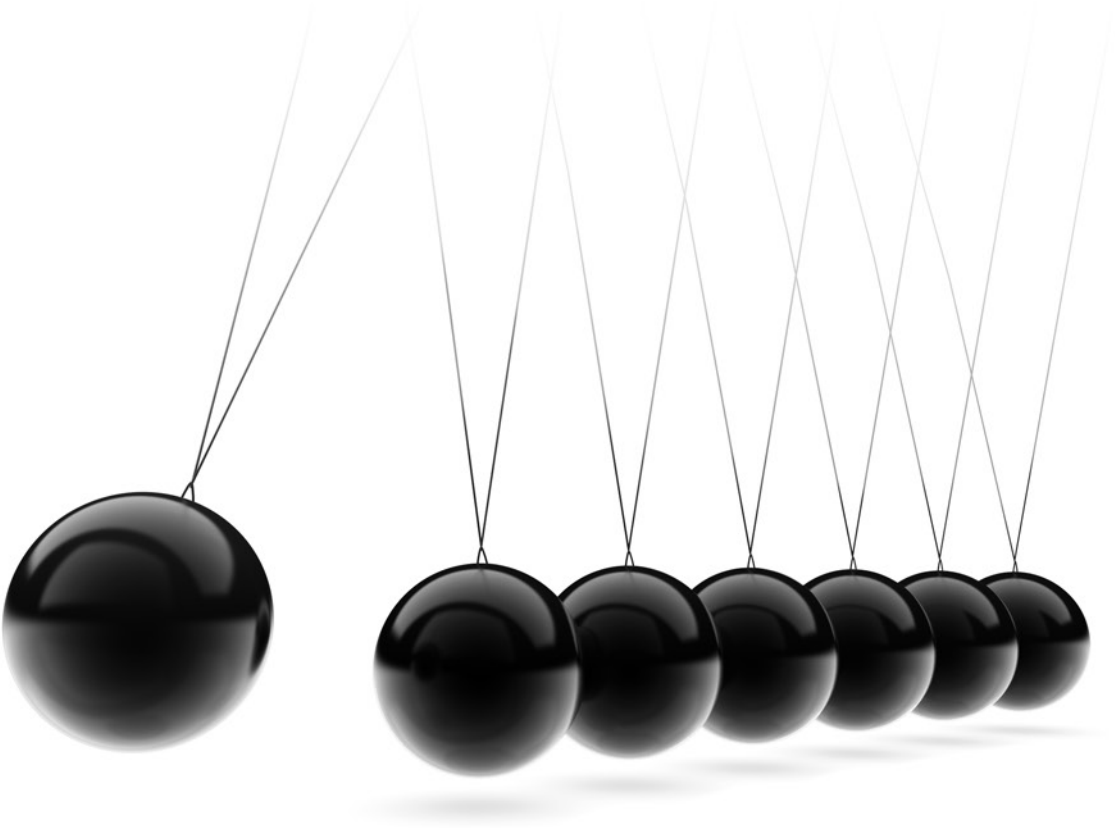


Samenvatting

Depressie is een heterogene aandoening met een hoge prevalantie en morbiditeit. De hoge ziektelast van depressie wordt gedeeltelijk veroorzaakt door het chronische en recidiverende beloop. De etiologie van depressie is complex waarbij zowel genetische- als omgevingsfactoren een rol spelen. Het is van groot belang om de predictoren van recidivering te weten omdat deze kennis nodig is voor preventie van recidivering. In de afgelopen 20-30 jaar hebben verschillende studies onderzoek gedaan naar de prevalentie en predictoren van recidivering. Er was tot nog toe hiervan geen systematisch overzichtsartikel gemaakt en met name was er geen vergeleking tussen de verschillende echelons (2e lijn, 1e lijn of algemene bevolking). In **hoofstuk 2** is het overzichtsartikel weergegeven. De conclusie was dat het percentage van recidivering in de GGZ hoog is (tot 85% in 15 jaar) en dat het voor deze patiëntenpopulatie zinvoller is om een inschatting te maken *wanneer* dan *of* een patiënt een recidief zal krijgen. Verder werd geconcludeerd dat het recidiveringsrisico van depressie bij diegenen die door de huisarts behandeld worden vergelijkbaar is met patiënten die in de GGZ in behandeling zijn en dat het recidiveringsrisico in de algemene bevolking lager is (35% in 15 jaar). Klinische factoren (aantal eerdere episoden en subklinische restverschijnselen) zijn waarschijnlijk de meest belangrijke predictoren van tijd tot recidief en sociodemografische factoren zijn vermoedelijk niet geassocieerd met recidivering. Verder werd er geconcludeerd dat er slechts een beperkt aantal studies zijn verricht in de algemene bevolking en de eerste lijn en met name weinig prospectieve studies. In het overzichtsartikel zijn genetische en neuro-endocriene predictoren (HPA-as) niet onderzocht. In **hoofdstuk 3** werden de predictoren in de algemene bevolking onderzocht. Het cumulatieve recidief percentage was 42.0% na 20 jaar. Uit multivariate analyses bleek dat jonge leeftijd, een hoog aantal eerdere episoden, een ernstiger laatste depressieve episode, traumatische jeugdervaringen en aanhoudende problemen significant predictoren waren voor recidief. In dit cohort was het recidief risico aanzienlijk maar lager in vergelijking met patiënten die behandeld worden in de eerste of tweede lijn. Dus ook individuen uit de algemene bevolking kunnen een langdurig risico hebben op een recidief en factoren die recidief voorspellen zijn vooral ziekte- en stress gerelateerde factoren. Ook werd gevonden dat het risico op recidief afhing van het aantal risicofactoren dat een individu heeft; het cumulatieve recidief percentage na 10 jaar was 3.4% bij personen zonder de eerdere genoemde predictoren, 19.0% bij personen met 1 risicofactor, 26.6% bij personen met 2 predictoren, 56.5% voor diegenen met 3 predictoren en 65.0% bij diegenen met 4 of meer predictoren. In **hoofdstuk 4** werd tijd tot recidief van depressie en de betrokken predictoren onderzocht in de eerste en tweede lijn. Belangrijkste bevindingen waren dat er geen significant verschil was in tijd tot recidief tussen patiënten die in de GGZ en die in de eerste lijn werden behandeld. Bij multivariate analyse waren een positieve familie voorgeschiedenis voor depressie en eerdere episoden van depressie geassocieerd met tijd tot recidief. De predictoren verschilden niet per setting. In

hoofdstuk 5 werd onderzocht of HPA-as parameters geassocieerd waren met tijd tot recidief. Het onderzoek bevestigde eerder onderzoek dat een hogere cortisol ochtend curve, welke gerelateerd is aan de sensitiviteit van de HPA-as, de kwetsbaarheid voor een recidief verhoogd ook al is de depressie al lange tijd in remissie. De dexamethason suppressie test en avond cortisol waarden waren niet geassocieerd met recidief en het hogere risico bij een hoge cortisol ochtend curve was niet afhankelijk van ernstige levensgebeurtenissen. In **hoofdstuk 6** werd onderzocht of polymorfismen van de glucocorticoïd en mineralocorticoïd receptor geassocieerd zijn met risico of recidief. Associaties werden niet gevonden en ook werden geen interacties met stress gerelateerde factoren gevonden. In **hoofdstuk 7** werden de bevindingen en beperkingen van de studies besproken, de implicaties voor de praktijk belicht en werden suggesties gedaan voor verder onderzoek om te komen tot een beter begrip van recidivering van depressie. Een uitdaging zal zijn of personen met een hoog risico op recidivering na een eerste episode van depressie kunnen worden geïdentificeerd. Een risico taxatie instrument kan hierbij ondersteunend zijn. Zodoende kan met gerichte behandeling recidivering mogelijk verder voorkomen worden.

Dankwoord



Dankwoord

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