Chronic depression

Determinants and consequences of chronic major depression in the general population

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Chronische depressie

Determinanten en consequenties van chronische depressie in engere zin (DSM-III-R) in de algemene bevolking

(Met een samenvatting in het Nederlands)

Proefschrift

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Contents

CHAPTER 1

INTRODUCTION

1.1 Introduction

Unipolar major depressive disorder (MDD) represents an important and worldwide public health problem (Judd, 1997). In recent general population studies a one-year prevalence of MDD was found of 4-10% and a lifetime prevalence of 15-17% (Regier et al, 1993; Kessler et al, 1994; Offord et al, 1996; Bijl et al, 1998a). MDD has serious consequences: it is associated with important limitations in social and occupational functioning (Wells et al, 1989; Hayes et al, 1995). The loss of human capital asssociated with MDD is alarmingly high and still increasing. The World Health Organization identified therefore MDD as the fourth ranked cause of disability-adjusted life years and premature death worldwide (Murray & Lopez, 1996). In the year 2020 MDD will be the second leading cause of disability only to be surpassed by ischaemic heart disease (WHO, 2001).

The consequences of MDD are compounded and extended by the fact that MDD has a high tendency towards relapse, recurrence and chronicity (Keller, 1994). Knowledge of the development of these unfavourable courses of MDD may guide the development of more effective treatment strategies to prevent them (Judd, 1997). The subject of this thesis is chronicity of major depressive disorder, its determinants and its consequences in daily functioning. The main aims of the study are to examine:

1. the duration of a major depressive episode and the rate of a chronic duration in the general population,
2. the determinants of a (chronic) duration,
3. the consequences of a longer duration on daily functioning.

In this introductory chapter I will elaborate on the background of the study and summarise a review of the literature. Next, I will discuss the research questions and the study design more extensively and finally I will give an outline of the thesis.

1.2 Course of major depressive disorder

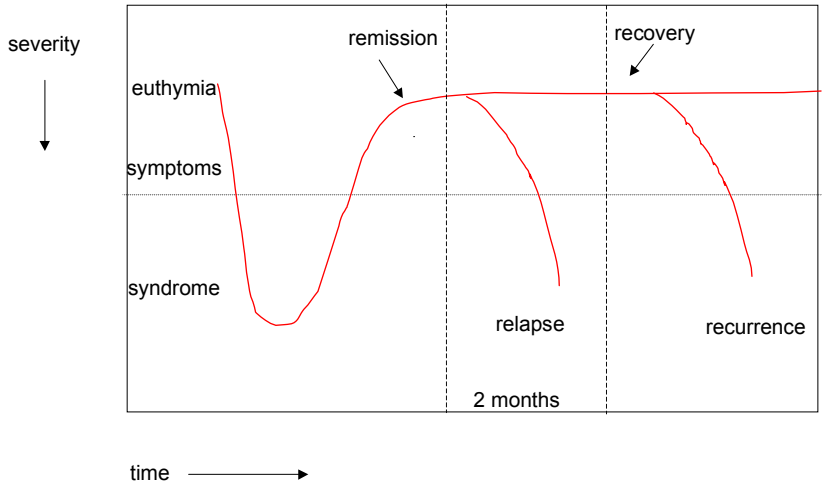
In 1889 Kraepelin drew attention to the course of affective disorders. He described a duration of 2 or 3 months for depressive episodes in bipolar illness but 9 to 12 months for melancholic depression and in a minority of patients a chronic course of more than 2 years was found (Kraepelin, 1899). This was the start of a long tradition of clinical research in the course of affective disorders (see Angst, 1988). This research was hampered, however, by lack of agreement on definitions and not until recently, proposals were made to define critical changes in the course of depression (Frank et al, 1991; Prien et al, 1991). According to the USA National institute for Mental Health (NIMH) definition (Keller et al, 1992) the outcome of a major depressive episode can be described as follows: complete remission of symptoms can transgress into recovery when the remission has lasted two months. If symptoms return before two months it is called a relapse; a return of symptoms after two months is called a recurrence. An incomplete remission of symptoms is called partial remission (fig. 1).

Recent research (Judd et al, 1998) has revealed that the clinical course of MDD is very pleiomorphic and varies from subtreshold syndromes, single episodes (short or long), multiple recurrent episodes, with or without interepisodic recovery, residual symptoms after an episode and to chronicity.

This makes the time frame of observation an important issue. It is possible to study

the day to day changes in depressive symptomatology during a major depressive episode (MDE). In clinical practice an intermediate time frame of months to one or two years is more common, as this matches the average duration of treatment for MDE. The life-time course of MDD in years in terms of recurrences of new MDEs and

Figure 1: Outcome of major depressive episode



residuals symptoms is seldom observed by a clinician but can be obtained from cohort studies with regular follow-up. It is obvious that these different time frames yield very different perspectives on the course of MDE and MDD. The course of MDE can be studied within a time frame of several months, while the study of the course of MDD requires many years. The time frame of observation has also important implications for assessing the incidence or prevalence of MDD. With cross-sectional identification of cases many cases will be missed and those with longer duration will be overrepresented (fig.2)

1.2.1 Definition and classification of chronicity

With the atheoretical format and operationalised symptoms criteria of the DSM-III (APA, 1980) the classification of depression became based on symptom patterns, symptom severity and course. In the DSM-III, III-R and IV (APA, 1980; 1987; 1994) at least five depressive symptoms with a duration of at least two weeks were required for a classification of MDD. There has been only a minor change of MDD criteria between the DSM-III-R and the DSM-IV: i.e. the addition of the criteria of social dysfunctioning (table 1).
Next to MDD the dysthymic disorder was introduced in the DSM-III as a chronic depression with a mild and protracted course. For a classification of dysthymia it was required that there had been no major depressive episode in the two year of mild chronic depression. In that case a major depression in partial remission should be classified. Dysthymia and MDD can be diagnosed together, the “double depression”. In the DSM-III-R (APA, 1987) a chronic course specifier was introduced for major depressive episodes that persisted, either in partial remission or at the criterion level

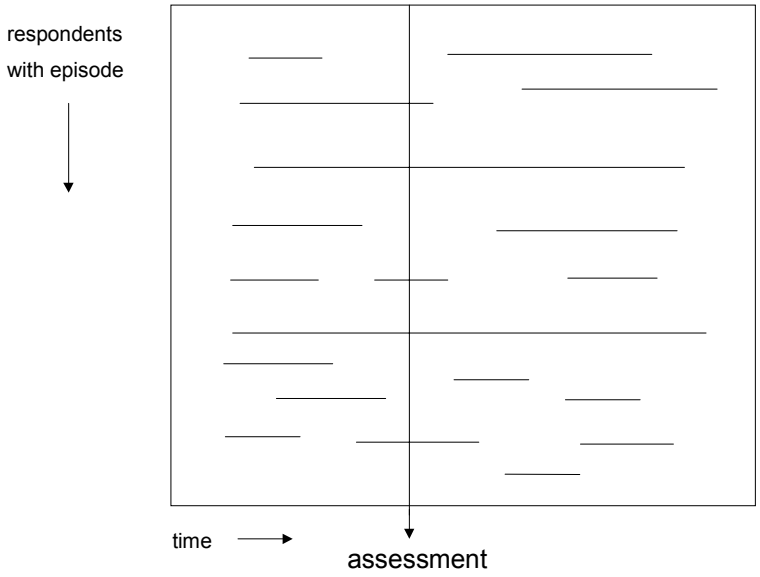
for more than two years. It was noted that in 20 to 35% of cases a chronic course develops.

Table 1: Classification of depressive disorders

Classification	DSM-III	DSM-III-R	DSM-IV
Major Depressive Disorder (MDD)	*5 out of 9 symptoms duration ≥ 2 weeks*	*5 out of 9 symptoms duration ≥ 2 weeks*	*5 out of 9 symptoms duration ≥ 2 weeks impairments in functioning*
Chronic MDD	-	*no period of 2 months without depressive symptoms ≥ 2 years*	*full criteria for MDD ≥ 2 years*
Dysthymia	*mild depression ≥ 2 years but no MDD*	*mild depression ≥ 2 years and no MDD, not preceded by MDD*	*mild depression ≥ 2 years and no MDD, not preceded by MDD*
Double depression	*dysthymia + MDD*	*dysthymia + MDD*	*dysthymia + MDD*

In the DSM-IV (APA, 1994) the requirements for a chronic course of major depressive episodes were made more stringent: at least two-year duration of depressive symptoms at the criteria level for MDD. For recurrent episodes the course specifier 'with or without interepisodic recovery' was introduced.
So, both in the DSM-III-R and the DSM-IV chronic depression is defined in two different forms: chronic MDD and dysthymic disorder. The differentiation between the two disorders is based on severity, chronicity and persistence of nearly identical symptoms. The cardinal feature of dysthymia is a chronically depressed mood that is

Figure 2 : Effect of cross-sectional identification of cases with depressive episodes[*1]

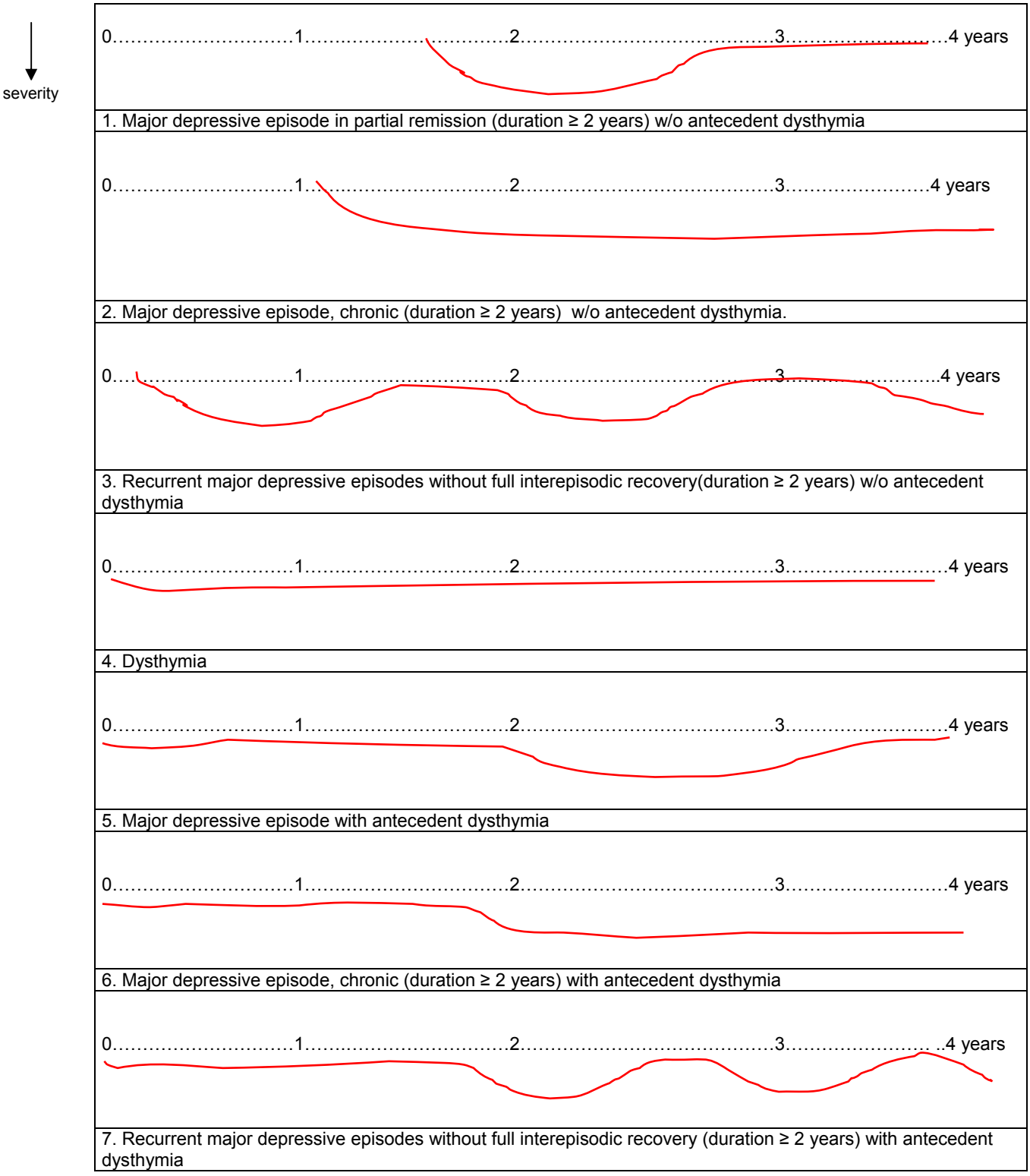


present for most of the day, more days than not, for at least two years and there are at least two additional symptoms. For a diagnosis of MDD the depressed mood must be present for most of the day, nearly every day for at least two weeks together with at least four additional symptoms (APA, 1987; 1994).
Researchers and clinicians tend to broaden the DSM-IV definition of chronicity:

- a duration of more than one year is sometimes defined as chronic (Angst, 1988).
- a period of symptomatic 'non-recovery' (partial remission) during two years is defined as chronic (Scott, 1988; Keller et al, 1986).

In addition, subtreshold depressive syndromes can be observed in the course of illness, such as minor depression and subsyndromal depressive symptoms (Judd et al, 1998) and these subtypes can also follow a chronic course.
Several chronic course patterns can thus be distinguished (fig 3). Only pattern 2 and 6 fulfil the DSM-IV definition of a chronic course of major depressive disorder.
In this research we will employ a broad definition of the chronic course of major depression. We start with a one-year definition of chronicity and later on employ the two-year definition of non-recovery, including comorbid dysthymia and thus combine type 1, 2, 3, 5, 6, 7.
An important issue is whether these different patterns represent different disorders or just variations of the same disorder? Research into the differences and similarities of the different forms of chronic depressions is limited. In one study (McCullough, 2000) no clinical relevant differences on sociodemographic, clinical course, symptomatology, psychosocial factors and general functioning were found between patients with double depression and chronic major depression. In line with previous thinking on the differences between dysthymia and MDD (Akiskal, 1994) there seems to be arguments to consider various forms of (chronic) depressions as different course configurations in a spectrum concept of affective illness (McCullough, 2000).

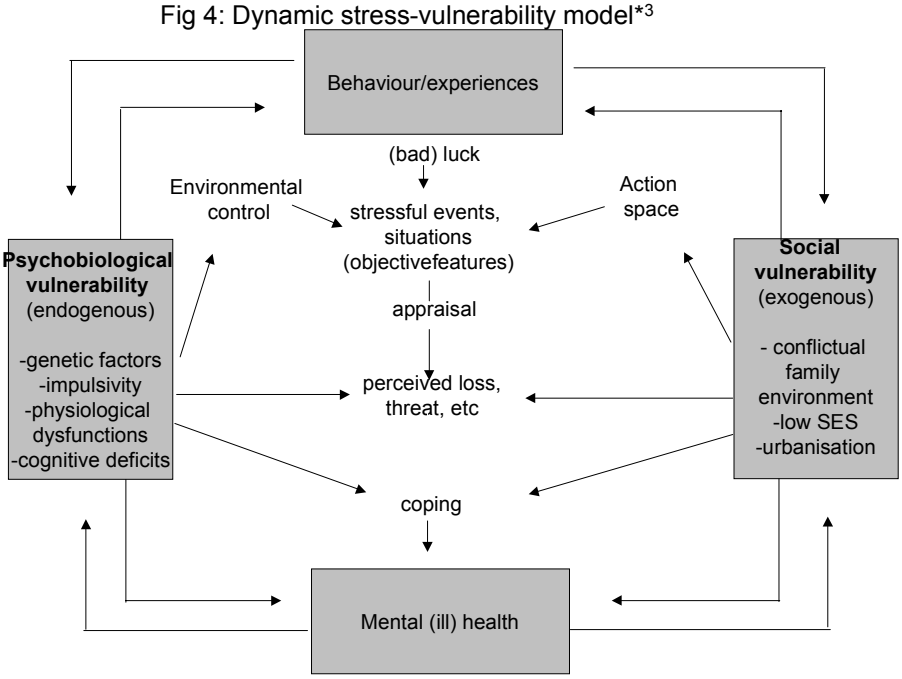
Figure 3: Different types of chronic major depressives episodes*[2]



1.3 Determinants of the course of depression

Because of the heterogeneous nature of the course of MDE, it is of great importance for clinicians to be able to predict a prognosis. A prognosis guides treatment decisions, it provides the clinician with a norm to monitor the course of the illness in a patient and it can be communicated to patients and their relatives to get an idea of the future consequences of the disorder (van den Brink et al, 2001). However, predicting a prognosis in individual cases is difficult. The prognostic skills of clinicians are still underdeveloped (van den Brink et al, 2001) and lack a theoretical basis.
At present, stress-vulnerability models are the most widely used theories on the development and continuation of depression (Brown & Harris, 1987; Goldberg et al, 1990). A comprehensive variant of these models, the dynamic stress-vulnerability model (DSV- model) (Ormel & Neeleman, 2000) describes how personal biography, environment, events and psychopathology influence each other (fig. 4).

Fig 4: Dynamic stress-vulnerability model*[3]



The DSV-model proposes that individual mental health, expressed, for example, by habitual levels of anxiety, depression and impulsive behaviour, is relatively stable over time just like somatic functions as blood pressure. This habitual symptom level reflects the person's psychobiological and social vulnerability. Psychobiological vulnerability consists of endogenous factors (genetic, deviant temperamental style, dysfunctional physiological systems) and social vulnerability is exogenous determined (low socio-economic status, urbanicity, conflictual family environment). Fluctuations in symptom levels within the individual are due to the experiences of life events and depend on how the individual appraise the events and cope with them. Individuals differ not only with respect to their habitual symptom levels but also with respect to the degree at which their symptom level fluctuates following event exposure. The nature of the events people experience is determined by random change but also by the individuals' freedom to act and the control they have over their environment. Freedom to act is limited by exogenous social and physical features of individuals'environment. Environmental control reflects more endogenous, person-linked factors. For instance, low social status implies relatively little freedom to act and social competence relatively more environmental control.

The DSV-model is characterised not only by the dynamic nature of the equilibrium of mental health it proposes, but also by the continuous interplay between its various parameters such as individual genetic make-up, personality and socio-economic status as they develop over time, and the occurrence of life events.
According to the DSV-model, determinants of the development and the persistence of depression can be distinguished in:

- Demographic factors (age and gender). These demographic factors will be taken apart as they refer to psychobiological vulnerability as well as to social vulnerability.
- Psychobiological vulnerability factors.
- Social vulnerability factors.
- (Stressful) life events including longstanding difficulties (financial problems, interpersonal problems) (Brown & Harris, 1987). Life events can act as provoking agents for the development of depression but also as sustaining agents for the continuation of depression. (Lack of) social support is considered a sustaining factor (Brown & Harris, 1987) but it can also reflect social vulnerability.
- Levels of psychopathology.

We performed a literature review on the determinants of the prognosis of depression with a special focus on a chronic course of depression (see chapter 2) and have classified the determinants which have been found to be associated with a longer duration of depression according to the DSV-model (table 2).
Data on age and gender were inconsistent. Social vulnerability (low socio-economic status, poor education) increases the risk of longer duration of depression and chronicity. From the psychobiological vulnerability factors we found personality characteristics (premorbid neuroticism), adverse early youth experiences and prior psychiatric and physical illness to predict longer duration of depression. The data on life events and social support are inconsistent but longstanding interpersonal difficulties seem to influence the course of depression negatively. Illness-related factors, however, were found as the strongest predictors of persistence of depression: severity of the depressive episode, duration of the (previous) episode and comorbidity (with somatic disorders, alcohol addiction, anxiety disorders and possibly dysthymia).

Table 2: Potential determinants of persistence of depression from the literature.

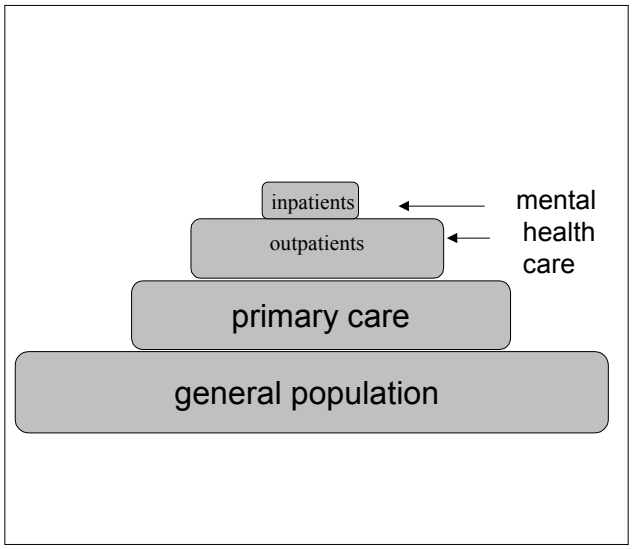
Determinant	Results
Demographic factors	
Age	no association (1), younger age (2)
Gender	female (1), no association (3)
Social vulnerability	
Education	low level (1)
Social economic status	low (4)
Marital status	being married (4); no partner (5)
Psychobiological vulnerability	
Youth experiences	childhood adversity (8,9)
Personality characteristics	high neuroticism (7,2)
Previous psychiatric illness	other psychiatric illness (4)
Somatic illness	presence of somatic illness (2)
Sustaining factors	
Negative life events	no association (6)
Ongoing difficulties	interpersonal difficulties (8,9)
Social support	lack of support (9); no association (6)
Illness-related factors	
Severity of depression	severe (1,4,5,6)
Comorbidity	with dysthymia (4), anxiety disorders (10), alcohol dependence (11)
Previous episodes	multiple (1); no association (4)
Duration of (previous) episode	long (1,4,7)

(1) Sargeant et al, 1990; (2) Keitner et al, 1992; (3) Simpson et al, 1997;(4) Keller, 1994; (5) Mueller et al, 1996; (6) Paykel et al, 1996; (7) Scott et al, 1992; (8) Brown & Moran, 1994; (9) Brown et al, 1994; (10) Ormel et al, 1993; (11) Mueller et al, 1994.

1.3.1 Methodological issues

The available studies on duration and chronicity of depression yielded many inconsistent results (see chapter 2). Methodological shortcomings and differences between the studies are probably responsible for this. Different definitions of recovery were used and a distinction between a persistent and a recurrent course was not always made. Furthermore, the studies were subject to two kinds of bias. Lead time bias arises because depressed persons were not recruited at a similar point in time in the course of the disorder; mostly prevalent cases were included. This leads to an oversampling of cases with longer duration (fig. 2). Lead time bias is avoided by selecting only individuals with newly originated episodes of MDE. This can only been done in a prospective study design with several, consecutive, measurements. Referral filter bias arises because selected populations of depressed inpatients or outpatients were employed (fig. 5). In these clinical populations cases with longer duration of depression will also be overrepresented (Cohen & Cohen, 1984).
To avoid the referral filter bias, the duration of MDE should be studied in people with depression selected from the general population. The course of MDD in the general population is probably different from depressed in- and outpatients as the milder, briefer and first MDEs are represented more in the general population (Costello 1990). Determinants of the course in the general population may also differ from clinical populations. Some evidence suggests that life events and social support are mainly an issue in depressive episodes of brief duration (McLeod et al, 1992) or first episodes (Kendler et al, 2000). This is consistent with Post's (1994) kindling hypothesis, which holds that initial episodes of depression are triggered by these psychosocial factors while later episodes arise more spontaneously. So, it is expected that illness-related factors will be less and life events and social support more important as predictors of duration in the general population.

Fig 5: Referral filter bias: depressed individuals can be recruited from different populations.



Another methodological issue is the association between treatment and chronicity. There is an apparent connection between chronicity and undertreatment (Keller, 1994; Scott et al, 1992). Adequate treatment is supposed to prevent chronicity. However, in an observational study treatment seeking was found to be associated with longer duration of depression (Coryell et al, 1994). The probable explanation for this unexpected finding is that care utilisation is associated with clinical characteristics of the depression, such as severity and duration of the episode. These characteristics, in turn, affect the outcome of treatment negatively. A further elucidation of the associations between clinical characteristics of the depression, care utilisation and outcome of care is necessary.

1.4 Consequences of depression

MDD has been found associated with severe limitations in psychological well-being and daily functioning that were equal or greater than those of other major chronic medical conditions such as diabetes and arthritis (Wells et al, 1989) and greater than those of other forms of psychopathology (Ormel et al, 1994; Bijl & Ravelli, 2000). Functional disability varies directly with the level of depressive symptom severity during the course of illness and even subsyndromal symptomatic and minor depressions are associated with significant disability and dysfunction. The high tendency toward recurrence, relapse and chronicity of MDD contributes to the invalidating effects on functioning (Judd et al, 2000).
The disability associated with MDD affects most areas of everyday functioning (Hayes et al, 1995;Judd et al, 2000). Especially social and occupational functioning is strongly impaired by depression (Ormel et al, 1993).
The impact of depression on occupational productivity is an issue of profound societal importance. Decreased capacity to work and impaired work productivity contribute to the significant societal burden of depression in the USA (Hirschfeld et al, 2000). In the Netherlands MDD is also considered as one of the diseases with the highest burden of disease in terms of reduced life expectancy and lost productivity (Melse & Kramers, 1997).

There is no standardised, widely accepted definition of social functioning but it is described as the individual's ability to perform and fulfil normal social roles. The ability to maintain and enjoy relationships may be affected by depression and the resulting additional stresses on interpersonal relationships may create a vicious circle, contributing to the chronic, recurrent nature of depression (Hirschfeld et al, 2000).
Social and occupational functioning is gaining increasing importance in relation to the treatment and outcome assessment of medical disorders. In general, the clinical management of medical conditions has tended to focus largely on clinical signs and symptoms. However, impairments in social and occupational functioning, rather than health status itself, are often the deciding factor leading people to seek health care (Hirschfeld et al, 2000). So, there is now increasing recognition of the need to consider the recovery of depressed patients in broader terms than merely as improvement in symptoms, by assessing the effect of depression on patient's work and social functioning (Furukawa et al, 2001).
Although research on the association between depression and functional disability is extensive, little is known, however, about their temporal relationship (Ormel & von Korff, 2000). Clinical experience suggests that persistence of depression leads to progressive deterioration in functioning which in turn may further hamper recovery but empirical data on this association between functional disability and duration of depression, however, are lacking. Elucidating the association between duration of a depressive episode and functional disability is of obvious clinical importance.

1.5 Netherlands Mental Health Survey and Incidence Study (NEMESIS)

The present research is part of a general population survey: the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl et al, 1998b) with three waves in 1996 (T_0), 1997 ($T_1 = T_0 + 12$ months) and 1999 ($T_2 = T_0 + 36$ months). All respondents, whether with or without mental disorders at the time of the initial interview, were monitored for the duration of the study. The aim of the study was to obtain data on the following subjects:

- The prevalence of psychiatric morbidity amongst adults (18 through 64 years of age), in terms of both discrete and comorbid psychiatric disorders as well as the co-occurrence of psychological and (mainly chronic) somatic ailments. Psychiatric diagnoses were based on the DSM-III-R classification (APA, 1987).
- The consequences of mental disorders in terms of care use and care needs, quality of life and functional impairments.
- The incidence and course of disorders. With repeated measurements it was possible both to identify incident cases and to monitor the course of existing disorders over time, in relation to changing life circumstances.
- Determinants of the emergence and the course of mental disorders; in particular, sociodemographic characteristics, distressing recent and early life events (e.g. family history), care received, personality and vulnerability traits (e.g. neuroticism, locus of control), and support from the social environment. Biological and physical examinations are not provided for in NEMESIS.

The relevant large-scale population surveys that have been carried out in several countries in the last decade (National Comorbidity Survey (Kessler et al, 1994) in the United States, National Psychiatric Morbidity Surveys (Jenkins et al, 1997) in Great Britain, Mental Health Supplement to the Ontario Health Survey (Boyle et al, 1996)

in Ontario, Canada were all cross-sectional. NEMESIS is the first large-scale nation-wide prospective population study.
NEMESIS was conducted by the Netherlands Institute of Mental Health and Addiction (Trimbos Institute) in Utrecht and financial support had been received from the Netherlands Ministry of Health, Welfare and Sport (VWS), the Medical Sciences Department of the Netherlands Organisation for Scientific Research (NWO), and the National Institute for Public Health and Environment (RIVM).

1.5.1 Sample

NEMESIS is based on a multistage, stratified, random sampling procedure. The first step was to draw a sample of 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 determined 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 national government Minister of Public Health, Welfare and Sport requesting them to take part. Shortly thereafter they were contacted by telephone by the interviewers. Households with no telephone or with unlisted numbers (18%) were visited in person. One respondent was randomly selected in each household, the member with the most recent birthday, on the condition that he or she was between 18 and 64 years of age and sufficiently fluent in Dutch to be interviewed. Persons who were not immediately available (due to circumstances such as hospitalisation, travel or imprisonment) were contacted later in the year. Since institutionalisation in hospital is 10.5 days on average and imprisonment is on average 75 days in the Netherlands, only a small proportion of long-term institutionalised people has not been included. Their numbers are small compared to the total population, and it is to be expected that this will affect the reported outcomes in a negligible way.
To establish contact, the interviewers made a minimum of ten phone calls or visits to a given address at different times of the day and week, if necessary. Respondents received no remuneration, but only a token of appreciation at the end of the interview.
To optimise response and to compensate for possible seasonal influences, the initial data collection phase was spread over the entire period from February through December 1996. No adjustments had to be made to the procedure in the course of the fieldwork, and hence no additional respondents were drawn from specific groups. 7076 Persons were interviewed in the first wave. The response was 69.7% of the adult persons eligible for interviewing. No proxy information was collected. Item nonresponse was negligible as a result of the computerised interviewing. Persons who declined to take part in the full interview (despite our offer of a 50-guilder gift certificate) were asked to furnish several key data (age, gender) and to fill in the GHQ-12, a screener for current mental health problems (Goldberg & Williams, 1998; Koeter & Ormel, 1991). Some 43.6% of the refusers agreed to do this. These nonresponders were found to have a slightly lower average GHQ score (that is, to be in better mental health) than the respondents (1.16 versus 1.22). But their psychiatric morbidity, estimated with the aid of a logistic regression model (GHQ score, sex, age and urbanity as the predictors), did not significantly differ from that of the respondents.

At T_1, 1458 respondents (20.6%) were lost to attrition and at T_2, a further 822 (14.6%) were lost. 4796 Respondents were interviewed at all three waves. Psychopathology did not have a strong impact on attrition: at T_1 12-months agoraphobia (odds ratio (OR), 1.96) and social phobia (OR, 1.37), and at T_2 12-months major depression (OR, 1.37), dysthymia (OR, 1.80) and alcohol dependence (OR, 1.83), adjusted for demographic factors, were associated with attrition (de Graaf et al, 2000a; de Graaf et al, 2000b).

1.5.2 Instruments

Prevalence, incidence and course of psychiatric disorders:

The diagnoses of psychiatric disorders in NEMESIS at T_0, T_1 and T_2 were based on DSM-III-R (APA, 1987). The instrument used to determine the diagnoses was the ***Composite International Diagnostic Interview (CIDI)*** Version 1.1 (computerised version) (Smeets & Dingemans, 1993). The CIDI is a structured interview developed by the World Health Organization (WHO) (WHO 1990; Robins et al, 1988) on the basis of the Diagnostic Interview Schedule (DIS) and the Present State Examination (PSE). It was designed for use by trained interviewers who are not clinicians. The CIDI 1.1 has two diagnostic algorithms to compute diagnoses according to the criteria and definitions of both DSM-III-R and ICD-10. The CIDI is now being used world-wide (International consortium in Psychiatric Epidemiology) and WHO field research has found high interrater reliability (Wittchen et al, 1991; Cottler et al, 1991), high test-retest reliability (Semler et al, 1987; Wacker et al, 1990) and acceptable validity (Semler 1989; Spengler & Wittchen 1989; Janca et al, 1992; Leitmeyer 1990; Farmer et al, 1987; Farmer et al, 1991; Wittchen et al, 1989; Wittchen 1994), with the exception of acute psychotic symptoms, which are difficult to ascertain in a structured interview (Helzer et al, 1985; Anthony et al, 1985). In NEMESIS, clinical reinterviews were administered whenever psychotic symptoms were evident, using questions from the Structured Clinical Interview for DSM-III-R (SCID), an instrument with proven reliability and validity for the diagnosis schizophrenia (Spitzer et al, 1992). The NEMESIS diagnoses of schizophrenia and other non-affective psychotic disorders at T_0 are based on the data from these clinical reinterviews. The following DSM-III-R diagnoses were recorded in the NEMESIS dataset: mood disorders (depression, dysthymia, bipolar disorder), anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalised 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. To all respondents aged 55 and older the ***Mini Mental State Examination (MMSE)*** (Folstein et al, 1975) was also administered, which can detect the presence of disorders of cognitive function. However, no cases at all were encountered that reached the threshold value (which would have resulted in terminating the interview). Next to the CIDI a **Life Chart Interview** (LCI; Lyketsos et al, 1994) was introduced at T_2 to assess duration of psychopathology retrospectively. The LCI was designed to obtain information on several aspects of personal history intertwined with the course of psychopathology. The method draws from the literature on autobiographical memory and uses age- and calendar-liked landmarks and life change anchors to prime recall. The LCI proved practicable and useful (Eaton et al, 1997) and the test-retest and interrater reliability of a similar life chart instrument were satisfactory (Hunt & Andrews, 1995).

Determinants of the development and course of mental disorders:
Socio-demographic factors were assessed at T_0 (and re-assessed on changes at T_1 and T_2): age, gender, urbanicity of place of residence, educational attainment, employment status and cohabitation status.
Personality characteristics were assessed at T_0, T_1 and T_2: neuroticism was assessed with the ***Groninger Neuroticism Questionnaire*** containing 14 items (Ormel, 1980). Locus of control was assessed with the 5-item ***Mastery Scale*** (Pearlin & Schooler, 1987), with high scores on mastery corresponding to an internal locus of control.
Psychosocial factors: Childhood experiences of emotional neglect, emotional or physical abuse or sexual abuse before age 16 were recorded at T_0. Life events were recorded at T_0, T_1 and T_2 using a ***questionnaire developed from the Life Events and Difficulties Schedule (LEDS)*** (Brown & Harris, 1987). It covered nine positive and nine negative life events and three ongoing difficulties. The life events were classified as changes in health status, changes in employment status, changes in important relationships, changes in the family, changes in social contacts, traumatic experiences (all the above events being experienced by either the respondent or a significant other); changes in living conditions, expected changes in the future, and attainment or non-attainment of an important goal (events experienced by the respondent only). The ongoing difficulties were classified as relationship problems, conflicts at work/school or other difficulties including financial problems. The respondents' subjective experience of the life events and ongoing difficulties was used as a variable. The subjective experience of social support was measured at T_0, T_1 and T_2 by the ***Social Support Questionnaire for Satisfaction with the supportive transactions (SSQS)*** (Suurmeijer et al, 1996; Doeglas et al, 1996) with 23 items.
Physical illness was assessed at T_0 and T_2 with a questionnaire listing 31 mostly chronic somatic conditions.

Consequences of mental disorders:
Functional disability was measured at T_0, T_1 and T_2 by the ***Short Form-36 Health Survey (SF-36)*** (Ware & Sherbourne 1992; Ware et al, 1997). Good reliability and validity of the instrument are reported (McHorney et al, 1993; McHorney et al, 1994; Burke et al, 1995; Aaronson et al, 1998). The SF-36 includes 36 items that form eight scales. The scoring was done according to the guidelines of Ware & Sherbourne (1992). The scale physical functioning (10 items) pertains to limitations as a result of health problems on such daily activities as going up and down stairs, bathing, getting dressed and lifting shopping bags. The scales role limitations (physical problem*)* (4 items) and role limitations (emotional problems*)* (3 items) measure problems with work or other daily activities in the past four weeks as a consequence of physical health problems and emotional problems respectively. The scale vitality (4 items) pertains to feelings with regard to energy and tiredness. The scale social functioning (2 items) pertains to limitations on such social activities as visiting friends and family. The scale pain (2 items) measures the amount of bodily pain and limitations as a result of it. The scale general health perception (5 items) measures the individual's subjective evaluation of his or her general health. The scale mental health (5 items) pertains to feelings of depression or nervousness during the past four weeks.
Care utilisation was asked for at T_0 for the past year, at T_1 (for the period between T_0 and T_1) and at T_2 (for the period between T_1 and T_2). Both professional care (primary

care and specialised mental health care) as informal care (e.g. an alternative care provider, traditional healer, self-help group, telephone helpline) were asked for.

1.6 Aims of the study and structure of the thesis

The following research questions were formulated:

1. What is the duration of MDE and the rate of chronic duration of MDE in the general population?
2. What are the determinants of (chronic) duration of MDE in the general population?
3. What are the consequences of a longer duration of MDE in daily functioning in the general population?
4. What is the association between clinical features of major depression, care utilisation and outcome in the general population?

Based on the initial literature review (chapter 2), our hypothesis were:

1. Duration of MDE is shorter and prevalence of chronicity is lower in the general population compared to clinical populations.
2. Life events and social support are more and illness-related factors are less important as determinants of duration in the general population compared to clinical populations.
3. Longer duration of MDE lead to more functional disability in the general population.
4. Use of professional care is more likely in individuals with more severe MDEs and/or with longer duration but the outcome of care is less favourable compared to individuals with milder and briefer MDEs.

The thesis will follow the chronological development of the research. We started with a review of the literature on predictors of chronicity of major depression (chapter 2). Next, we performed the first two studies with the data of T_0 and T_1. In chapter 3 the determinants of one-year poor outcome of DSM-III-R major depression in the general population were examined. This study was a replication of an earlier general population study (Sargeant et al, 1990) but with an extension to potential determinants of poor outcome. The purpose of this study was to find the relevant determinants of the course of major depression in the general population. In chapter 4 care utilisation and outcome of care of DSM-III-R major depression in the general population were analysed. The aim of this study was to examine the association of clinical features of major depressive disorder with care utilisation and outcome of care in the general population.
Next, three studies were performed with the data of T_0, T_1 and T_2. In chapter 5 duration of newly originated MDEs over a period of two years was studied and in chapter 6 determinants of duration of MDEs were analysed, using the 'dynamic stress-vulnerability model' as a conceptual framework. In chapter 7 the consequences of longer duration of MDEs were examined, by analysing the association between duration of MDEs and functional disability.
In chapter 8 the main results of the study will be discussed and the possible implications for clinical practice, mental health policy and future research will be given.

Notes: figures are taken from *[1] Beekman & Ormel, 1999; *[2] McCullough, 2000; *[3]Ormel & Neeleman, 2000.

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CHAPTER 2

Predictive factors for chronicity of depression
A literature review

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Summary
This is a literature review of factors that predict chronicity (duration: two years) in major depressive episodes in adult populations. A chronic course develops in 9% to 19% of depressed patients. The most prominent predictors of chronicity are illness-related factors: duration and severity of the depressive episode, number of previous episodes, and comorbidity (with somatic disorders, alcohol addiction, anxiety disorders and possibly dysthymia). Premorbid neuroticism and lower socioeconomic status also predict chronicity. Life events have not been shown to predict chronicity, and the effects of social support and interpersonal problems remain unclear. There is evidence that early treatment with antidepressant medication is effective in preventing chronicity, particularly for high-risk patients.

Introduction

Depression was long regarded as a disorder with a benign course of illness. Most episodes of depression were thought to be transitory. Such beliefs were strongly informed by the work of Kraepelin, who emphasised the favourable prognosis of the manic-depressive disorder in comparison to schizophrenia. Therapeutic optimism received a further boost from the introduction of antidepressant medications in the 1950s (Paykel, 1994). Yet depressive disorders frequently take a chronic course, and this has come into increasing focus in recent decades (van den Hoofdakker & Ormel, 1987; Scott, 1988; Keller, 1994a,b). The present article reviews the literature on depression to identify factors that can predict a chronic course in adults. It considers the implications these may have for treatment and points out areas that need further study.

Chronic depression refers here to the chronic form of the unipolar major depressive disorder (major depression) as defined by the Diagnostic and Statistical Manual IV (DSM-IV, American Psychiatric Association APA, 1994). For our literature study we additionally examined depressions diagnosed with other classification systems such as DSM-III and DSM-III-R (APA, 1980, 1987), the International Classification of Diseases (ICD) Versions 9 and 10 (World Health Organization, 1978, 1992), the Research Diagnostic Criteria (RDC; Spitzer et al, 1978) and the Bedford College Criteria (BCC; Finlay-Jones et al, 1980).

The course of a major depressive episode is highly varied. Often no full recovery is made, but the depressive symptoms merely ease (partial remission). An estimated 40%-60% of all adequately treated depressions achieve full remission, 30% achieve partial remission and 20% show no improvement at all (Fawcett, 1994; Cornwall & Scott, 1997). It is important to adequately define the terms recovery, remission and partial remission. For this we refer to Frank et al (1991) and Prien et al (1991). The average duration of a depressive episode is six months (Angst, 1988). Chronic depression is variously defined as persisting for more than one year or more than two years, with a preference for the two-year definition (Angst, 1988). There is no consensus in the literature as to what criteria the course of a depressive episode must satisfy to be classified as chronic. DSM-IV defines chronic depression as a condition where the full criteria for a major depressive episode have been continuously met for two years or more. Scott (1988) and Keller et al (1986) additionally allow for a period of symptomatic ‘non-recovery’ during a two-year episode, so that a period of partial remission falls within their definition. A further

problem is that a reduction in the number and severity of symptoms frequently occurs within the course of depression, without any accompanying improvement in social and occupational functioning (Scott, 1988).
DSM-IV distinguishes two forms of chronic depression: a chronic major depressive episode and dysthymic disorder. The distinction lies mainly in the number of symptoms and in the persistence of the condition. A major depressive episode can also occur within the course of a dysthymic disorder, a condition known as double depression (Keller & Shapiro, 1982).

Method
The available research studies on the course of depressive illness suffer from a wide range of methodological problems that make them difficult to compare – dissimilar samples of patients, various definitions used to document the course of illness, different follow-up intervals and different instruments used to assess depression or its severity. An additional difficulty is that the various factors identified as determining the course of illness also influence one another, thus confounding the results (Maj, 1994). This article reports on a literature study based on PsychLit ®, Medline ® and Excerpta Medica ®, using the keywords 'chronic depression', 'major depression' and 'course'. We selected all articles since 1980 that met the following criteria: they dealt with (major) depression as defined by the criteria of DSM III/III-R/IV, ICD 9/10, RDC or BCC; they specified how the diagnosis was established; they assessed potential predictive factors with standardised instruments; they assessed the course of illness prospectively; they reported and analysed the dropout rate; they used a definition of recovery that specified the nature and severity of the symptoms and the duration of recovery; and they reported any relevant information about treatment. We identified a total of 58 articles and selected 8 of them that satisfied our criteria (see table). We will discuss these below, supplemented by information from several other studies that indirectly provided important data on the course of depression.

Results
We investigated many factors that could potentially be linked to a chronic course of depression. We will discuss the most important of these below, after first determining the prevalence of chronic depression.

Prevalence
For clinical populations, a prevalence of chronic depression (lasting at least two years) between 9% and 19% has been found (Keller et al, 1992; Scott et al, 1992; Brown et al, 1994; Ormel et al, 1993; Keller 1994a,b). This is consistent with earlier estimates made in overview articles based on older literature (Angst, 1988; Scott, 1988). The Collaborative Study of the Psychobiology of Depression (CDS) by the National Institute of Mental Health (NIMH) in the USA is the largest clinical study ever done on the course of (major) depression, examining 431 depressed patients at six-month intervals (Keller et al, 1982; Keller et al, 1992; Keller, 1994a,b; Hirschfeld et al, 1986; Coryell et al 1990; Coryell et al, 1994; Mueller et al, 1996). Of the patients with unipolar depression, 19% had not recovered after two years, 12% not after five years (Coryell et al, 1990) and 7% not after ten years (Mueller et al, 1996).
General population studies have not yet yielded any prevalence figures for chronic depression (at least two years' duration). Although its' prevalence in the community is believed to be lower than in treated populations (Kendler et al, 1997; McLeod et al,

1992), it is unclear whether the course of depression would be essentially different (Costello, 1990). Coryell et al (1994) found no difference in duration of depression between the CDS clinical sample and a non-clinical sample composed of patients' partners and family members and other control subjects recruited from the community – 60% recovered within six months and 70% within one year. Clearly this sample was not representative of the general population.

Demographic data

Although the prevalence of depressive disorders is known to be higher for women than for men (Blazer et al, 1994; Bijl et al, 1997), no gender differences have been found in clinical populations with regard to the risk of a chronic course (Zlotnick et al, 1996; Simpson et al, 1997). One population study did find women to be more at risk for chronic depression (one-year duration), but this effect was seen only above age 30 (Sargeant et al, 1990). An early age of onset has been implicated as a risk factor in a clinical population (Keitner et al, 1992) but not in the general population (Sargeant et al, 1990). In terms of socio-economic status, Keller et al (1992; 1994a,b) found an association between low income and chronicity for the CDS clinical population, and Sargeant et al (1990) linked a low level of education to chronicity in the general population.

Clinical features

A more severe episode of depression, expressed in numbers of symptoms (Sargeant et al, 1990) or in a need for hospitalisation (Keller et al, 1992; Keller, 1994a,b), has been found a predictor of persisting depression. A prior history of depressive episodes (Sargeant et al, 1990) or hospital admissions (Keitner et al, 1992) are other risk factors. However, the strongest of all predictors of chronicity appears to be the duration of previous episodes (Sargeant et al, 1990; Keller et al, 1992; Keller, 1994a,b). In other words, chronicity predicts chronicity.

Another key factor appears to be whether a depressive episode arises spontaneously or follows upon a somatic illness or another mental illness. The latter form, known as secondary depression, is more likely to take a chronic course than a primary episode (Coryell et al, 1994; Keller et al, 1992; Keller, 1994a,b). Comorbidity with somatic disorders (Keitner et al, 1992), with alcohol addiction (Mueller et al, 1994) and with anxiety disorders (Coryell et al, 1994) all increase the likelihood that depression will persist. The latter finding was also done by Ormel et al (1993) in a study of patients in general practice settings.

The CDS (Keller, 1994a,b) found a substantial overlap between dysthymia and major depression, with 26% of patients with RDC major depression having a concurrent dysthymic disorder. Interestingly, the group with double depression recovered faster from the depressive disorder than the group with major depression only, but the underlying dysthymic disorder persisted and relapse set in sooner. By contrast, the Medical Outcome Study (MOS; Wells et al, 1992) found a poorer prognosis for recovery from double depression and a general population study (Sargeant et al, 1990) found that depressive disorders in men lasted longer when comorbid with dysthymia. A comorbid dysthymic disorder thus appears to worsen the prognosis for major depression, by increasing the risk of either chronicity or recurrence. It should be noted that the diagnostic criteria for dysthymia have been modified over the years, making it difficult to interpret such findings accurately. In the studies cited, dysthymia was diagnosed under the DSM-III criteria, which allow major depression to precede

the dysthymic period, whereas DSM-III-R and DSM-IV would classify this not as dysthymia but as major depression in partial remission.

Personality factors

Once a depressive episode is in progress, it is often difficult to reliably determine the patient's premorbid personality, as trait and state characteristics become confounded (Katschnig & Nutzinger, 1988). There are indications, nonetheless, that premorbid 'neurotic personality traits', as assessed by the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975), predict a chronic course of major depression (Scott et al, 1992). It is also believed (see Scott 1998) that experiencing a depression can bring about personality changes. In the CDS, Shea et al (1996) assessed partners and family members of depressed patients together with other control subjects from the community twice in a six-year period. The 28 persons who experienced their first-ever depressive episode during this six-year period were compared to 528 persons who had never had a depression. Personality was assessed with a comprehensive series of questionnaires. Subjects who experienced a depression showed no personality changes after it, but they did have higher premorbid scores for introversion and emotional dependency. Although little research has been done yet on the chronicity of depression in relation to personality disorders as classified by DSM, there is some evidence that treatment response is poorer when depression coincides with a personality disorder (O'Boyle & Hirschfeld, 1994). This implies a greater risk of chronicity.

Life events and social support

No evidence was found in the selected studies for any effects of recent life events as predictors of chronicity, but we should note that different instruments were used to assess life events. One study of depressed women in treatment (Brown et al, 1994) did link a chronic course of depression to adverse childhood experiences (sexual or physical abuse or neglect) and to current interpersonal problems. These findings were confirmed for lower-class depressed women in an identical study in the community (Brown & Moran, 1994). Because both studies used depressions of long duration as an exclusion criterion, depressive episodes of recent onset were overrepresented. Keitner et al (1992) found that poor family relations had an adverse effect on the duration of depression. Keller et al (1992, 1994a,b) identified being married as a risk factor, whereby relationship quality was a possible influence. A study of depressed older patients and 23 depressed patients under age 65, who were followed for two years until recovery occurred, found a strong association in the younger group between low social support and the duration of the depressive episodes (Alexopoulos et al, 1996). By contrast, an investigation of the effects of psychosocial variables on the 15-month course of depression in 70 patients with severe and recurring depressive episodes found no relationship between social support or life events and the patients' recovery or relapse (Paykel et al, 1996). A group of 19 chronically depressed patients from the CDS sample was compared by Hirschfeld et al (1986) with 20 patients who recovered within one year, with the two groups matched on age, gender, primary versus secondary depression and prior duration of depression. Here again, neither life events nor social support showed any relation to the outcomes.

Biological factors
No biological factors have been shown to predict chronicity, but very little research has been done on this issue because chronically depressed people are often excluded from any such studies (Scott, 1988). Some evidence does exist that familial loading for mood disorders elevates the risk of chronicity (Scott, 1998; Kendler et al, 1997).

Treatment
There is an apparent connection between chronicity and undertreatment. Many chronically depressed patients receive no or inadequate treatment. In the CDS, many of the longest-term depressed patients had taken the lowest dosages of antidepressant medications (Keller, 1994a,b). Scott et al (1992), in their study of 55 hospitalised depressed patients, found the duration of the preceding period without treatment to be the strongest predictor of chronicity. On the basis of their findings, the authors advise early intensive treatment to prevent chronicity. Coryell et al (1994) found, on the other hand, that the group who sought treatment had the longest duration of depression. Their explanation is that people seek treatment for depression only when it persists for a longer period of time.

Discussion
Most of the studies we selected to review are still subject to some criticism. Some of the research samples are quite small (Scott et al, 1992; Ormel et al, 1993) or are not fully representative of the patient population. The CDS sample, for instance, contained only referrals to university centres, and the study by Brown et al (1994), was made up of women only. Several predictive factors for chronicity nonetheless emerge from these studies. These include the duration and the severity of depression, the number of previous depressive episodes, occurrence secondary to other conditions, and premorbid neuroticism. Comorbidity with somatic disorders, alcohol addiction, anxiety disorders and possibly dysthymia is also implicated. Although the role of the various demographic factors remains.
unclear, low social status does appear to be a factor. Whether life events have any influence is also unclear, and any links to social support or interpersonal problems needs to be confirmed in replication studies.
Although the preponderance of studies carried out on hospitalised patients may very well have influenced our findings, we nevertheless come to the hypothesis that clinical features of the illness itself (duration, severity, previous episodes, comorbidity) gradually increase in importance during a long-term course of unipolar depression, whereas psychosocial factors play a major part during the early course of the illness. Other research has also suggested that psychosocial factors are mainly an issue in depressive episodes of brief duration (McLeod et al, 1992). This is consistent with Post's (1994) kindling hypothesis, which holds that initial episodes of depression are triggered by psychosocial factors while later episodes arise more spontaneously, and with the notion of vulnerability (Ormel, 1997), which incorporates both clinical features and personality factors.
What implications does this have for therapeutic practice? On the basis of the studies that investigated effects of antidepressant treatments (Scott et al, 1992; Coryell et al, 1994), we conclude that prompt treatment at the onset of a depressive episode is urgently indicated for a substantial proportion of the depressed patients, especially for those who exhibit risk factors for chronicity. Any loss of time not only means

longer suffering for the patient but also appears to increase the risk of chronicity. The existing Dutch protocol for the treatment of depression (de Groot, 1995) can serve as a guideline. Yet not all depressed individuals necessarily need prompt treatment. Many depressive episodes remit spontaneously; if this happens within a short time, then a strategy of watchful waiting seems justified for such patients. Effective recognition both of these patients and of the patients who will not recover spontaneously is therefore essential. This will require further research both in clinical populations and in the community. Such research will also need to verify whether the prompt initiation of treatment in patients with an increased risk of a chronic course of depression can indeed prevent their illness from becoming chronic.

Table: Course and determinants of course of major depressive episodes.

	population	follow-up	diagnostic classification (1)	(major) depression (N)	course instrument (2)	drop-out	(major) depression > 1 year	(major) depression > 2 year	predictors for chronicity
Sargeant et al (1990) Epidemiologic Catchment Area Study (ECA)	general population	1 year	DSM-III	423	DIS	18.7%	19% poor outcome		female>30 year duration episode low education severity of episode previous psychiatric illness
Coryell et al (1994)	patients/ relatives /general population	6 year	RDC	575	LIFE	28%	30% non-recovery	15% non-recovery	
Ormel et al (1993)	primary care patients	3,5 year	Bedford College criteria	20	PSE	20%	21% non-remission	12% non-remission	comorbidity with anxiety disorders
Scott et al (1992)	inpatients	2 year	RDC	55	HRDS	11%	50% non-recovery	9% non-recovery	interval before treatment neuroticism
Keller et al (1992); Keller (1994a,b) Collaborative study of the Psychobiology of Depression (CDS)	in- and outpatients	2 year	RDC	431	LIFE	6%	30% non-recovery	19% non-recovery	severity of episode duration previous episodes secundary depression prior hospitalisation low income married
Keitner et al (1992)	inpatients	1 year	DSM-III	78	HRDS	10%	50% non-recovery		younger age of onset dysfunctional family prior hospitalisation comorbidity lenght hospitalisation
Brown et al (1994)	in-and outpatients (female)	2 year	Bedford College criteria	125	PSE	19%	41% non-remission	16% non-remission	adverse youth experiences interpersonal problems
Paykel et al (1996)	in- and outpatients	15 mnths	DSM-III-R	70	HRDS	9%	14% non-remission (15 mnths)		

(1) DSM = Diagnostic and Statistical Manual; RDC = Research Diagnostic Criteria
(2) DIS = Diagnostic Interview Schedule; LIFE = Longitudinal Interval Follow-up Evaluation; PSE = Present State Examination; HRDS = Hamilton Rating Scale for Depression:.

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CHAPTER 3

Determinants of poor one-year outcome of DSM-III-R major depression in the general population. Results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS)

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Summary
Objective *To investigate risk factors of poor one-year outcome of major depression in the general population and to compare the results with data from clinical populations.*
Method *Psychiatric diagnoses were determined in a representative sample (N = 7076) of the Dutch general population, using the Composite International Diagnostic Interview (CIDI) at baseline and 12 months later. A broad range of potential risk factors was evaluated.*
Results *28.3% of the depressed persons at baseline were depressed 12 months later. Younger age, severity of depression, longer duration of previous episodes, the presence of anhedonia and early awakening, external locus of control and multiple negative life events appear to be risk factors.*
Conclusion *Poor outcome of major depression is frequent in the general population. Largely the same risk factors are involved as in clinical populations.*

Introduction

In recent years attention has been focused on the poor outcome of depressive disorder in terms of relapse, recurrence or chronicity (1-3). Prospective studies on outcome of major depression have concentrated on relapse and recurrence (4-7), on chronicity (8-12) or either outcome (13,14). In other studies (15,16) no distinction between relapse, recurrence or chronicity was made. Several risk factors of poor outcome were identified and they can be categorised as follows:

1. Sociodemographic factors: lower socio-economic status was found a risk factor for chronicity (1,10); older age is associated with an increased risk for relapse (4) but younger age for recurrence (5). Female sex was found a risk factor for recurrences (7) but not for chronicity (17,18).
2. Clinical factors: younger age of onset and greater severity of illness are risk factors for chronicity (1,10,15); longer length of depressive episodes for recurrences and chronicity (1,7,10) and higher number of previous episodes for relapses, recurrences and chronicity (1,4-7,10). Comorbidity with alcohol dependence was found a risk factor for chronicity (14), with somatic illnesses and anxiety disorders for poor outcome (15, 16), and with dysthymia (1,4) for relapse, recurrence and chronicity.
3. Personality characteristics: higher neuroticism is a risk factor for chronicity (9).
4. Psychosocial factors: more negative childhood experiences and more ongoing difficulties were associated with chronicity (11). An influence from other negative life events on relapse or chronicity was not found (13) and the findings on social support on chronicity are contradictory (8,12,13).
5. Treatment factors: length of period before antidepressant treatment was found a risk factor for chronicity (9). Undertreatment with antidepressants has been linked up with relapse, recurrence and chronicity (1) but in observational studies no causal relations between treatment and outcome can be made.

Our conclusion from these studies is that risk factors for relapse, recurrence and chronicity do overlap but are probably not identical. Clinical factors appear to be the strongest predictors of poor outcome of depression (19). However, clinical populations (both inpatient and outpatient) were overrepresented in these studies in question. The only population-based study with a prospective design and using a

standardised diagnostic interview (the Diagnostic Interview Schedule (DIS) (20)), is the Epidemiologic Catchment Area (ECA) study (21). This study found a one-year non-recovery of 23.5% and some clinical factors (greater severity, greater length of previous episodes) and sociodemographic factors (lower level of education, women above 30 years) were found to be associated with poor outcome. Psychosocial factors were not assessed in this study.
The study we report here on is the first one to relate the one-year outcome of DSM-III-R major depression in a representative sample of the general population to a broad range of potential risk factors: sociodemographic factors, clinical factors, personality characteristics and psychosocial factors (negative childhood experiences, positive and negative life events, ongoing difficulties and social support). We aim to verify the findings of the ECA study regarding rate of poor outcome in the general population but we also had the opportunity to gain a more comprehensive understanding of risk factors of poor outcome. Our expectation is that in the general population psychosocial factors will have a stronger influence on the adverse outcome of major depression than in clinical populations.

Material and Methods

Sampling

Data have been derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (22,23). NEMESIS is a prospective survey in the Dutch adult general population (aged 18 to 64). The analyses presented here are based on data from the first and second wave in 1996 and 1997. NEMESIS is based on a multistage, stratified, random sampling procedure. The first step of this large longitudinal study was to draw a sample of 90 Dutch municipalities. The stratification criteria were urbanicity (5 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 them to take part. 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 he or she was 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 hospitalisation, 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.
To optimise response and to compensate for possible seasonal influences, we spread the initial fieldwork over the entire period from February through December 1996. No adjustments had to be made to the procedure in the course of the fieldwork, and hence no supplemental respondents were drawn from specific social groups. On 7076 persons sufficient data were gathered, a response rate of 69.7% (22).

Diagnostic instrument
Diagnoses of psychiatric disorders according to DSM-III-R (24) are based on the Composite International Diagnostic Interview (CIDI), Version 1.1 (computerised version) (25). The CIDI is a structured interview developed by the World Health Organization (26) and has been found to have high interrater reliability and high test-retest reliability for most diagnoses (27). The following DSM-III-R diagnoses were recorded in the NEMESIS dataset: schizophrenia and other non-affective psychotic disorders, mood disorders (bipolar disorder, major depression, dysthymia), anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalised anxiety disorder, obsessive-compulsive disorder), eating disorders and psychoactive substance use disorders (alcohol or drug abuse and dependence, including sedatives, hypnotics and anxiolytics). We present data recorded at baseline (T_0) in 1996 and at the first follow-up 12 months later (T_1). As in the ECA study (21) we defined a poor outcome of depression as meeting the criteria for DSM-III-R major depression both in the six-month period preceding T_0 and in the six-months preceding T_1. As the CIDI obtains no information on the course of disorder between two assessments it is actually not possible to differentiate between a relapsing, recurrent or chronic course. Prevalence rates were calculated using the hierarchical rules of the DSM, thus excluding major depressive episodes occurring in schizophrenic and other psychotic disorders or in bipolar disorders.

Potential risk factors
Independent variables assessed at baseline (T_0) in the study were as follow:
Sociodemographic factors. Gender, age, educational attainment, household situation and employment status.
Clinical factors. Using the CIDI, we obtained information on the following: age of onset, categorised as early (≤18 years) or late (> 18 years); severity of depression, categorised according to DSM-III-R; type of symptoms (CIDI-items were grouped according to the nine DSM-III-R A-criteria for major depressive episode plus three additional melancholic symptoms: anhedonia, early morning awakening [> 2 hours] and diurnal variation); recurrent episodes (with recovery between episodes of at least 2 months), categorised yes or no; mean duration of previous episodes, categorised as brief (≤ 24 weeks) or long (> 24 weeks); previous psychiatric hospitalisations; and comorbidity with other DSM–III-R axis I disorders. In order not to exclude any disorder, we calculated psychiatric comorbidity using the six-month prevalences without applying the hierarchical DSM rules. The comorbid disorders we deemed relevant were substance dependence, anxiety disorders, dysthymia and eating disorders. Comorbidity with somatic illnesses was assessed by means of a questionnaire listing 31 mostly chronic somatic conditions. Respondents were also asked whether they had received treatment for any of these conditions in the preceding 12 months.
Personality characteristics. Neuroticism was assessed with the Groninger Neuroticism Questionnaire containing 14 items (28). The internal reliability of the questionnaire in our research cohort was satisfactory (Cronbach's $\alpha = 0.72$). Locus of control was assessed with the 5-item Mastery Scale (29), with high scores on mastery corresponding to an internal locus of control. The internal reliability of this

questionnaire in our research cohort was satisfactory (Cronbach's α = 0.79). The outcomes of both scales were categorised as high, medium or low.
Psychosocial factors. 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 categorised as 'never or once' versus 'more than once' and the answers for sexual abuse as 'never' versus 'at least once'.
In addition to the above-mentioned factors at T_0 we evaluated several psychosocial factors measured at T_1. Life events were recorded on a questionnaire developed from the Life Events and Difficulties Schedule (LEDS) (30). It covered nine positive and nine negative life events and three ongoing difficulties in the period between T_0 and T_1. The life events were classified as changes in health status, changes in employment status, changes in relationship, changes in the family, changes in social contacts, traumatic experiences (all the above events being experienced by either the respondent or a significant other); changes in living conditions, expected changes in the future, and attainment or non-attainment of an important goal (events experienced by the respondent only). The ongoing difficulties were classified as relationship problems, conflicts at work/school or other difficulties including financial problems. The respondents' subjective experience of the life events and ongoing difficulties was used as a variable. The outcome was categorised as 0, 1-2 or ≥ 3 for positive events, and as 0, 1, or ≥ 2 for negative events and ongoing difficulties.
The subjective experience of social support between T_0 and T_1 was measured by the Social Support Questionnaire for Satisfaction with the supportive transactions (SSQS) (31,32) with 23 items. The internal reliability of the SSQS in our research cohort was high (Cronbach's α = 0.91). The outcome was categorised as low, medium or high.
Finally, at T_1 the respondents were asked whether they had sought *professional help* for their depressive complaints in the past 12 months; categorized as 'yes'or 'no'. The sources of care included informal care (for instance physiotherapist/haptonomist, alternative care provider, self-help group), primary care, ambulatory mental health care and residential mental health care.

Data analysis
Unadjusted odds ratio's (OR) and their 95% confidence intervals (95% CI) were calculated by means of logistic regression analyses in SPSS 8.0, with depression status (yes/no) at T_1 as outcome variable. All variables found to be significantly correlated ($p \leq 0.05$) with depression status at T_1 in the bivariate analyses were entered into the multiple regression analysis (method backward). We also carried out analyses with probability weights in STATA version 5.0 to evaluate the effects of attrition; the results did not diverge significantly on relevant outcomes, so we report only the results of the unweighted analyses.

Results
Rate of poor outcome
At T_0, 305 persons met the criteria for a major depression in the preceding six months. At T_1, 72 of them (23.6%) had been lost to attrition. In 10 cases

schizophrenia or bipolar disorder was diagnosed and those were excluded. Of 223 who remained, 63 (28.3%) met the criteria for major depression in the preceding six months and 160 (71.7%) did not. Of those 160,
48 (30%) still had one or more other diagnoses at T_1: eating disorder (1), dysthymic disorder (2), substance abuse or dependence (19) and anxiety disorder (36). In 43 of these cases this diagnosis had already been present at T_0 as an comorbid diagnosis.

Effects of attrition
The attrition (23.6%) in the research cohort was only slightly higher than that in the total sample (20.6%). In the total sample, attrition was only weakly associated with psychopathology at baseline, but not with depression (33).

Risk factors
Table 1 shows all potential risk factors of poor outcome with the outcomes of the bivariate analysis. Only two sociodemographic factors were found to be associated with poor outcome: female gender and unemployement. Amongst the clinical factors severity of depression, and especially depression with psychotic features, was strongly associated with poor outcome. At the symptomatic level, psychomotor agitation or retardation, anhedonia and early morning awakening showed significant relations to poor outcome. Comorbidity with dysthymia and with anxiety disorders did appear to constitute a higher risk. The latter association is attributable to generalised anxiety disorder (GAD) (OR 2.46, 95% CI 1.26-4.80), social phobia (OR 2.06, 95% CI 1.03-4.11) and simple phobia (OR 3.05, 95% CI 1.61-5.77) (not in table). Comorbidity with eating disorders, substance dependence and somatic illnesses were not significantly related to an adverse course.
Of the personality characteristics assessed, high neuroticism was found to be strongly associated with poor outcome and medium and high levels of mastery reduced the risk of a poor outcome almost equally. Both neuroticism and mastery were correlated with the severity of depression at baseline (neuroticism: Pearsons r = 0.26, $p \leq 0.01$; mastery: Pearsons r = 0.22, $p \leq 0.01$). Amongst the psychosocial factors, adverse childhood experiences were not found to be associated with a poor outcome, but the subjective experience of two or more negative life events and one or more ongoing difficulty between T_0 and T_1 was associated with an adverse course. Interestingly, the subjective experience of a medium level of social support but not a high level, was associated with a favourable effect on course. We next performed two multiple regression analyses on the variables found significant in the bivariate analysis, correcting for age and gender. In the first analysis we included variables measured at T_0 only (model 1). To limit the number of variables we transformed age into a continuous variable (unadjusted OR 0.98, 95% CI 0.96-1.01) and severity of depression into a dichotomous variable (mild and moderate versus severe with or without psychotic features) (unadjusted OR 3.47, 95% CI 1.89-6.38). Age was now found to be significantly associated with poor outcome, with the risk decreasing the higher the age (table 2). Unemployment and gender were lost in the model. Several clinical factors remained in the model but comorbidity with dysthymia and with anxiety disorders were lost, probably because of their correlation with severity of depression (comorbid anxiety disorders: Pearson r = 0.34, $p \leq 0.01$; comorbid dysthymia: Pearson r = 0.20, $p \leq 0.01$). Personality factors (represented by mastery) remained,

with medium and high levels of mastery associated with a favourable outcome. Neuroticism was lost, probably because of its strong negative correlation with mastery (Pearson r = -0.57; $p \leq 0.01$).
Our second model also included those psychosocial factors recorded at T_1 that were found significant in the bivariate analysis, namely negative life events, ongoing difficulties and social support. The subjective experience of multiple negative life events was found to be strongly associated with poor outcome (table 2). Ongoing difficulties were lost in the model, probably because of their correlation with negative life events (Pearson r = 0.38 ; $p \leq 0.01$). The effect of social support reversed in comparison with the bivariate analyses, but did not reach significance level, probably because of the positive correlation between mastery and social support (Pearson r = 0.27; $p \leq 0.01$).

Use of professional care
At T_1 79 of the respondents had had some form of professional care in the preceding 12 months. As expected, in bivariate analysis the use of professional care was strongly associated with poor outcome (OR 8.27, 95% CI 4.29-15.93) and professional care was correlated with several clinical factors at baseline like severity of depression (Pearson r = 0.32; $p \leq 0.01$), comorbid dysthymia (Pearson r = 0.18; $p \leq 0.01$) and comorbid anxiety disorder (Pearson r = 0.20; $p \leq 0.01$). When we added use of professional care to the second model of the multiple regression analysis, this factor remained as the strongest predictor of poor outcome and severity of depression was lost in this model as a result of the correlation between use of professional care and severity of depression. As we were primarily interested in the predictors of the natural course of depression we decided not to include use of professional care in the final model.

Table 1: Potential risk factors of poor outcome of major depression: unadjusted odds ratio's (OR) and 95% confidence intervals (95% CI).

Variable	N = 223	OR	95% CI
Sociodemographic factors			
Gender (Female)	144	**2.13**	**(1.10-4.13)**
Education			
Low	62	1.33	(0.60-2.95)
Medium	91	0.93	(0.44-1.98)
High	14	0.71	(0.17-2.90)
University	54	1	
Age			
18-24	15	1.36	(0.34-5.39)
25-34	58	1.32	(0.47-3.69)
35-44	71	1.06	(0.39-2.92)
45-54	53	0.79	(0.27-2.33)
55-64	26	1	
No partner	106	1.20	(0.67-2.15)
No employment	96	**2.22**	**(1.23-4.02)**
Clinical factors			
Recurrence	100	0.82	(0.45-1.47)
Onset before 18 years	44	1.08	(0.52-2.23)
Duration previous episodes (long)	121	**2.76**	**(1.47-5.18)**
Previous hospitalisations (yes)	19	2.50	(0.96-6.48)
Severity of depression			
Mild	84	1	
Moderate	49	1.28	(0.52-3.17)
Severe	68	**3.09**	**(1.46-6.58)**
With psychotic features	22	**7.22**	**(2.59-20.14)**
Symptoms			
Depressed mood	208	2.69	(0.59-12.30)
Loss of interest	182	2.16	(0.90-5.16)
Sleep disturbances	213	0.57	(0.16-2.11)
Changes in appetite	168	1.79	(0.86-3.75)
Fatigue	203	1.64	(0.53-5.11)
Agitation/retardation	102	**2.08**	**(1.15-3.76)**
Worthlessness/guilt	174	1.47	(0.70-3.10)
Suicidality	181	1.86	(0.81-4.27)
Cognitive disturbances	206	-	
Anhedonia	146	**3.32**	**(1.61-6.83)**
Early morning awakening	84	**2.35**	**(1.30-4.27)**
Diurnal variation	148	0.84	(0.45-1.54)
Comorbidity			
Dysthymia	72	**2.81**	**(1.54-5.14)**
Anxiety disorders	117	**3.78**	**(1.98-7.21)**
Eating disorders	2	2.56	(0.16-40.64)
Substance dependence	23	1.74	(0.71-4.25)
Somatic illnesses	117	1.42	(0.78-2.57)

- : could not be estimated due to collinearity.

Table 1: Potential risk factors of poor outcome of major depression: unadjusted odds ratio's (OR) and 95% confidence intervals (95% CI) (continued)

Variable		N = 223	OR	95% CI
Personality characteristics				
Neuroticism				
Low		66	1	
Medium		76	1.67	(0.73-3.82)
High		81	**3.44**	**(1.57-7.53)**
Mastery				
Low		84	1	
Medium		82	**0.31**	**(0.15-0.62)**
High		57	**0.27**	**(0.12-0.61)**
Psychosocial factors				
Negative youth experiences		133	1.85	(0.99-3.44)
Positive life events	0	77	1	
	1-2	79	1.09	(0.55-2.17)
	≥ 3	67	0.85	(0.41-1.78)
Negative life events	0	84	1	
	1	72	1.89	(0.89-4.03)
	≥ 2	67	**3.10**	**(1.48-6.52)**
Ongoing difficulties	0	117	1	
	1	75	**2.88**	**(1.49-5.59)**
	≥ 2	31	**3.30**	**(1.40-7.77)**
Social support				
Low		92	1	
Medium		70	**0.25**	**(0.11-0.54)**
High		61	0.53	(0.26-1.07)

Bold = significant $p \leq 0.05$

Table 2: Potential risk factors of poor outcome of major depression. Multivariate regression analysis (method = backward), adjusted odds ratio's (OR) and 95% confidence intervals (95% CI): model 1(baseline variables) and model 2 (baseline variables and variables measured at T_1).

Variable		Model 1*[1]		Model 2*[2]	
		OR	95% CI	OR	95% CI
Sociodemographic factors					
Age (continuous)		0.95	(0.92-0.99)	**0.94**	**(0.90-0.97)**
Gender (female)		**- -**		- -	
No employment		**- -**		- -	
Clinical factors					
Duration previous episodes (long)		2.52	(1.21-5.20)	**3.50**	**(1.56-7.89)**
Severity of depression (severe / with psychotic features)		2.12	(1.05-4.27)	**2.25**	**(1.03-4.90)**
Agitation/retardation		**- -**		- -	
Anhedonia		2.58	(1.16-5.76)	**2.88**	**(1.21-6.86)**
Early morning awakening		2.94	(1.40-6.21)	**3.27**	**(1.45-7.42)**
Comorbid dysthymia		**- -**		- -	
Comorbid anxiety disorders		**- -**		- -	
Personality characteristics					
Neuroticism					
Low		**- -**		- -	
Medium		**- -**		- -	
High		**- -**		- -	
Mastery					
Low		1		1	
Medium		0.30	(0.14-0.67)	**0.24**	**(0.10-0.59)**
High		0.39	(0.16-0.94)	0.51	(0.19-1.37)
Psychosocial factors					
Positive life events	0			- -	
	1-2			- -	
	≥ 3			- -	
Negative life events	0			1	
	1			2.12	(0.83-5.43)
	≥ 2			**5.69**	**(2.12-15.24)**
Ongoing difficulties	0			- -	
	1			- -	
	≥ 2			- -	
Social support					
Low				1	
Medium				1.30	(0.54-3.15)
High				0.41	(0.14-1.17)

Bold = significant $p \leq 0.05$; - - = variable was lost in the multiple regression analysis.
*[1] the 'explained' variation of model 1 is Nagelkerke $R^2 = 0.30$.
*[2] the 'explained' variation of model 2 is Nagelkerke $R^2 = 0.41$.

Discussion

What are the major results of this study? A poor one-year outcome of major depression is frequent in the general population; 28.3% of those with a major depression at baseline are still (or again) depressed after one year and this is higher than the 23.5% found in the ECA study (21). Comparing our results with the ECA study, we found, next to clinical factors, also personality characteristics as important risk factors for a poor outcome; just as in clinical populations. In addition, the influence of multiple negative life events also appears considerable. This suggests that depressed individuals in the general population are basically subject to the same risk factors of poor outcome as clinically (i.e. identified) depressed patients. One might postulate a certain vulnerability conferred by characteristics of depression (severity, duration and melancholic symptoms) in conjunction with personality characteristics.

Notably, several variables were less prominent in our study than in studies of clinical populations. We found no relation between socio-economic status and poor outcome nor between comorbidity with somatic illnesses and poor outcome. The latter could reflect a phenomenon in the general population, but it could also indicate that the measurement for the somatic condition was inadequate. A new and clinically relevant finding is that the melancholic symptoms anhedonia and early morning awakening are prognostic for a unfavourable course of depression. The presence of psychotic features also appears to be a risk factor, as has previously been noted (34).

Personality characteristics were found to have a considerable influence on the course of depression, but their role is complicated by the fact that they were assessed at baseline and were correlated with severity of depression. Thus, the question is whether one is assessing personality characteristics, aspects of depression or both - the state / trait issue (35).

Psychosocial factors were not as prominent as expected. Our results suggest that adverse childhood experiences do not contribute much to an adverse course. This is in contrast with earlier results (36), but in agreement with later studies by the same group (37). An alternative explanation is that our method may be inadequate for assessing childhood experiences. We also found that neither social support nor positive life events are sufficient to prevent an adverse course, and that multiple negative life events had a strong negative influence. Other research has noted a strong influence of negative as well as positive life events on the course of milder forms of depression [see for an overview Jenaway & Paykel (38)]. We would like to stress, though, that the apparent effects of social support, life events and ongoing difficulties in our design must be interpreted with caution. Their status in the course of a disorder is complex. We assessed social support, life events and ongoing difficulties at T_1, - that is, the situation between at T_0 and T_1 – and the question therefore arises whether these are risk factors for an unfavourable outcome or consequences of the disorder. Or more specifically, do negative life events contribute to an adverse course of depression or do depressed individuals generate more negative life events, as proposed by the stress generation hypothesis (39)? The latter hypothesis has been confirmed for recurrent depression (40) but there are no conclusive data for chronic depression.

Treatment is an even more complex issue in studying outcome of depression in a naturalistic design because of its strong confounding influence (1,4,18). The

relationship between the severity and duration of depression and the entering of treatment has been firmly established (41) and we found the same association between clinical factors and care utilisation.
There are some limitations in this study. In the first place we were not able to differentiate between a relapsing, recurrent or chronic one-year course. Although this hampers the comparison with the results of clinical studies, we conclude that most of the risk factors we found, were associated with chronicity in previous research (1,9-11), suggesting that poor outcome in our study consists predominantly of chronicity of depression. In future research however, the course of any psychiatric disorder in the general population should be followed with a more sophisticated instrument. Secondly, in the NEMESIS sample homeless and chronically institutionalised people are not represented, so the most serious and incapacitating forms of psychopathology are probably underrepresented. This probably decreases the rate of poor outcome. Thirdly, the questionnaires for the assessment of somatic comorbidity, childhood experiences and life events and ongoing difficulties were all developed for the present large-scale population survey and they need further validation.

What are the possible clinical implications of our results? Depressed patients who are at risk of poor outcome - those with younger age, severe depression, melancholic symptoms (anhedonia and early morning awakening), longer duration of previous episodes, external locus of control – deserve extra attention from their doctors. Strategies have been recommended to improve outcome like swift start of adequate treatment and continuation of this treatment (42). Hopefully, these strategies will improve the prognosis of major depression.

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CHAPTER 4

Care utilisation and outcome of DSM-III-R major depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS)

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Summary
Objective *To assess care utilisation, individual characteristics, and clinical and functional outcomes for various modalities of professional care in people with DSM-III-R major depression.*
Method *Psychiatric diagnoses were determined at baseline and 12 months follow-up in a representative sample (N = 7076) of the Dutch population, using the Composite International Diagnostic Interview (CIDI).*
Results *45.3% of the 223 individuals with major depression received professional care in the 12 months between baseline and follow-up, and 42.6% of these were treated with antidepressant medication. Higher level of care was associated with clinical factors and functional limitations. Clinical outcomes were poorly correlated with functional outcomes. Mild to moderate effects in functional outcome were found for all care modalities.*
Conclusion *Outcome of antidepressant treatment can be improved and such treatment should focus on the more severe forms of depression. Functional outcome assessment is recommended in addition to clinical assessment.*

Introduction

Depressive disorder is a widespread condition (1,2) that can cause serious functional impairment and reduced quality of life (3,4). Although treatment could do much to ease the consequences of depression, the condition is underrecognised in primary care (5) and it is undertreated with antidepressant medication in both primary care and specialised mental health care (6,7). International (8-10) and national (11) guidelines for the assessment and treatment of depression have been developed to enhance the quality of care for depressed individuals, and data on care utilisation and treatment outcome is now needed to evaluate their effects (12,13). Ideally, any reliable determination of treatment outcome should include an assessment of functioning, but most findings so far are based on depression status (14).
Thus, 12-months recovery rates of 50 to 70% have been reported for depressed inpatients and outpatients (15-18). Only fragmentary data is available on outcomes in primary care: in Seattle (USA) (19) and Groningen (the Netherlands) (5), 70% and 67% of baseline cases no longer qualified for major depression at 12-months follow-up. However, it is problematic to compare the outcome of depressed patients treated in different levels of care, because they have been found to differ considerably on socio-demographic variables (20) and clinical factors (21). The resulting selection bias can be overcome by analyzing general population samples. The present study draws on the baseline and 12-months data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a population-based cohort study of mental health. It addresses two basic questions:

1. What are the characteristics of persons with major depression who receive different modalities of professional care, i.e. primary care, mental health system care (MHS care), and antidepressant medication?
2. What are the clinical and functional outcomes for the differential care modalities?

Methods

The Netherlands Mental Health Survey and Incidence Study is a prospective study on the prevalence, incidence, course and outcome of psychiatric disorders in a representative sample (N = 7076) of the general population aged 18-64 (22). We have previously reported on our sampling procedure and response (23). The data presented here were recorded at baseline (T_0) in 1996 and at follow-up 12 months afterward (T_1). Diagnoses of DSM-III-R (24) psychiatric disorders were based on the Composite International Diagnostic Interview, Version 1.1 (computerised version) (25). The CIDI is a structured interview, developed by the World Health Organization (1990) (26), which has been found to have high interrater reliability, high test-retest reliability and high validity for most diagnoses (27). As described earlier (23), depression status at T_0 was defined as meeting the criteria for DSM-III-R major depression in the the 6-month period preceding T_0; depression status at T_1 was defined as meeting the criteria for DSM-III-R major depression in the 6 months preceding T_1. Prevalence rates were calculated using the hierarchical rules of the DSM, thus excluding major depressive episodes occurring in the course of schizophrenic and other psychotic disorders or bipolar disorders.

Characteristics of depressed individuals

Sociodemographic variables recorded at T_0 were gender, age, urbanicity of place of residence, educational attainment and employment status.

Clinical factors. Using the CIDI, we obtained information on the following dimensions of illness at T_0: severity of major depression, categorised in mild-moderate versus severe with or without psychotic features according to DSM-III-R; recurrent episode (with recovery between episodes of at least two months), categorised yes or no; mean duration of previous episodes, categorised as brief ($\leq$ 24 weeks) or long (> 24 weeks); and comorbidity with other DSM–III-R axis I disorders. In order not to exclude any disorder, we calculated psychiatric comorbidity using the six-months prevalences without applying the hierarchical DSM rules. For comorbid disorders we selected affective disorders (anxiety disorders and dysthymia). Comorbidity with somatic illnesses was assessed by means of a questionnaire listing 31 mostly chronic somatic conditions for which respondents had received treatment in the preceding 12 months.

Functional disabilities. Functional disabilities were assessed at T_0 and T_1 with the Short-Form-36 Health Survey (SF-36) (28,29). Good reliability and validity of this instrument have been demonstrated (30-33). The SF-36 consists of 36 items forming eight scales. The scoring was performed in accordance with the guidelines of Ware & Sherbourne (28) on a 0-100 scale, with 100 defined as maximum functioning. Because we were interested in role functioning, we used the scales “role limitations due to emotional problems” (3 items, Cronbach’s α = 0.79), which records problems with work or other daily activities in the previous four weeks as a consequence of emotional problems, and “social functioning” (2 items, Cronbach’s α = 0.71) which assesses limitations on social activities like visiting friends and relatives.

Care utilisation

The respondents were asked at T_1 whether they had received help for mental problems within the past 12 months. We distinguished three levels of care:

1. No care or exclusively informal care (e.g. from an alternative care provider, traditional healer, self-help group, telephone helpline, physiotherapist / haptonomist) or care provided by non-drug-prescribing professionals (company physician, social worker; home care worker/district nurse).
2. Primary care (general practitioner).
3. MHS care, including ambulatory mental health care (crisis care, community mental health care institute, psychiatric outpatient clinic at a psychiatric or general hospital, alcohol and drugs counselling centre, psychiatrist, psychologist or psychotherapist in private practice, psychiatric day care centre) and residential mental health care (psychiatric hospital, inpatient addiction clinic, psychiatric division of general hospital, sheltered accommodation).

In addition treatment with antidepressants was asked for by presenting the names of various frequently prescribed antidepressants as a reminder.
For the analysis, we combined level of care and use of antidepressants to distinguish five separate modalities of care: 1) no professional care, 2) primary care without antidepressants, 3) primary care with antidepressants, 4) MHS care without antidepressants, 5) MHS care with antidepressants.

Outcome assessment We used depression status at T_1 as our clinical outcome measure and changes in the two types of role functioning between T_0 and T_1 as our functional outcome measures.

Analyses
Univariate analyses were carried out using chi-square tests for cross-classified categorial variables, and t-tests and analysis of variance for continuous variables, to asses differences in depressed persons with different levels and modalities of care. Changes in role functioning were described using an analogy of Cohen's effectsize d (34) defined as:
$d_i = (x_{i0} - x_{i1})/ Sd\ x_{i0}$; where x_{i0} = role functioning at T_0, x_{i1} = role functioning at T_1 and Sd = standard deviation as measured at T_0. The interpretation of d is as follows: d = 0 (no effect), d = .20 (small effect), d = .50 (medium effect), d = .80 (large effect) (33).

Results
At T_0 305 persons met criteria for major depression in the preceding six months. At T_1 , 72 (23.6%) of them had been lost to attrition. In 2 cases schizophrenia and in 8 cases bipolar disorder was diagnosed and those cases were excluded. Of the remaining 223, 63 (28.3%) still or again met the criteria for major depression in the preceding six months and 160 (71.7%) did not.
The attrition (23.6 %) in the depression subcohort was only slightly higher than that in the total sample (20.6 %). Attrition was only weakly associated with psychopathology at baseline, and not with depression in the total sample (36) and the attrition in the depression subcohort was not associated with severity of depression, role dysfunctioning or care utilisation.

Care utilisation
Of the 223 persons with major depression at T_0, 101 (45.3%) had received some sort of professional care for their mental problems between T_0 and T_1; 51 (22.9%) received primary care only and 50 (22.4%) MHS care. The other 122 (54.7 %) did not receive professional help. Some 43 (42.6%) of the 101 persons who came in contact with professional care received antidepressant medication; 37.3% of those with primary care and 48.0% of those with MHS care took antidepressants. In primary care, 25 subjects had severe depression, 12 of whom took antidepressant medication. In MHS care, 32 had severe depression and 18 of them took antidepressants.
A higher level of care was significantly associated with more severe depression, more comorbid anxiety, longer duration of previous episodes, and poorer role functioning at T_0. The use of antidepressants was associated with not being employed, with more severe depression and more comorbid anxiety disorders (table 1).

Clinical and functional outcome in relation to care utilisation
Clinical outcome Substantial differences in outcome emerged for the different care modalities, with the best outcomes in non-treated subjects (table 2). Outcomes were poor for subjects treated with antidepressants, especially for those in MHS care.
Functional outcome At T_0, a pattern was evident whereby subjects without professional care functioned best and those treated with antidepressants in MHS care functioned worst. At T_1, improvement was found in all modalities of care, but the order of ranking was unchanged (table 2). Significant improvements in role limitations due to emotional problems were found in all modalities, except for primary care with antidepressants; significant improvements in social functioning were found for subjects without professional care, those in primary care without antidepressants and in MHS care without antidepressants. In the total study cohort no changes in functioning were found.
For both types of role functioning, moderate effects were observed in subjects treated in MHS care, comparable to the effects in those without professional care. The effects were slightly better for those treated in primary care without antidepressants, and slightly worse for those treated in primary care with antidepressants.
Low correlation's were found between clinical outcome and changes in social functioning (Pearson r = 0. 20) and moderate correlation's between clinical outcome and changes in role limitations due to emotional problems (Pearson r = 0.61).

table 1: Characteristics of individuals with major depression in different levels of care and with and without antidepressant medication.

	No care (1)	**Primary care (2)**	**MHS care (3)**		p	**No AD**	**AD**		p
	122	51	50			58	43		
Sociodemographic variables	%	%	%	X^2	p	%	%	X^2	p
Gender (female)	63.3	64.7	70.0	0.92	0.63	69.0	65.1	0.17	0.68
Age				14.29	0.08			2.03	0.73
18-24 years	7.4	3.9	8.0			5.2	7 .0		
25-34	28.7	11.8	34.0			24.1	20.9		
35-44	31.1	31.4	34.0			36.2	27.9		
45-54	21.3	33.3	20.0			25.9	27.9		
55-64	11.5	19.6	4.0			8.6	16.3		
Education				6.31	0.39			0.75	0.86
Low	27.3	28.0	30.0			28.1	30.2		
Medium	38.8	50.0	38.0			45.6	41.9		
High	7.4	8.0	2.0			3.5	7.0		
University	26.4	14.0	30.0			22.8	20.9		
Urbanicity (urban)	89.3	90.2	96.0	1.98	0.37	91.4	95.3	0.60	0.44
No partner	47.5	39.2	56.0	2.85	0.24	43.1	53.5	1.07	0.30
No employment	36.9	49.0	52.0	4.27	0.12	39.7	65.1	6.40	**0.01**
Clinical factors									
Severity depression (high)	27.0	49.0	64.0	22.18	**0.00**	46.6	69.8	5.41	**0.02**
Somatic comorbidity (yes)	45.9	62.7	58.0	4.88	0.09	56.9	65.1	0.70	0.40
Comorbid anxiety (yes)	44.3	49.0	76.0	14.64	**0.00**	43.1	88.4	21.56	**0.00**
Comorbid dysthymia (yes)	26.2	41.2	50.0	9.93	0.07	39.7	53.5	1.91	0.17
Duration previous episode (long)	47.5	56.9	68.0	6.16	**0.05**	55.2	72.1	3.01	0.08
Recurrence (yes)	45.9	41.2	46.0	0.36	0.84	48.3	37.2	1.23	0.27
Functioning T_0	mean (SD)	mean (SD)	mean (SD)	F	p	mean (SD)	mean (SD)	T	p
Role limitations due to Emotional problems	64.2 (39.6)	50.3 (42.4)	35.3 (40.1)	9.46	**0.00***	44.3 (43.0)	41.1 (40.4)	0.38	0.71
Social functioning	75.0 (22.6)	62.5 (27.9)	56.1 (22.6)	12.82	**0.00***	61.4 (26.2)	56.5 (24.6)	0.96	0.34

MHS care = mental health system care, AD = antidepressants,
SD = standard deviation
Bold : significant $P \leq 0.05$
* $1 \neq 3$

table 2: Clinical and functional outcomes of individuals with major depression in various modalities of care.

	Total cohort	No care	Primary care without AD	Primary care with AD	MHS care without AD	MHS care with AD
N	5606	122	32	19	26	24
Depression status						
No MD T_1		104	23	9	18	6
MD T_1		18	9	10	8	18
Good outcome %		85.2	71.9	47.7	69.2	25.0
Role limitations due to emotional problems Mean (SD)						
T_0	92.0 (23.5)	64.7 (39.3)	50.0 (42.3)	50.9 (43.6)	37.2 (43.5)	33.3 (36.8)
T_1	92.4 (23.1)	82.1 (33.1)	77.1 (40.1)	64.9 (45.1)	56.4 (46.0)	45.8 (40.3)
Δ $T_1 - T_0$	0.4 (27.8)	**17.4** (41.3)	**27.1** (50.4)	14.0 (57.0)	**19.2** (59.0)	**12.5** (44.8)
d (SE)		0.44 (0.09)	0.64 (0.21)	0.32 (0.30)	0.44 (0.27)	0.34 (0.25)
Social functioning Mean (SD)						
T_0	89.4 (18.0)	75.0 (22.6)	62.8 (29.0)	62.0 (26.8)	60.6 (22.7)	52.2 (22.3)
T_1	89.2 (17.4)	82.8 (19.8)	76.5 (20.3)	66.5 (31.8)	68.8 (23.1)	60.9 (30.3)
Δ $T_1 - T_0$	- 0.2 (19.7)	**7.7** (22.7)	**13.7** (32.2)	4.5 (32.4)	8.2 (32.8)	**8.8** (32.4)
d (SE)		0.34 (0.09)	0.47 (0.20)	0.17 (028)	0.36 (0.29)	0.39 (0.30)

MD = major depression, AD = antidepressant, MHS care = mental health system care
SD = standard deviation, d = effect size, SE = standard error
Bold : significant $P \leq 0.05$

Discussion

Care utilisation We found higher care utilisation for persons with major depression than in the USA (27.7%) (37) but lower than previously found in the Netherlands (63.8%) (38), based also on NEMESIS data. However, the studies are difficult to compare as we used a different prevalence measure of major depression (six months versus one year) and a more strict definition of professional care. Data on care utilisation have to be interpreted carefully, because such figures generally do not reveal the exact chronological and causal relations between a depressive episode and care-seeking behaviour. For example, in our data we expected some individuals, with a major depression in the six months prior to T_0, to utilise care before T_0 but not in the period between T_0 and T_1. Indeed, we found an additional 49 individuals with care utilisation in the period of six months before T_0, as a result of which total care utilisation increased to 67.3% in the period six months before T_0 till T_1.

One important finding in our study is that more intensive treatment is related to more severe or comorbid depression, suggesting that the distribution of care is rather appropriate in the Netherlands. We also found that patients treated within different levels of care, differ only on clinical factors and role dysfunctioning, and not on socio-demographic variables. This is in contrast with the results of a study in the USA (20). Possibly, our finding reflects the greater accessibility of the health care system in the Netherlands, coupled with an increasing readiness to seek help for major depression, irrespective of socio-demographic differences.

Antidepressant treatment was associated mainly with clinical factors: severity of depression and comorbid anxiety disorders; whereas the greater use of antidepressants by people outside paid employment might also be an indirect consequence of more severe forms of depression, that have already led to unemployment or sick-leave. On the other hand, our findings that only 52.6 % of those with a severe depression received antidepressants is an indication that undertreatment with antidepressants is still a problem. According to the guidelines antidepressants are especially recommended for more severe depressions (8-11).

Outcome We must emphasise that in this naturalistic study design efficacy of the various modalities of care cannot be evaluated; our results refer to effectiveness of care. We found that professional care is not always necessary to improve depression: the prognosis for mildly depressed persons without significant limitations in role functioning is favourable. Public health programs should therefore be focussed on individuals with more severe depression and with greater limitations in functioning. In comparison with other research on both primary care and (5,19) and MHS care (15-18) the clinical outcomes of professional care in our study were in the lower range. This is attributable to the poor outcome in antidepressant treated patients, who had prognostic unfavourable characteristics. Possibly, inadequacy in the implementation of treatment or poor compliance of patients, or both, are responsible for this poor outcome.

As far as functional outcome was concerned, substantial improvements were achieved in most modalities of care. We cannot rule out that this is due to a learning effect from longitudinal design as described earlier (39). However, the improvements were unevenly distributed over the different care modalities, and they were large enough to be significant and clinically relevant. It thus seems reasonable to conclude

that depressed individuals who receive treatment do improve substantially in functioning, but that such progress is not sufficient for many of them, with severe or anxiety comorbid depression, to recover from the depression itself.
Clinical outcome and functional outcome were only weakly correlated. Although there could be methodological reasons for this -depression status was a dichotomous measure and functioning was a continuous one- we believe it further underlines the need to asses the two types of outcome separately.

Limitations
Since homeless and chronically institutionalised people are not represented in the NEMESIS sample, the severest and most incapacitating forms of depression are probably underrepresented.
1. Our assessment of care utilisation was based on self-reports only and was not verified in medical records; this might affect the validity of the results.
2. Psychotherapeutic treatment of major depression was not explicitly studied.
3. The small numbers of depressed subjects in the various care modalities limit the power of the statistical analyses.

Implications
There seems to be room to improve the outcomes of professional care for those subjects with severe or anxiety comorbid major depressive disorder. The use of antidepressants should be directed in particular at the severe forms of depression and the effectiveness of antidepressant treatment must be improved. New and promising treatment strategies with a combination of psychotherapy and antidepressant medication (40), can possibly be employed for these cases.
Care utilisation and outcome of depressive disorder need to be monitored extensively, bearing in mind that depressed patients, treated with different modalities of care, differ in clinical characteristics and functional limitations. Since depression status alone is a rather crude measure of outcome, we recommend that functional assessment be included in future research.

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CHAPTER 5

Duration of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS)

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Summary
Background *Data on duration of major depressive episodes (MDE) in the general population are sparse.*
Aims *To asses duration of MDE and its clinical and sociodemographic determinants in a study group drawn from the general population with newly originated episodes of DSM-III-R major depression.*
Method *The Netherlands Mental Health Survey and Incidence Study is a prospective epidemiologic survey in the adult population (N= 7076), using the Composite International Diagnostic Interview (CIDI). Duration of MDE over two years was assessed with a life chart interview.*
Results *Median duration of MDE was 3.0 months; 50% recovered within 3 months, 63% within 6 months, 76% within 12 months and nearly 20% had not recovered at 24 months. Determinants of persistence were severity of depression and comorbid dysthymia. A recurrent episode predicted shorter duration.*
Conclusions *Although half of those affected with MDE recovered rapidly, the risk of chronicity (duration 24 months or more) was considerable. This underlines the necessity of diagnosing and treating those at risk.*
Declaration of interest *NEMESIS is supported by the Netherlands Ministry of Health, Welfare and Sport (VWS), the Medical Sciences Department of the Netherlands Organisation for Scientific Research (NWO), and the National Institute for Public Health and Environment (RIVM).*

Introduction

The study of the natural history of major depressive episodes (MDE) and its determinants is essential to understanding the nature of the illness and may guide the development of more effective treatment strategies (Judd, 1997). Duration of MDE has been found to vary widely, with median durations between 3 and 12 months and rates of chronicity (duration 24 months or more) between 10% to 30% (Keller et al, 1982; Angst, 1988; Keller et al, 1992; Coryell et al, 1994; Angst & Preisig, 1995; Mueller et al, 1996; Solomon et al, 1997; Furukawa et al, 2000). The variation may be explained by different definitions of recovery. Moreover, the previous studies were subject to two kinds of bias. Lead time bias arises because depressed persons were not recruited at a similar point in time in the course of the disorder; mostly prevalent cases were included. Referral filter bias arises because selected populations of depressed inpatients or outpatients were employed. It is expected that both kind of bias lead to an overrepresentation of chronic cases (Cohen & Cohen, 1984).
To avoid these sources of bias, the duration of newly originated MDE should be studied in people with depression selected from the general population. In a 13-15 year follow-up of the Baltimore site of the Epidemiologic Catchment Area Study, a median duration of MDE of 8-12 weeks was found (Eaton et al, 1997). The Life Chart Interview (LCI) (Lyketsos et al, 1984) was used to determine the onset and duration of MDE. Owing to the long follow-up period, dating of episodes was global and limited to one year.
With regard to determinants of episode duration, living without a partner (Mueller et al, 1996), comorbid dysthymia (Kelleret al, 1982) and severity of depression (Mueller

et al, 1996; Keller et al, 1992; Furukawa et al, 2000) have been found to predict longer duration of episode.
The primary aims of our study were (1) to investigate duration of MDE in detail over a period of two years in a cohort with newly originated episodes (first or recurrent) from the general population and (2) to study potential sociodemographic and clinical determinants of episode duration. A secondary aim was to asses the effect of referral filter bias (by comparing episode duration across levels of care).

Material and methods

Sampling

Data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Methods are described elsewhere (Bijl et al, 1998; Vollebergh et al, 2001). Briefly, NEMESIS is a prospective psychiatric epidemiologic survey in the Dutch adult general population (aged 18 to 64) with three waves in 1996 (T_0), 1997 (T_1) and 1999 (T_2). It is based on a multistage, stratified, random sampling procedure. One respondent was randomly chosen in each selected household. Interviewers made up to 10 phone calls or visits to an address at different times of the day and days of the week to make contact. To optimise response and offset any seasonal influences, the initial fieldwork extended from February to December 1996. In the first wave, sufficient data was gathered on 7076 persons, a response rate of 69.7%. At T_1, 1458 respondents (20.6%) were lost to attrition and at T_2, a further 822 (14.6%) were lost. 4796 Respondents were interviewed at all three waves. Psychopathology did not have a strong impact on attrition: at T_1 12-months agoraphobia (odds ratio (OR), 1.96) and social fobia (OR, 1.37), and at T_2 12-months major depression (OR, 1.37), dysthymia (OR, 1.80) and alcohol dependence (OR, 1.83), adjusted for demographic factors, were associated with attrition (de Graaf et al, 2000*a*; de Graaf et al, 2000*b*).

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 (computerised version; Smeets & Dingemans, 1993). The CIDI is a structured interview developed by the World Health Organization (WHO, 1990) which has been found to have acceptable interrater reliability and test-retest reliability for most diagnoses, including major depression (MD) (Wittchen, 1994). The following DSM-III-R diagnoses are recorded in the NEMESIS dataset: schizophrenia and other non-affective psychotic disorders, mood disorders (bipolar disorder, major depression, dysthymia), anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalised anxiety disorder, obsessive-compulsive disorder), eating disorders and psychoactive substance use disorders (alcohol or drug abuse and dependence, including sedatives, hypnotics and anxiolytics.

Study cohort
In order to include only newly originated episodes of MD (first or recurrent cases of MD), respondents with a diagnosis of two-year prevalence of MD at T_2 but no one-month prevalence of MD diagnosis at T_1 were identified (N= 273). Those diagnosed with bipolar disorder or a primary psychotic disorder were exluded.

Characteristics of participants with depression
Sociodemographic variables recorded at T_0 were gender, age, educational attainment, cohabitation status and employment status.
Clinical factors Based on the CIDI, the following information on the index episode of DSM-III-R major depression was obtained:

- Severity of depression, categorised in mild-moderate versus severe with or without psychotic features according to DSM-III-R.
- First or recurrent episode according to the DSM-III-R.
- Comorbidity with other DSM–III-R Axis I disorders. The comorbid disorders included were dysthymia, anxiety disorders and substance abuse or dependence. Psychiatric comorbidity was assessed without applying the hierarchical DSM rules.

Care utilisation
At T_2 respondents were asked whether they had received help for mental problems within the past 24 months. We distinguished three levels of care:

- No care or exclusively informal care (e.g. from an alternative care provider, traditional healer, self-help group, telephone helpline, physiotherapist).
- Primary care (general practitioner).
- Mental health system care, including ambulatory mental health care (crisis care, community mental health care institute, psychiatric outpatient clinic at a psychiatric or general hospital, alcohol and drugs counselling centre, psychiatrist, psychologist or psychotherapist in private practice, psychiatric day care centre) and residential mental health care (psychiatric hospital, inpatient addiction clinic, psychiatric division of general hospital, sheltered accommodation).

Duration of major depressive episode
The duration of MDE was assessed retrospectively at T_2, using the Life Chart Interview (LCI; Lyketsos et al, 1994). To improve recall, we used memory cues such as personal events, birthdays or holidays in the past two years. Psychopathology was assessed over periods of three months and for each period we recorded:

- duration of depressive symptoms (less than half / half/ most/ whole of the three-month period). For the analyses this was dichotomised as ‘six weeks or less’ versus ‘more than six weeks’.
- severity of depressive symptoms (no or minimal severity/ mild/ moderate/ severe/ very severe). This was dichotomised as ‘no or minimal severity’ versus ‘at least mild severity’.

Using this information on duration and severity, each three-month period was scored as follows: *i* = no or minimal depressive symptoms; *ii* = at least mild severity with brief duration (≤ 6 weeks); and *iii* = at least mild severity with longer duration (> 6 weeks).

Recovery was defined as no or minimal depressive symptoms in a three months period, thereby extending the US National Institute for Mental Health (NIMH) definition of recovery (Keller et al, 1992) with one month. No distinction was made between remission and recovery (Frank et al, 1991) because the data did not allow for such precision.
Duration of MDE was calculated by summing the three-months periods until recovery. A single period *ii* or a period *ii* at the beginning or at the end of MDE was counted as 1.5 months, all other periods were counted as 3 months.
Because administration of the LCI was time-consuming and not relevant for the entire NEMESIS sample, and because interviewers were not aware of DSM-III-R diagnoses derived from the CIDI, the use of the LCI was made dependent on a probe question (PQ) about whether the respondent had felt depressed for any period of more than two weeks since T_0.
In the study cohort, 23 (8.4%) of the 273 respondents did not respond affirmatively to the PQ. No significant differences were found between PQ-positive responders and PQ-negative responders on sociodemographic and clinical variables. The duration of MDE was determined for the first depressive episode recorded in the LCI. Ten respondents responded affirmatively to the PQ but reported no three-month period of depressive symptoms; they were classified as having had MDE of brief duration, set arbitrarily at 0.5 months.

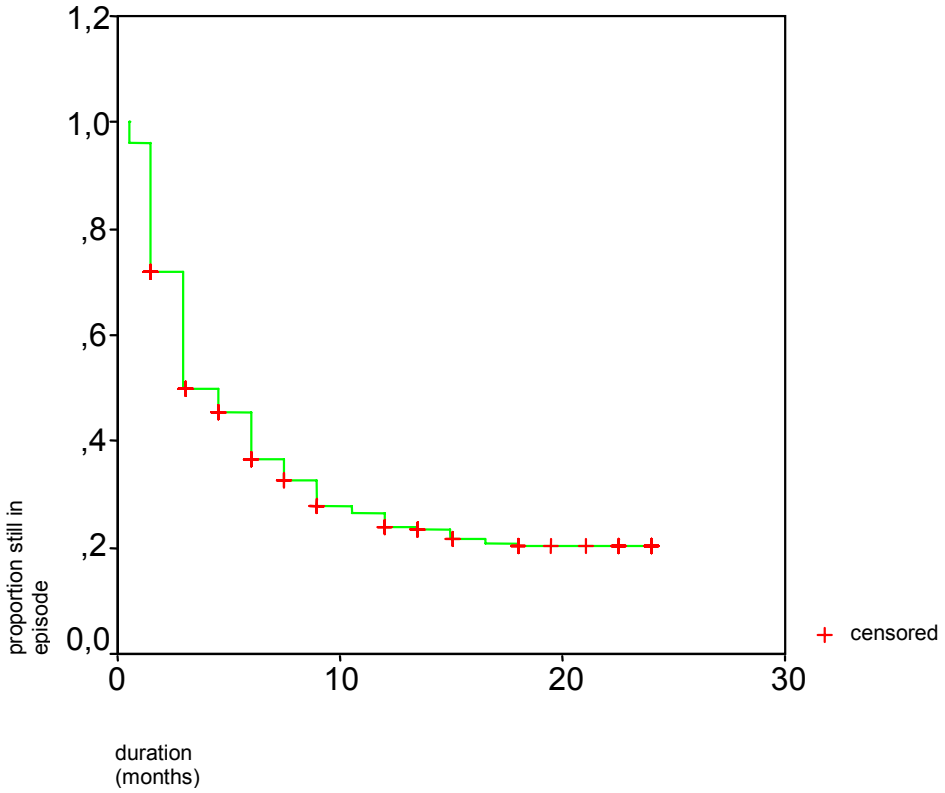
Analyses
Duration of MDE was calculated using survival analysis. The cumulative probability of recovery was estimated with the Kaplan-Meier product limit (Hosmer & Lemeshow, 1999). This technique describes all respondents over time, either to the event of interest, in this case recovery, or until they are lost to further follow-up (censoring). The effect of censored data is minimised by including all respondents who began the observation period regardless of whether they finished it. Median survival time is the first recovery at which cumulative survival reaches 0.5 (50%) or less. Mean survival time is not the arithmetic mean but is equal to the area under the survival curve for the uncensored cases. We used the statistical package SPSS for Windows 8.0 (SPSS Inc., 1998). Survival curves for cohorts selected from different levels of care were compared using the log rank test.
A stepwise Cox proportional hazards model was used to test the association between sociodemographic and clinical variables and duration of MDE. The hazard ratio (HR) is the increase (or decrease) in risk of the event of interest, incurred by the presence or absence of a certain variable.

Results
Duration of major depressive episode
In 64 cases (25.6%) the follow-up period ended before recovery (censored cases). The survival curve is presented in fig 1. The median time to recovery was 3.0 months (95% CI 2.2-3.8 months) and the mean time to recovery with the upper limit of 24 months was 8.4 months (95% CI 7.3-9.5 months). Of the respondents, 50% (95% CI 44- 56%) recovered within 3 months; 63% (95% CI 57-69%) within six months; 76% (95% CI 70-82%) within 12 months and 80% (95% CI 74-86%) within 21 months. All

cases with a duration greater than 21 months were censored cases, so cumulative survival at 24 months could not be calculated but was near 80%.

Determinants of episode duration
More than two third of the respondents were female. In 43.2% the index MDE was a recurrent episode and comorbid dysthymia was infrequent (table 1).
None of the sociodemographic variables predicted the outcome. Of the clinical variables, the presence of comorbid dysthymia and severity of the index episode predicted longer episode duration and the index episode being a recurrent episode predicted shorter episode duration (table 2). Entering these three variables into a multivariate Cox regression model (method backwards) did not alter the hazard ratios substantially but the presence of comorbid dysthymia was only just statistically significant.

figure 1: Survival curve of a cohort (N=250) with newly originated (first or recurrent) major depressive episodes in the general population.



We also performed survival analyses for these three clinical variables. The survival curves are shown in fig. 2. A severe depression lenghtens the median duration from 3.0 months (95% CI 2.5-3.5) to 7.5 months (95% CI 5.1-10.0) and the mean duration from 7.5 months (95%CI 6.2-8.8) to 10.5 months (95% CI 8.5-12.5). The presence of comorbid dysthymia lenghtens the mean duration from 7.7 months (95%CI 6.6-8.8) to 13.7 months (95% CI 9.5-18.0). No median duration with comorbid dysthymia was determined as cumulative survival did not reach 0.5 (50%). A recurrent episode shortens the duration from median 6.0 months (95% CI 4.3-7.7) to 3.0 months (95% CI 2.4-3.6) and mean of 10.2 months (95% CI 8.6-11.8) to 6.1 months (95% CI 4.7-7.5)

table 1: Sociodemographic and clinical characteristics and care utilisation of a cohort (N=250) with newly originated major depressive episodes (first or recurrent) in the general population.

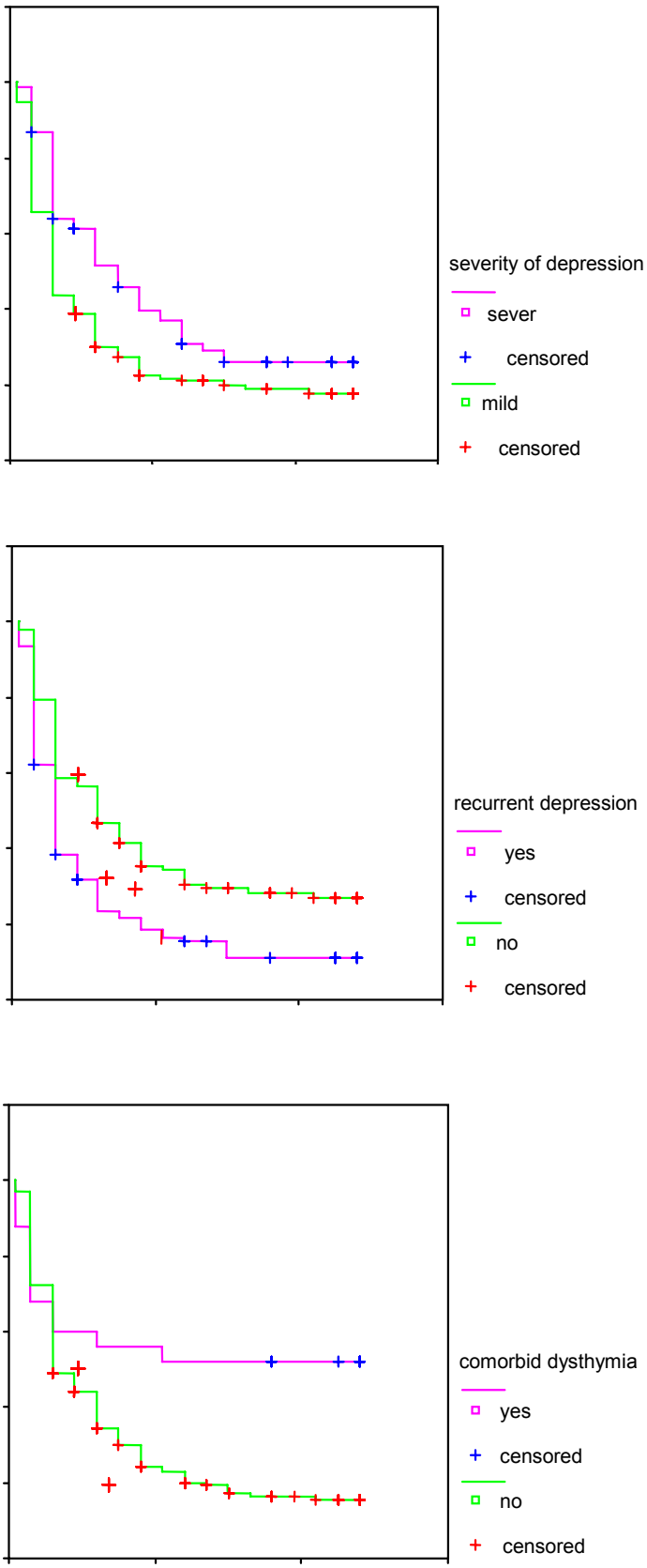
Variable	**%**
sociodemographic variables	
Gender (female)	66.8
Age	
18-24 years	6.4
25-34	36.4
35-44	26.8
45-44	21.1
55-64	9.2
Education	
Low	3.6
Medium	37.6
High	31.2
university	27.6
Living with partner (yes)	63.6
Paid employment (yes)	70.0
clinical variables	
Severe depression	30.4
Recurrent depression	43.2
Comorbid dysthymia	10.0
Comorbid anxiety disorder	34.0
Comorbid substance abuse /dependence	10.4
care utilisation	
No professional care	32.8
Primary care	38.8
MHS care	28.4

MHS care = mental health system care

table 2: Hazard ratios of determinants of episode duration (bivariate and multivariate models)

	Bivariate model			multivariate model		
Determinants	*hazard ratio*	*95% CI*	*p*	*hazard ratio*	*95% CI*	*p*
severe depression	0.67	0.49-0.92	0.02	0.70	0.51-0.97	0.03
recurrent depression	1.67	1.25-2.22	0.00	1.62	1.21-2.16	0.00
comorbid dysthymia	0.47	0.26-0.84	0.01	0.55	0.30-1.00	0.05

figure 2: Survival curves of a cohort (N=250) with newly originated (first or recurrent) major depressive episodes in the general population influenced by 1) severity of depression determinants, 2) recurrent depression, 3) comorbid dysthymia (legenda see fig. 1).

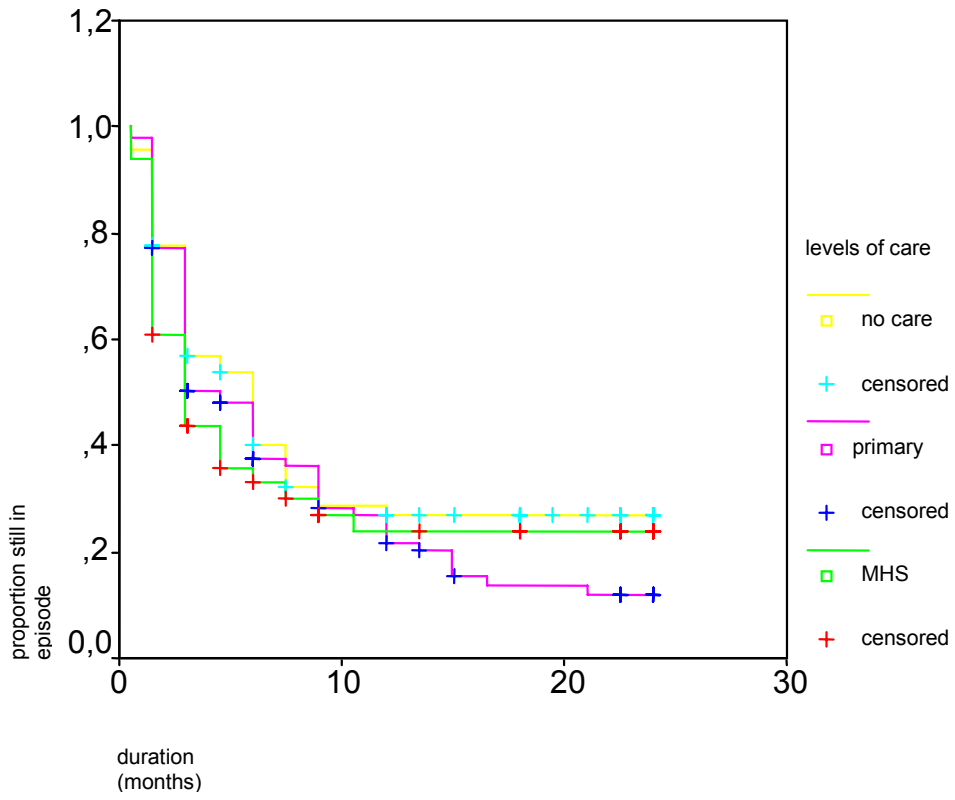


Duration of episode across different levels of care

Of all the respondents 67.2% had received professional help for their mental problems within the past 24 months (table 1). The survival curves for respondents stratified with different levels of care are shown in fig.3.

In those without professional care median duration of MDE was 3.0 months (95% CI 2.1-3.9 months) while mean duration (with the upper limit of 24 months) was 8.1 months (95% CI 6.0-10.1 months). In respondents with only primary care median duration of MDE was 4.5 months (95% CI 3.4- 5.6 months) while mean duration (with the upper limit of 24 months) was 7.8 months (95% CI 6.3- 9.4 months). In those with mental health system care median duration of MDE was 6.0 months (95% CI 3.9- 8.1 months) while mean duration (with the upper limit of 24 months) was 9.5 months (95% CI 3.9-8.1 months). Statistically, the differences in time to recovery in the different modalities of care were not significant (log rank 1.79, df = 2, p = 0.41).

figure 3: Survival curves of a cohort (N=250) with newly originated (first or recurrent) major depressive epsiodes in the general population according to whether they received mental health system care, primary care or no professional care.



Discussion

This is the first detailed estimation of duration of MDE in the general population. We found a median duration of MDE of 3.0 months, which is in the lower range of duration found in clinical populations (Keller et al, 1982; Angst, 1988; Keller et al, 1992; Coryell et al, 1994; Angst & Preisig, 1995; Solomon et al, 1997; Furukawa et al, 2000) but in line with findings from the general population (Eaton et al,1997). Around 20% of the depressed subjects had a chronic course (duration ≥ 24 months) which is very similar to findings in clinical populations (Keller et al, 1992; Angst, 1988; Keller et al, 1992; Coryell et al, 1994; Angst & Preisig, 1995; Solomon et al, 1997; Furukuwa et al, 2000).

Determinants for persistence were similar to those in clinical populations. Clinical characteristics such as severity of the index episode and the presence of comorbid dysthymia were predictors of a longer duration. Moreover, we found a shorter duration for recurrent episodes. This differs from the clinical population of the NIMH-Collaborative Depression Study (CDS) (Solomon et al,1997) in whom a similar duration of subsequent episodes was found. Shortening of duration with subsequent episodes might be a characteristic of the general population, as Eaton et al (1997) also found.

The high rate of chronicity in the general population is the most conspicuous and unexpected finding of our study. In both treated and untreated people with depression the risk of a chronic course (duration 24 months or more) was considerable. Referral filter bias could not be demonstrated, as no association was found between level of care and episode duration. This is remarkable since we found level of care to be associated with more severe depression earlier (Spijker et al, 2001). An explanation for the lack of association between episode duration and level of care could be that hospitalised depressed patients, with the most severe form of psychopathology, were probably underrepresented in NEMESIS.

The strenght of our design is that it enabled us to study the duration of MDE in a cohort with newly originated episodes from the general population, avoiding lead time and referral filter bias. A limitation of the method employed is that duration of MDE was retrospectively assessed using the LCI. We believe, however, that this method of assesment of duration, with a combination of prospectively (CIDI) and retrospectively (LCI) obtained data, is the best in practice for general population surveys. The LCI proved practicable and useful (Eaton et al, 1997) and the test-retest and interrater reliablity of a similar life chart instrument was satisfactory (Hunt & Andrews, 1995). We recognise that the reliability of retrospectively assessed data on psychopathology is questionable owing to recall problems, but this improves with shorter time intervals (Lyketsos et al*,* 1994) as in our design.

It was not possible using the LCI to determine whether a period with depressive complaints continuously met the DSM-III-R criteria of MDE. Therefore, in our analyses of duration we included both MDE and it's preceding and succeding subtreshold depressive syndromes. Also cases with comorbid dysthymia were included (10% of the respondents), somewhat increasing the chronicity rate. However, the inclusion of subtreshold depressive syndromes and dysthymia reflects the naturalistic course of MDE better and may have more clinical relevance (Judd et al, 1998).

In conclusion, the natural course of MDE in the general population has remarkable characteristics: Although half of those affected recovered rapidly (within three months), the rate of recovery slowed toward 12 months, virtually coming to a standstill after 12 months. Almost 20% of the depressed participants had not recovered at 24 months. These findings have important implications for prevention and treatment. Both in treated and in non-treated subjects, the risk for persistence was considerable. For untreated individuals it is essential that the depressive condition is detected and that treatment is offered. For treated individuals it is essential to identify lack of treatment response and to adjust the therapy accordingly. The clinical characteristics of the index episode seems to be the best clue to identifying people at risk of non-recovery; but a more detailed risk profile is certainly needed.

Clinical implications

- Half of those affected with major depressive epsiodes (MDE) recovered within three months.
- The risk of chronicity (duration ≥ 24 months) was considerable and underlines the necessity of diagnosing and treating those at risk.
- Treated and untreated people with MDE share the same risk of chronicity.

Limitations

- In the study sample homeless people and long-term residents of care institutions were not represented, so the most serious and incapacitating forms of psychopathology were underrepresented, probably decreasing the reported chronicity rate.
- The course of MDE was not strictly assessed following the DSM-criteria, limiting the comparability of our results with other research.
- The follow-up period in this study was only two years and we have no data on the longer course of MDE in the general population.

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CHAPTER 6

Determinants of persistence of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS)

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Submitted

Summary
Objective *Data on determinants of persistence of major depressive episodes (MDE) are inconsistent due to methodological shortcomings of the studies involved. We examined determinants of persistence of MDE in subjects from the general population (N=250) with newly originated episodes of DSM-III-R major depression.*
Method *The Netherlands Mental Health Survey and Incidence Study is a prospective epidemiological survey in the adult population (N= 7076), using the Composite International Diagnostic Interview (CIDI). Various potential determinants (longstanding psychobiological and social vulnerability factors, sustaining factors and illness-related factors) were assessed.*
Results *Determinants of persistence were severity of the index episode, longer duration of previous episodes, (chronic) physical illness and lack of social support. A recurrent episode predicted shorter duration.*
Conclusions *Just as in clinical populations, illness-related factors seem to be the strongest predictors of persistence of MDE. A thorough assessment of each depressed patient on the predictors of persistence is advisable.*

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Introduction

Persistence of depression is a common and major clinical problem (1). Being able to predict persistence is of obvious clinical and theoretical importance. However, compared to the literature on the aetiology of depression, relatively little is known about the factors predicting the prognosis of depression. Using the 'dynamic stress-vulnerability model' (2), we have classified factors which in the literature have been found to be associated with duration of the episode into (i) demographic factors, (ii) longstanding social and psychobiological vulnerability factors, (iii) sustaining factors and (iv) illness-related factors (i.e. characteristics of the index-episode) (table 1). The available studies yielded inconsistent results (17). Lower socio-economic status, prior psychiatric and physical illness, and personality characteristics (high neuroticism/ low level of mastery) are important vulnerability factors for persistence, while the effect of the sustaining factors is unclear. Overall, however, the existing data suggest that characteristics of the index episode (severity, duration, comorbidity with other psychiatric disorders) are the strongest predictors of persistence. Methodological shortcomings and differences between the studies are probably responsible for most of the inconsistencies in the data: different definitions of recovery were used; a distinction between a persistent and a recurrent course was not always made; and the studies were subject to both referral filter bias (selected populations of depressed in- or outpatients were employed) and lead-time bias (depressed persons were not recruited at a similar point in time in the course of the disorder).
In an earlier paper, we assessed duration of newly originated major depressive episodes (MDE) in the community using a life chart method. We found a median duration of 3.0 months (95% CI 2.2-3.8 months), while for nearly 20% of the

depressed subjects duration exceeded 24 months (18). The aim of the present paper was to examine predictors of persistence of MDE, using the 'dynamic stress-vulnerability model' as a conceptual framework.

table 1: Potential determinants of persistence of depression from the literature.

Determinant	Results
demographic factors	
Age	older (3), younger (4)
Gender	female (3, 5), no association (6)
social vulnerability	
education	low level (3)
social economic status	low (7)
marital status	being married (7); no partner (8)
psychobiological vulnerability	
youth experiences	childhood adversity (9,10)
personality characteristics	high neuroticism (11,15); low mastery (4)
previous psychiatric illness	other psychiatric illness (7)
somatic illness	presence of somatic illness (5)
sustaining factors	
negative life events	multiple (4); no association (12)
ongoing difficulties	interpersonal difficulties (9,10)
social support	lack of support (9); no association (12)
illness-related factors	
severity of depression	severe (3,4,7,8,13,14,15)
Comorbidity	with dysthymia (7), anxiety disorders (16), alcohol dependence (15)
previous episodes	multiple (3); no association (7)
duration of (previous) episode	long (3,4,7,11,13)

Method

Sampling and diagnostic procedure

Data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Methods are described elsewhere (18,19). Briefly, NEMESIS is a prospective psychiatric epidemiological survey in the Dutch adult general population (aged 18 to 64) with three waves in 1996 (T_0), 1997 (T_1) and 1999 (T_2). It is based on a multistage, stratified, random sampling procedure. One respondent was randomly chosen in each selected household. Interviewers made up to 10 phone calls or visits to an address at different times of the day and days of the week to make contact. To optimise response and offset any seasonal influences, the initial fieldwork extended from February to December 1996. These procedures were approved by the ethics committee of the Netherlands Institute of Mental Health and Addiction.

In the first wave, sufficient data was gathered on 7076 persons, a response rate of 69.7%. At T_1, 1458 respondents (20.6%) were lost to attrition and at T_2, a further 822 (14.6%) were lost. 4796 Respondents were interviewed at all three waves. Psychopathology did not have a strong impact on attrition: at T_1 12-months agoraphobia (odds ratio (OR), 1.96) and social phobia (OR, 1.37), and at T_2 12-months major depression (OR, 1.37), dysthymia (OR, 1.80) and alcohol dependence (OR, 1.83), adjusted for demographic factors, were associated with attrition (20,21). Diagnoses of psychiatric disorders according to DSM-III-R (22) were based on the Composite International Diagnostic Interview (CIDI), Version 1.1 (computerised version) (23). The CIDI is a structured interview developed by the World Health

Organization (24) which has been found to have high interrater reliability and high test-retest reliability for most diagnoses, including major depression (MD) (25).
A cohort (N= 250) with newly originated episodes of MDE (first or recurrent cases) was assembled, by identifying respondents with a diagnosis of two-year prevalence of MD at T_2 but no one-month prevalence of MD diagnosis at T_1. Those diagnosed with bipolar disorder or a primary psychotic disorder were excluded. Duration of MDE was assessed at T_2 with the Life Chart Interview (LCI) (18,26).

Determinants for persistence

1. *Demographic factors age and gender (recorded at T_0).*
2. *Social vulnerability factors* the following variables were used to represent social vulnerability: educational attainment and cohabitation status (recorded at T_0).
3. *Psychobiological vulnerability factors*

- negative youth experiences were assessed at T_0. 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 categorised as 'never or once' versus 'more than once' and the answers for sexual abuse as 'never' versus 'at least once'.
- neuroticism was assessed at T_0 with the Groninger Neuroticism Questionnaire containing 14 items (27). The internal reliability of the questionnaire was satisfactory (Cronbach's $\alpha = 0.74$). The outcome was categorised as high (highest quartile), medium (following quartile) or low (lower half).
- previous psychiatric illnesses were assessed at T_1 using the CIDI: lifetime prevalences of dysthymia, anxiety disorders, substance abuse or dependence and any psychiatric diagnosis were assessed.
- physical illness at T_0 was assessed with a questionnaire listing 31 mostly chronic somatic conditions. Diagnoses were recorded only if the respondents had received treatment. The answers were categorised as yes or no.

4. *Sustaining factors*

- life events were recorded at T_2 using a questionnaire developed from the Life Events and Difficulties Schedule (LEDS) (28). It covered nine positive and nine negative life events and three ongoing difficulties in the period between T_1 and T_2. The life events were classified as changes in health status, changes in employment status, changes in important relationships, changes in the family, changes in social contacts, traumatic experiences (all the above events being experienced by either the respondent or a significant other); changes in living conditions, expected changes in the future, and attainment or non-attainment of an important goal (events experienced by the respondent only). The ongoing difficulties were classified as relationship problems, conflicts at work/school or other difficulties including financial problems. The respondents' subjective experience of the life events and ongoing difficulties was used as a variable. The outcome was categorised as 0, 1-2 or ≥ 3 for positive events, and as 0, 1, or ≥ 2 for negative events and ongoing difficulties.
- social support between T_1 and T_2 was measured at T_2, using the Social Support Questionnaire for Satisfaction with the supportive transactions (SSQS) (29,30) with 23 items. The internal reliability of the SSQS was high (Cronbach's $\alpha = 0.85$).

The outcome was categorised as low, (lower third) medium (medium third) or high (upper third).

5. Illness-related factors

- using the CIDI, the following information on the index episode of DSM-III-R major depression was obtained at T_2: severity of depression (mild-moderate versus severe with or without psychotic features); first or recurrent episodes according to the DSM-III-R; mean duration of previous episodes, categorised as brief (≤ 12 weeks) or long (> 12 weeks); and comorbidity with other DSM-III-R axis I disorders. We calculated psychiatric comorbidity without applying the hierarchical DSM rules. The comorbid disorders deemed relevant were dysthymia, anxiety disorders and substance abuse or dependence.

Statistical analyses

Cox proportional hazards models were used to test the associations between the various determinants and duration of MDE (31). The dependent variable was time to recovery and the hazard ratio (HR) is the increase (or decrease) in risk, incurred by the presence or absence of a certain prognostic factor. In this analysis a HR < 1.0 stands for a decrease in the "risk" of recovery meaning a longer duration of the episode.

A multivariate analysis was performed (method backward; p_{in}= 0.05 and p_{out} = 0.10) with the variables found significant in the bivariate analysis, correcting for age and gender.

Further analyses were carried out to study the two-way interactions between the variables found significant in the bivariate analyses and gender and age. For these analyses the variables age, neuroticism, life events and social support were dichotomised.

The Cox proportional hazards model assumes that the magnitude of the effects of predictor variables is constant over time. To test this assumption, we analysed the effects of determinants early and late in the depressive episode separately. For this purpose the sample was posthoc split at the median point of episode duration (3.0 months) according to Kendler et al (32). For the early phase of the episode all observations were used and those duration's that were greater than the median were censored at the median duration. In the analysis of the late phase of the episode, all those who had recovered at the median duration were excluded from the analyses (N= 128).

Results

Determinants of episode duration

Of the vulnerability factors (chronic) physical illness and of the sustaining factors the occurrence of more than two negative life events and lower social support were found to be significantly associated with longer duration of episode (table 2). Of the illness-related factors severity of the index episode, comorbid dysthymia, the index episode being a recurrent episode and longer duration of previous episodes were all significantly associated with episode duration.

In a multivariate model (chronic) physical illness, lower social support, severity of the index episode and longer duration of previous episodes reduced the likelihood of

recovery with respectively 30%, 37%, 29% and 37%. The index episode being a recurrent one increased the likelihood of recovery with 54% .
Comorbidity with dysthymia was lost in the model, probably because of it's correlation with duration of previous episodes (Pearson r = 0.28, p < 0.01).

Interactions
We investigated possible interactions between the variables found significant in the bivariate analysis and age and gender in a model including the main effects. Two significant interactions terms were found (not in table): age x negative life events (HR = 0.50, 95%CI 0.25-1.00, p= 0.05) and age x comorbid dysthymia (HR = 0.30, 95%CI 0.09-0.98, p = 0.05). In a multivariate model (method backwards), including the remaining variables found significant in bivariate analysis, only age x negative life events remained in the model (HR = 0.47, 95%CI 0.28-0.81, p = 0.01).

Phase-dependent effect of determinants
Early in the phase of a depressive episode only illness-related variables were found to be significantly associated with episode duration: severity of the index episode, the index episode being a recurrent episode and longer duration of previous episodes (table 3). Multiple negative life events just failed to reach significance (HR = 0.66, 95%CI 0.42-1.04, p = 0.07) (not in table).
In a multivariate model severity of the index episode and longer duration of previous episodes reduced the likelihood of recovery with respectively 42% and 48 %, while the index episode being a recurrent one increased the likelihood of recovery with 50%.
Later on in the episode younger age (18-24 y), medium and high level of neuroticism, (chronic) physical illness, lower social support, comorbid dysthymia and the index episode being a recurrent one were significantly associated with episode duration (table 3). In a multivariate model a medium level of neuroticism, (chronic) physical illness and comorbid dysthymia reduced the relative risk of recovery with 49 %, 42% and 81% respectively.

table 2: Determinants of episode duration of major depressive epsiodes in a cohort of the general population.

		bivariate			multivariate		
Determinants	***N=250***	***HR *[1]***	***95% CI***	***p***	***HR***	***95% CI***	***P***
demographic factors							
gender (female)	167	1.07	0.79-1.46	0.66			
age 18-24 y	16	1.30	0.61-2.78	0.49			
25-34y	91	1.38	0.78-2.44	0.27			
35-44y	67	1.12	0.62-2.03	0.71			
45-54y	53	1.10	0.59-2.04	0.76			
55-64y	23	1					
social vulnerability							
education low	9	0.66	0.24-1.84	0.43			
medium	94	1.06	0.73-1.52	0.77			
high	78	1.21	0.83-1.75	0.33			
university	69	1					
living without partner	91	0.94	0.70-1.28	0.71			
psychobiological vulnerability							
negative youth experiences	81	1.16	0.85-1.57	0.35			
neuroticism low	150	1					
medium	59	0.76	0.53-1.09	0.14			
high	41	0.76	0.50-1.16	0.20			
previous psychiatric illness*[2]							
dysthymia	41	0.89	0.53-1.18	0.26			
anxiety disorders	121	0.92	0.69-1.22	0.56			
subst abuse/dep	63	0.95	0.68-1.32	0.35			
any diagnosis	186	0.91	0.66-1.26	0.58			
physical illness	133	**0.66**	**0.49-0.88**	**0.00**	**0.70**	**0.52-0.94**	**0.01**
sustaining factors							
positive life events 0	69	1					
1-2	111	1.23	0.86-1.77	0.26			
≥ 3	70	1.05	0.71-1.56	0.81			
negative life events 0	45	1					
1	72	0.95	0.62-1.44	0.80			
≥ 2	133	**0.67**	**0.46-0.98**	**0.04**	x	x	X
ongoing difficulties 0	124	1					
1	93	0.92	0.68-1.26	0.60			
≥ 2	33	0.77	0.49-1.21	0.25			
social support low	82	**0.64**	**0.45-0.92**	**0.02**	**0.63**	**0.44-0.91**	**0.01**
medium	85	0.91	0.65-1.28	0.60	0.89	0.63-1.25	0.50
high	83	1			1		
illness-related factors							
severity of depression	76	**0.67**	**0.49-0.92**	**0.02**	**0.71**	**0.51-0.98**	**0.04**
comorbid dysthymia	25	**0.47**	**0.26-0.84**	**0.01**	x	x	X
comorbid anxiety	85	0.81	0.60-1.10	0.18			
comorbid subst abuse/dep[3]	26	0.81	0.51-1.31	0.39			
recurrent depression	108	**1.67**	**1.25-2.22**	**0.00**	**1.54**	**1.14-2.07**	**0.00**
duration prev episodes (long)[4]	116	**0.58**	**0.44-0.79**	**0.00**	**0.63**	**0.46-0.85**	**0.00**

*[1] HR = hazard ratio, *[2] life time prevalences, [3]subst abuse/dep = substance abuse or dependence, [4]prev = previous, x = lost in the mulivariate model, **bold = p ≤ 0.05**

table 3: Determinants of episode duration in major depressive episodes in a cohort of the general population, early versus late in episode*[1].

	early (≤ 3months) (N= 250)						***late (> 3 months) (N= 122)***					
	bivariate			***multivariate***			***bivariate***			***multivariate***		
Determinants	***HR**[2]***	***95% CI***	***p***	***HR***	***95% CI***	***P***	***HR***	***95% CI***	***p***	***HR***	***95% CI***	***p***
demographic factors												
age 18-24 y	0.81	0.31-2.09	0.66				**3.94**	**1.02-15.29**	**0.05**	x	x	x
25-34y	1.11	0.58-2.13	0.75				2.51	0.76-8.32	0.13			
35-44y	0.93	0.47-1.84	0.84				2.01	0.59-6.87	0.26			
45-54y	0.97	0.48-1.97	0.93				1.68	0.47-6.04	0.42			
55-64y	1						1					
psychobiological vulnerability												
neuroticism low	1						1			1		
medium	0.91	0.55-1.49	0.70				**0.50**	**0.27-0.96**	**0.04**	**0.51**	**0.27-0.98**	**0.04**
high	1.17	0.80-1.73	0.41				**0.41**	**0.19-0.89**	**0.02**	0.58	0.26-1.27	0.17
physical illness	0.76	0.54-1.08	0.12				**0.48**	**0.29-0.79**	**0.00**	**0.58**	**0.35-0.97**	**0.04**
sustaining factors												
social support low	0.73	0.46-1.14	0.17				**0.46**	**0.26-0.83**	**0.01**	x	x	x
medium	1.12	0.75-1.68	0.58				0.56	0.30-1.03	0.06			
high	1						1					
illness-related factors												
severe depression	**0.58**	**0.38-0.87**	**0.01**	**0.58**	**0.38-0.88**	**0.01**	0.91	0.55-1.50	0.71			
comorbid dysthymia	0.81	0.43-1.55	0.53				**0.14**	**0.04-0.60**	**0.01**	**0.19**	**0.05-0.80**	**0.02**
recurrent depression	**1.66**	**1.17-2.35**	**0.00**	**1.50**	**1.06-2.14**	**0.02**	**1.63**	**0.99-2.69**	**0.05**	1.56	0.94-2.58	0.08
dur prev eps (long) *[3]	**0.48**	**0.33-0.69**	**0.00**	**0.52**	**0.35-0.76**	**0.00**	0.91	0.55-1.51	0.71			

*[1] only variables found significant are reported, *[2] HR = hazard ratio, *[3] dur prev eps = duration previous episodes, x = lost in the mulivariate model, **bold = p ≤ 0.05**

Discussion

This is the first report on determinants of duration in newly originated major depressive episodes in a cohort from the general population. A broad range of potential determinants was investigated. Illness-related factors were found as the strongest predictors of a longer duration of the episode: i.e. severity of the index episode and a longer duration of previous episodes. The index episode being a recurrent episode was associated with a shorter duration. Lack of social support was found associated with longer duration and (chronic) physical illness had a predictive value on the duration of later depressive episodes. Determinants of duration in the early phase of the episode differed from determinants later on in the episode: in the first three months only illness-related factors predicted duration but when the episode persisted personality characteristics, (chronic) physical illness and comorbid dysthymia became important.

What are the most conspicuous results compared with the literature?

The effect of age on duration was complex. Only later on in a depressive episode higher age was associated with longer duration and an interaction of age with multiple negative life events was found, suggesting that multiple negative life events have more effect on duration of episode at higher ages.

Unexpectedly, vulnerability factors hardly affected duration of episodes in our study. In contrast to studies from the USA (3,7,8) we found no influence of social vulnerability. Negative youth experiences as a longstanding vulnerability factor did not affect duration of depressive illness later in life. This seems inconsistent with earlier findings in depressed women (9,10). Contrary to these studies, we assessed the negative youth experiences at baseline before the occurrence of the depressive

episode. In this way no confounding was introduced, which seems to substantiate our finding. An alternative explanation is that youth experiences may act via the personality domain: we found negative youth experiences associated with neuroticism (not reported) and with longer duration later on in the episode.
A previous non-depressive psychiatric illness did not contribute to episode duration, which is in contrast to findings in depressed in- and outpatients (7). However, longer duration of previous depressive episodes was associated with persistence. It may be argued that this illness-related factor also belongs to the vulnerability domain.
A (chronic) physical illness, measured previous to the onset of the depressive episode, was found a predictor of persistence. This is in line with previous studies among older people (33).
We found perceived lack of social support to be the only important sustaining factor for persistence. Multiple negative life events affected outcome negatively but in the multivariate model this effect disappeared. Ongoing difficulties were previously identified as important predictors of the persistence of depressive episodes in depressed women (9,10) but we could not replicate these findings in our study. However, it should be noted that the sustaining factors were assessed over the same period as the index depressive episode and the question therefore arises whether these factors are risk factors for an unfavourable course or consequences of the disorder.
In accordance with the literature (3,4,7,8,11,13,14,15) we found illness-related factors (severity of the index episode and duration of (prior) episodes) to be the strongest predictors for persistence. The index episode being a recurrent one enhanced the speed of recovery. It seems likely that this finding refers to the 'kindling' phenomenon, implying that recurrent episodes might recover swiftly, only to relapse in another episode (34).

We consider as major strengths of our study that we included individuals from the general population with newly originated depressive episodes avoiding referral filter and lead time bias. Confounding was avoided by the assessment of potential risk factors prior to the occurrence of the index depressive episode. A possible weakness is the limited follow-up of two years. Moreover, although NEMESIS has a prospective design, the duration of depressive episodes during the two years between T_1 and T_2 was assessed retrospectively at T_2, thereby, possibly, introducing recall bias. We believe, however, that this method of assessment of duration, with a combination of prospectively and retrospectively obtained data, is the best feasible for general population surveys. A third possible limitation concerns the statistical analysis. The detailed assessment of duration of the depressive episodes enabled us to use survival analyses. However, we confirmed an earlier finding from Kendler et al (32) that the effects of determinants of duration differ in the early versus the late phase of the episode. This aspect affects the findings from the entire sample: namely the basic assumption for Cox proportional hazard model, that the magnitude of the effect of the predictor is constant over time, may be incorrect. Nevertheless, it is important to notice that the effects of the most important predictors (illness-related factors) were consistent.

Our findings, if replicated in future research, have important clinical implications.

Prognosis of duration of depression seems to rely mainly on factors that can be assessed relatively easy: (chronic) physical illness, lack of social support and illness-related factors such as severity of the index-episode and prior episodes and their duration. A thorough assessment of each depressed patient on these characteristics may help clinicians to predict prognosis and to indicate more aggressive treatment for those at risk for persistence.

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CHAPTER 7

Duration of depression and recovery and functional disability in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS)

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submitted

Summary
Background *Data on the temporal relationships between duration of depression and recovery and functional disability are sparse.*
Aims *To examine the associations between duration of depression and recovery and functional disability in subjects from the general population (N=250) with newly originated episodes of DSM-III-R major depression.*
Method *The Netherlands Mental Health Survey and Incidence Study is a prospective epidemiological survey in the adult population (N= 7076), using the Composite International Diagnostic Interview (CIDI). Duration of MDE and duration of recovery over two years were assessed with a life chart interview. Functional disabilities were assessed with the MOS-SF-36 and with absence days from work.*
Results *Functional disabilities and absence days in depressed individuals were not found to be associated with duration of depression. Functioning in daily activities improved with longer duration of recovery but social functioning not.*
Conclusions *In depressed individuals with protracted duration of illness, treatment of depressive symptoms will help to improve functioning. Improvements in daily activities and work can be expected with longer duration of recovery.*
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Introduction

Consequences of depression are severe in terms of reduced well being and functioning (Wells et al, 1989; Hayes et al, 1995), especially in occupational and social roles (Ormel et al, 1993). Functional disability has been found associated with severity of depression (Ormel et al, 1994; Judd et al, 2000) and synchrony of change in depression severity and the level of functional disability has been found. This implies that disability improves with a decrease of depressive symptoms but is pervasive and chronic when the depressive symptoms persists (Ormel et al, 1993; Spijker et al, 2001). Little is known, however, about the temporal relationship between depression and functional disability (Ormel & von Korff, 2000). For instance, clinical experience suggests that persistence of depression lead to progressive deterioration in functioning which in turn may further hamper recovery. Empirical data on this association between functional disability and duration of depression, however, are lacking. Data on the association between duration of recovery and functional disability, on the other hand, are inconsistent. Furukawa et al (2001) found further amelioration in functioning with longer duration of symptomatic remission but in earlier studies (Bauwens et al, 1991; Coryell et al, 1993) this could not be demonstrated. Elucidating the associations between duration of a depressive episode and functional disability on the one hand and duration of recovery and functional disability on the other is of great clinical importance as there is increasing recognition that the outcome of treatment of depression should be addressed in broader terms than improvement of symptoms (Angst et al, 1996; Spijker et al, 2001). In a cohort with newly originated MDE from the general population, we found duration of a major depressive episode (MDE) to vary widely, with a median duration of 3

months and a chronicity rate (duration ≥ 24 months) of almost 20% (Spijker et al, in press). In this paper we will investigate what the effects are of duration of depression and duration of recovery on functional disability.

Material and methods

Sampling

Data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Methods are described in detail elsewhere (Bijl et al, 1998; Spijker et al, in press). Briefly, NEMESIS is a prospective psychiatric epidemiological survey in the Dutch adult general population (aged 18 to 64) with three waves in 1996 (T_0), 1997 (T_1) and 1999 (T_2). It is based on a multistage, stratified, random sampling procedure. One respondent was randomly chosen in each selected household. Interviewers made up to 10 phone calls or visits to an address at different times of the day and days of the week to make contact. To optimise response and offset any seasonal influences, the initial fieldwork extended from February to December 1996. In the first wave, sufficient data was gathered on 7076 persons, a response rate of 69.7%. At T_1, 1458 respondents (20.6%) were lost to attrition and at T_2, a further 822 (14.6%) were lost. 4796 Respondents were interviewed at all three waves. Psychopathology did not have a strong impact on attrition: at T_1 12-months agoraphobia (odds ratio (OR), 1.96) and social phobia (OR, 1.37), and at T_2 12-months major depression (OR, 1.37), dysthymia (OR, 1.80) and alcohol dependence (OR, 1.83), adjusted for demographic factors, were associated with attrition (de Graaf et al, 2000*a*; de Graaf et al, 2000*b*).

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 (computerised version; Smeets & Dingemans, 1993). The CIDI is a structured interview developed by the World Health Organization (WHO, 1990) which has been found to have acceptable interrater reliability and test-retest reliability for most diagnoses, including major depression (Wittchen, 1994). The following DSM-III-R diagnoses are recorded in the NEMESIS dataset: schizophrenia and other non-affective psychotic disorders, mood disorders (bipolar disorder, major depression, dysthymia), anxiety disorders (panic disorder, agoraphobia, simple phobia, social phobia, generalised anxiety disorder, obsessive-compulsive disorder), eating disorders and psychoactive substance use disorders (alcohol or drug abuse and dependence, including sedatives, hypnotics and anxiolytics.

Study cohort

We included respondents with newly originated MDE (first or recurrent cases) between T_1 and T_2 i.e. those with a diagnosis of two-year prevalence of major depression at T_2 but no one-month prevalence of major depression diagnosis at T_1 (N= 273). Those diagnosed with bipolar disorder or a primary psychotic disorder were excluded. To examine the research questions the study cohort was split in two: those who were still depressed at T_2 (with a one month prevalence of major depression at T_2; N= 69) and those who have recovered at T_2 (without a one month prevalence of

major depression at T_2; N= 181).

Outcome measures

- Functional disabilities were assessed at T_2 with the Short-Form-36 Health Survey (SF-36; Ware & Sherbourne, 1992; Ware et al, 1997), for which good reliability and validity have been demonstrated (Aaronson et al, 1998). The SF-36 consists of 36 items forming eight scales. Scoring was performed in accordance with the Ware & Sherbourne (1992) guidelines on a 0-100 scale, with 100 defined as maximum functioning. Because we were interested in role functioning, we used the subscales 'role limitations due to emotional problems' (3 items), which records problems with work or other daily activities in the previous four weeks as a consequence of emotional problems; and 'social functioning' (2 items) which assesses limitations on social activities like visiting friends and relatives.
- Sickness absence in weeks between T_1 and T_2 was assessed at T_2 for respondents with (partial) employment between T_1 and T_2.

Independent variables

Duration of depression and duration of recovery were assessed retrospectively at T_2, using the Life Chart Interview (LCI; Lyketsos et al, 1994). To improve recall, we used memory cues such as personal events, birthdays or holidays in the past two years. Psychopathology was assessed over periods of three months and for each period we recorded:

- duration of depressive symptoms (less than half / half/ most/ whole of the three-month period). For the analysis this was computed as 0.75 month / 1.5 month / 2.25 months / 3 months.
- severity of depressive symptoms (no or minimal severity/ mild/ moderate/ severe/ very severe). This was dichotomised as 'no or minimal severity' versus 'at least mild severity'. Only periods with more than minimal severity were used in the analyses.

Duration of depression was calculated by adding up the duration of each three months period with depressive symptoms in the two year period of observation, starting from the first period of three months with depressive symptoms.
Duration of recovery was calculated by adding up each three months periods without depressive symptoms until T_2, starting from the last period of three months with depressive symptoms in the two years of observation.
Because administration of the LCI was time-consuming and not relevant for the entire NEMESIS sample, and because interviewers were not aware of DSM-III-R diagnoses derived from the CIDI, the use of the LCI was made dependent on a probe question (PQ) about whether the respondent had felt depressed for any period of more than two weeks since T_0.
In the study cohort, 23 (8.4%) of the 273 respondents did not respond affirmatively to the PQ. No significant differences were found between PQ-positive responders and PQ-negative responders on sociodemographic and clinical variables. There were 10 respondents who responded affirmatively to the PQ but reported no three-month period of depressive symptoms. We classified these as having had MDE of brief duration and set this duration arbitrarily at 0.5 months.

Co-variates

- gender, age were recorded at T_0. Employment status was recorded at T_2 because sickness absence (one of the outcome measures) was dependent on the employment status between T_1 and T_2.
- premorbid functioning was determined at T_1 by the assessment of the subscales 'role limitations due to emotional problems' and 'social functioning' of the MOS-SF-36.
- number of comorbid somatic disorders. This was assessed at T_2 with a questionnaire listing 31 mostly chronic somatic conditions for which respondents had been treated in the preceding 24 months.
- clinical factors. Using the CIDI, we obtained information on the following: severity of the index depressive episode (mild, moderate, severe with or without psychotic features according to the DSM-III-R); first or recurrent episode according to the DSM-III-R; comorbidity with other DSM-III-R axis I disorders. We calculated psychiatric comorbidity without applying the hierarchical DSM rules. The comorbid disorders deemed relevant were dysthymia and anxiety disorders.

Statistical analyses

The bivariate associations between duration of depression and recovery on the one hand and both premorbid functioning and the outcome measures at the other hand were analysed using ANOVA.

Bivariate regression analyses were performed to asses the association of duration of depression or duration of recovery, age and gender, employment status, premorbid functioning, the index episode being a recurrent one, severity of the index episode, psychiatric and somatic comorbidity with the outcome measures. The variables found significant ($p \leq 0.05$) were entered in a multiple regression model (method stepwise $p_{in}= 0.05$, $p_{out}= 0.1$) with age, gender and duration of depression or duration of recovery to asses the best fitted model.

Results

Study cohort

The mean age of the entire study cohort (N=250) was 41.7 y (SD 10.7); 66.8% was female and 73.6% was employed. For those who were still depressed at T_2 (N=69), the mean duration of their depression in two years prior to T_2 was 7.1 months (SD 6.5) and median duration 4.5 months and for those who had recovered at T_2 (N=181), the mean duration of their recovery over the two year follow-up period was 7.2 months (SD 7.8) and median duration 5.0 months (not in table).

In both cohorts functioning was significantly impaired at T_1 compared to the total NEMESIS-sample but no differences were found between the two cohorts (table 1). At T_2, functioning in both cohorts was still significantly impaired compared to the NEMESIS-sample but in the still depressed cohort significantly more than in the recovered cohort. Both cohorts had significantly more absence days than in the NEMESIS-sample, with most sickness days in the still depressed cohort.

table 1: Functional status and sickness absence over a two-year period in two cohorts with newly developed major depressive episodes from the general population (one cohort with still depressed individuals at T_2, and one cohort with recovered individuals at T_2) and in the total NEMESIS sample.

	depressed at T_2 (1)	**recovered at T_2** (2)	**NEMESIS** (3)		
Functioning	N = 69	N = 181	N = 4796		
Daily activities and work	mean SD	mean SD	mean SD	F	p
T_1	80.9 (34.2)	76.0 (38.1)	92.7 (22.5)	62.58	0.00*[1]
T_2	48.3 (41.8)	77.0 (38.1)	93.9 (20.9)	257.84	0.00*[2]
Social functioning					
T_1	78.8 (18.5)	78.8 (22.4)	89.5 (17.1)	51.17	0.00*[1]
T_2	57.1 (24.2)	78.7 (21.6)	89.4 (17.2)	175.91	0.00*[2]
	N = 48	N = 136	N = 3327		
Sickness absence T_1 - T_2	weeks SD	weeks SD	weeks SD		
	11.9 (18.3)	7.9 (14.8)	2.8 (8.6)	56.26	0.00*[2]

*[1] 3 ≠ 1,2; *[2] 1≠ 2≠ 3 ($p \leq 0.05$)

Duration of depression

In the still depressed cohort, functional disability and sickness absence at T_2 were analysed with differential duration of depression in the two years of observation (table 2). No significant differences in limitations in daily activities and social functioning were found between groups with differential duration of depression. Sickness absence increased, although not significant, with duration of depression ≥ 6 months.
In bivariate analyses only comorbid anxiety was significantly associated with limitations in daily activities at T_2: (β = - 0.28, SE = 9.79, p = 0.02). The multivariate model with comorbid anxiety, duration of depression and age and gender included only comorbid anxiety (β = - 0.28, SE = 9.79, p = 0.02) with R^2= 0.05.
Severity of the index episode (β = - 0.27, SE = 3.33, p = 0.03) and comorbid anxiety (β = - 0.30, SE = 5.66, p = 0.02) were bivariate significantly associated with social functioning at T_2. Only comorbid anxiety (β = - 0.29, SE = 5.66, p = 0.02) remained in the multivariate model with R^2= 0.08.
For those with employment (N= 48), none of the variables were significantly associated with duration of sickness absence.

table 2: Functional status and sickness absence by differential duration of depression over a two-year period in a still depressed cohort with newly developed major depressive episodes from the general population (N=69)

	Duration of depression in months					
	≤ 3 mnths	**3-6 mnths**	**6-12 mnths**	**12-24 mnths**		
Functioning	N = 31	N = 11	N = 13	N = 14		
	mean SD	mean SD	mean SD	mean SD	F	p
daily activities and work T_2	54.8 (43.5)	30.3 (37.9)	43.6 (43.9)	52.4 (38.6)	0.77	0.51
social functioning T_2	62.3 (23.6)	59.3 (27.8)	50.0 (21.9)	50.7 (24.1)	1.21	0.32
	N = 17	N = 7	N = 11	N = 13		
sickness absence T_1 - T_2	weeks SD	weeks SD	weeks SD	weeks SD		
	8.6 (15.2)	3.7 (5.5)	15.4 (25.0)	17.9 (19.0)	1.23	0.31

Duration of recovery

In the recovered cohort significant differences in daily activities were found at T_2 between groups with differential duration of recovery with worse functioning in daily activities in those with shortest duration of recovery (table 3). Also significant differences in social functioning were found at T_2 between those with a duration of recovery ≤ 3 months and those with a duration of recovery 6-12 months.

Significant differences in sickness absence were found with highest sickness absence in those with a duration of recovery of 6-12 months.
In bivariate analyses duration of recovery (β = 0.23, SE 0.41, p = 0.00), being employed (β = 0.17, SE 6.47, p = 0.02) and comorbid anxiety (β = - 0.15, SE 6.14, p = 0.05) were all significantly associated with limitations in daily activities at T_2. In a multivariate model with these determinants and duration of recovery and age and gender, duration of recovery (β = 0.23, SE 0.41, p = 0.00) and comorbid anxiety (β = - 0.15, SE 6.0, p = 0.04) both remained in the model with R^2= 0.08.
Social functioning at T_2 was significantly associated with social functioning at T_1 (β = 0.19, SE = 0.07, p = 0.01) and the multivariate model included only social functioning at T_1 with R^2= 0.04.
For those with employment (N= 136) only severity of the index episode (β = 0.23, SE = 1.45, p = 0.01) was significantly associated with duration of sickness absence and the multivariate model was the same with R^2= 0.05.

table 3: Functional status and sickness absence by differential duration of recovery over a two-year period in a recovered cohort with newly developed major depressive episodes from the general population (N=181)

	Duration of recovery in months					
	≤ 3 mnths (1)	**3-6 mnths** (2)	**6-12 mnths** (3)	**12-24mnths** (4)		
Functioning	N = 73	N = 26	N = 39	N = 43		
	mean SD	mean SD	mean SD	mean SD	F	p
daily activities and work T_2	62.1 (42.4)	83.3 (36.8)	95.7 (17.4)	81.4 (35.9)	8.18	0.00*[1]
social functioning T_2	73.2 (22.8)	79.2 (21.9)	88.5 (14.9)	79.0 (21.9)	4.53	0.00*[2]
	N = 48	N = 22	N = 30	N = 36		
sickness absence T_1 - T_2	weeks SD	weeks SD	weeks SD	weeks SD		
	4.2 (10.5)	5.2 (7.4)	15.1 (26.6)	3.7 (9.0)	5.40	0.01*[3]

*[1] 1 ≠ 3,4; *[2] 1 ≠ 3 ; *[3] 3 ≠ 1,4 (p ≤ 0.05)

Discussion

This is the first report on the associations of functional disability with duration of depression and duration of recovery in a cohort with newly developed major depressives episodes from the general population. Contrary to the clinical experiences, we did not find an association between duration of depression and functional disability in depressed individuals. In a subsequent analysis, severity of depression and comorbid anxiety were found as the strongest contributors to dysfunctioning in depressed individuals, as was found earlier (Ormel et al, 1993, Spijker et al, 2001). Functioning in daily activities improved with a longer duration of recovery but social functioning did not. This suggests a differential effect of duration of recovery on different domains of functioning.
Our findings support the notion of synchrony of change: worse functioning was found in actually depressed individuals and functioning improved after recovery of depression. We also found some evidence that dysfunctioning precedes a depression. This was demonstrated earlier in older populations (Prince et al, 1998) indicating bidirectional effects of depression and functioning (Ormel & Von Korff, 2001). Furthermore, residual effects on functioning after recovery could be demonstrated, as was found earlier in the general population (Bijl et al, 2001; Mojtabai, 2001). Our results suggest that functional disability is relatively stable and

chronic. Disability increases during a depressive episode and, after symptomatic recovery, returns to an (already impaired) premorbid level.
Sickness absence was substantial in both still depressed and recovered individuals. However, no significant associations between duration of depression and sickness absence were found. A possible explanation for this finding is that our estimation of sickness absence of longer duration might be inaccurate as a sick leave exceeding 12 months is usually grounds for medical retirement in the Netherlands.
The non-association between duration of depression and dysfunctioning we found may be the result of a methodological shortcoming of the study. The main outcome variables, the MOS subscales, were assessed at T_2 over the preceding four weeks. A repeated assessment of disability during the depressive episode would probably have given a better impression of changes in functioning.
We consider as major strengths of our study that we included individuals with newly originated depressive episodes, which enabled us to assess baseline functioning before the depressive episode. Furthermore, duration of depression and duration of recovery were carefully assessed with a life chart method. A limitation is that our follow-up was only two years. There is some evidence that a duration of depression, exceeding the two years, leads to more functional disability (Hays et al*,*1995). Another limitation of the method employed is that duration of MDE and duration of recovery were retrospectively assessed with the LCI. We believe, however, that this method of assessment of duration, with a combination of prospectively (CIDI) and retrospectively (LCI) obtained data, is the best feasible for general population surveys.
Although we could not demonstrate a powerful effect of duration on functional disability, our findings give no reason to underestimate the consequences of a longer duration of depression. Depression is associated with severe limitations in functioning, and each extra month in depression prolongs the suffering.
The implications of our findings for clinicians are important. We demonstrated that functioning deteriorates dramatically by actual depressive symptomatology and comorbid anxiety. After symptomatic recovery, functioning improves to premorbid level, irrespective of the length of the depression. Functioning in daily activities and work increases with longer duration of recovery. These findings should urge clinicians to treat depressive symptomatology (and comorbid anxiety) aggressively, even in depressed patients with a protracted duration of illness.

Limitations

- In the NEMESIS sample homeless and chronically institutionalised people were not represented, so the most serious and incapacitating forms of psychopathology were probably underrepresented.
- Functional disability was only assessed at baseline and follow-up, instead of repeated measurements during the follow-up period.
- The follow-up in this study was only two years and we have no data on a longer course of MDE and it’s subsequent functional disability in the general population.

Implications

- In depressed individuals with long-lasting episodes of major depression, functioning improved after recovery.
- Individuals who had recovered from depression, improved in daily functioning with longer duration of recovery.
- Functional disability is present before and after a depressive episode and increases during the episode.

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CHAPTER 8

DISCUSSION

Introduction

In this chapter the major findings of the thesis are discussed in the light of the initial hypotheses and the literature. In addition, I will elaborate on some of the secondary findings of the studies and on methodological issues. Finally, implications for the treatment of depressed patients and for mental health policy as well as new directions for research will be formulated.

Results

1. Research question: What is the duration of major depressive episodes (MDE) and the rate of chronic duration of MDE in the general population?
   Hypothesis: Duration of MDE is shorter and prevalence of chronicity is lower in the general population compared to clinical populations.

A median duration of MDE was found of 3 months (95% CI 2.2-3.8 months) and nearly 20% of those with MDE had a duration ≥ 24 months (chapter 5). This means that the medium-term prognosis for individuals with newly developed MDEs is fairly good; 50% recover within three months. But if the duration of an episode is more than three months the prognosis deteriorates progressively and with a duration of 12 months long-term chronicity has already been reached.

In order to compare the results with the ongoing research an updated and improved version of the literature review (chapter 2) can now be made, including the findings of this thesis (see table). Only one relevant new study was found (Furukawa et al, 2000). The ECA follow-up study (Eaton et al, 1997) was included although no potential determinants of course were investigated in this study. In this update attention was paid to the following aspects of the studies: were persistence and recurrence distinguished, had survival analysis been used and had lead time bias been avoided.

We could not confirm our initial hypothesis. The median duration of MDE of 3 months in the general population, is in the lower range compared to findings in clinical populations with median duration's between 3 and 12 months (Keller et al, 1982, 1984; Coryell et al, 1994; Brown & Moran, 1994; Brown et al, 1994; Ramana et al, 1995; Furukawa et al, 2000). The rate of chronicity (duration ≥ 24 months) of almost 20% is in the higher range compared to findings in clinical populations (Keller et al, 1982; 1984; Keitner et al, 1992; Scott et al, 1992; Ormel et al, 1993; Coryell et al, 1994; Brown & Moran, 1994; Brown et al, 1994; Ramana et al, 1995; Furukawa et al, 2000). Only in the ECA study (Eaton et al, 1997) an even higher rate of non-recovery was found but the retrospective assessment of the course of major depressive disorder (MDD) in this study was very global and probably inaccurate.

A possible explanation for the high rate of chronicity we found, is that one of the extended definitions of chronic depression was used in our research. Subthreshold depressive syndromes before and after a MDE and also double depressions were included. This broader definition of chronicity, however, probably better reflects the natural course of MDE better. Research on depressed patients (Judd et al, 1998) has indicated that the long-term course of MDD is characterised by a fluctuating between MDEs and subsyndromal and minor depressive symptoms and symptom-free intervals.

2. Research question: What are the determinants of (chronic) duration of MDE in the general population?
Hypothesis: Life events and social support are more and illness-related factors are less important as determinants of duration in the general population compared to clinical populations.

Illness-related factors (severity of the index episode, prior episodes and their duration) were the strongest predictors of duration of MDE. Lack of social support was associated with longer duration and (chronic) physical illness had a predictive value on the duration of later depressive episodes (chapter 6). Our earlier findings on determinants of poor one-year outcome of major depression already indicated that illness-related factors were the most important predictors of a poor prognosis (chapter 3).

The hypothesis was not confirmed. Effects of the life events and social support were indeed found, but altogether illness-related factors dominate the course of MDE in the general population. Therefore, the conclusion is that determinants of the (chronic) course of MDE in the general population and in clinical populations are essentially very much the same.

What are the most conspicuous results of our studies on determinants of course (see table)? Only a limited influence of the vulnerability domain was found. In contrast to studies from the USA (Sargeant et al, 1990; Keller et al, 1982, 1984; Keitner et al, 1992) no influence of social vulnerability was found (chapter 3, 6). Negative youth experiences as a longstanding vulnerability factor did not affect duration of depressive illness later in life (chapter 3, 6). This seems inconsistent with earlier findings in depressed women (Brown & Moran, 1994; Brown et al, 1994). Contrary to these studies, we assessed the negative youth experiences at baseline before the occurrence of the depressive episode (chapter 6). In this way no confounding was introduced, which seems to substantiate our finding. Of the personality characteristics an external locus of control was found a predictor of poor one-year outcome (chapter 3) but in our analyses of determinants of persistence of MDE over two years we found personality factors (neuroticism) only associated with persistence later on in the episode (chapter 6). A possible explanation for the inconsistency of our findings is that we assessed the personality factors during the depressive episode in the earlier study (chapter 3), thereby possibly introducing confounding. We could avoid this methodological shortcoming in the later study (chapter 6). The finding of Scott et al (1992) that high neuroticism predicted chronicity was also affected by this confounding. Our results suggest that the influence of personality factors on the duration of MDE is less important as previously thought. A previous non-depressive psychiatric illness was not found to contribute to episode duration, which is in contrast to findings in depressed in- and outpatients (Keller et al, 1982, 1984). However, longer duration of previous depressive episodes was associated with persistence (chapter 3, 6) and it may be argued that this illness-related factor also belongs to the vulnerability domain.

We found perceived lack of social support to be the only important sustaining factor for persistence (chapter 6). Initially, multiple negative life events were also found associated with poor one-year outcome (chapter 3). In our analyses with two year of observation multiple negative life events were again found to be associated with persistence but they did not remain in the final statistical model with the other

significant variables (chapter 6). Ongoing difficulties were previously identified as important predictors of the persistence of depressive episodes in depressed women (Brown & Moran, 1994; Brown et al, 1994) but we could not replicate these findings in our studies (chapter 3, 6). However, it should be noted that the life events, ongoing difficulties and social support were assessed over the same period as the index depressive episode and the question therefore arises whether these factors are risk factors for an unfavourable course or consequences of the disorder.
In accordance with the literature (Sargeant et al, 1990; Keller et al, 1982, 1984; Ramana et al, 1995; Paykel et al, 1996; Furukawa et al, 2000) illness-related factors (severity of the index episode and duration of (prior) episodes) were found as predictors for persistence (chapter 3, 6). The index episode being a recurrent one enhanced the speed of recovery (chapter 6). This latter finding differs from the clinical population of the CDS study where a similar duration of subsequent episodes was found (Solomon et al,1997) and from the results of Sargeant et al (1990) from the general population but it is in agreement with Eaton et al (1997) also from the general population. In our earlier study the depressive symptoms anhedonia and early awakening were found as predictors of poor outcome (chapter 3) but unfortunately, we had to limit the potential determinants in the later study and did not examine these depressive symptoms again. In contrast with the results of Ormel et al (1993) in depressed primary care patients and Keitner et al (1992) in depressed hospitalised patients comorbidity with other psychiatric disorders was not found to be associated with poor outcome (chapter 3) or longer duration (chapter 6), probably because we found comorbidity to be correlated with severity of depression (chapter 3) or duration of previous episodes (chapter 6).

3. Research question: What are the consequences of a longer duration of MDE in the general population?
   Hypothesis: Longer duration of MDE lead to more functional disability in the general population.

Contrary to the hypothesis, no association between duration of depression and functional disability in depressed individuals was found (chapter 7). In a subsequent analysis, severity of depression and comorbid anxiety were found as the strongest contributors to dysfunctioning in depressed individuals. We further demonstrated that functioning deteriorates dramatically by actual depressive symptomatology and comorbid anxiety. After symptomatic recovery, functioning improves to premorbid level, irrespective of the length of the depression. Furthermore, sickness absence was found to be substantial in depressed individuals.
The findings are in line with the literature on depression and functional disability. Functional disability has been found associated with severity of depression (Ormel et al, 1994; Judd et al, 2000) and comorbid anxiety (Ormel et al, 1993) and improves with a decrease of depressive symptomatology (Ormel et al, 1993).
As far as we know, no data exist on the temporal relationship between duration of depression and functional disability. Contrary to clinical experiences, the results suggest that longer duration of MDE is not associated with further deterioration in functioning.
As a secondary finding, functional disability was found to improve with a longer duration of recovery after a depressive episode (chapter 7). However, a differential

effect of duration of recovery was found on different domains of functioning: functioning in daily activities improved with a longer duration of recovery but social functioning did not. Residual effects on functioning after recovery could also be demonstrated: after a symptomatic recovery functioning seems to improve to a premorbid, already impaired, level.
These results are consistent with the findings of Furukawa et al (2001) who found further amelioration in functioning with longer duration of symptomatic remission but in earlier studies (Bauwens et al, 1991; Coryell et al, 1993) this could not be demonstrated. Also residual effects on functioning after recovery were earlier demonstrated in the general population (Bijl et al, 2000; Mojtabai, 2001).

4. Research question: What is the association between clinical features of major depression, care utilisation and outcome in the general population?
   Hypothesis: Use of professional care is more likely in individuals with more severe MDEs and/or with longer duration but the outcome of care is less favourable compared to individuals with milder and briefer MDEs.

Depressed individuals with professional care utilisation were found to be more severely and longer depressed and more functionally impaired than those without care. The one-year outcome for those with professional care utilisation was worse compared to those without care (chapter 4). This result seems to confirm the hypothesis and is in agreement with other research (Coryell et al, 1994).
However, in our analyses on duration of MDE we found only non-significant differences in duration of MDE in different levels of care with a longer duration in more specialised care (chapter 5). The most probable explanation for the inconsistency of the results is the effect of lead time bias. In the study on care utilisation (chapter 4) prevalent cases of major depression were included with a predominance of the more chronic cases in a higher level of care. In the study on duration of MDE (chapter 5) a cohort with newly developed MDEs was selected. The conclusion is that referral filter bias and lead time bias partly overlap and that the misleading effects of referral filter bias can largely be avoided by selecting individuals with newly developed episodes of psychopathology.
As a secondary finding, care utilisation for MDD in the Netherlands was found to be considerable. In a one year period 45.3 % (chapter 4) and in two years 67.2 % (chapter 5) of those with a major depression had had some form of professional care. Distribution of care in terms of intensity is rather satisfactory and based on clinical characteristics of depression and functional limitations. Depressed individuals, who do not use professional care, have milder depressions and milder limitations in functioning (chapter 4). Also antidepressant treatment was mainly associated with severity of depression and the presence of comorbid anxiety. The one-year outcome in terms of recovery from depression was best for those without professional care and worse for those treated with antidepressant in specialised mental health care. As far as functional outcome was concerned, substantial improvements in functioning were achieved in most modalities of care (chapter 4).
Care utilisation for persons with major depression in the Netherlands was higher than in the USA (27.7%) (Kessler et al, 1999) where, contrary to the Netherlands, next to clinical characteristics also sociodemographic variables were found to be associated with the distribution of care (Cooper-Patrick et al, 1994). However, in comparison with

other research on both primary care and (Simon et al, 1995; Tiemens et al, 1996) and specialised mental health care (Scott et al, 1992; Keller et al, 1992; Keitner et al, 1992; Picinelli & Wilkinson, 1994) the clinical outcomes of professional care in our study were in the lower range. This is attributable to the poor outcome in antidepressant-treated patients, who had prognostic unfavourable characteristics. Possibly, inadequacy in the implementation of treatment or poor compliance of patients, or both, are responsible for this poor outcome.

Methodological issues

Regarding the methodology of our studies there were several strengths, but also some limitations:

1. NEMESIS is a general population survey and has therefore the advantage of the non-selection of depressed individuals i.e. referral filter bias is avoided. Because of the multistage, stratified, random sampling procedure the representativeness of the study population is adequate. A limitation is that a small proportion of long-term institutionalised people has not been included. However, their numbers are small compared to the total population, and it is to be expected that this will have affected the reported results in a negligible way. Another limiation is the exclusion of those who were not sufficiently fluent in Dutch, thereby partly excluding ethnic minority groups.
2. The total response was satisfactory and non-responders did not significantly differ from responders in estimated psychiatric morbidity. Attrition could be confined to an acceptable rate for a general population study. Psychopathology did not have a strong impact on attrition: at T_1 12-months agoraphobia (odds ratio (OR), 1.96) and social phobia (OR, 1.37), and at T_2 12-months major depression (OR, 1.37), dysthymia (OR, 1.80) and alcohol dependence (OR, 1.83), adjusted for demographic factors, were associated with attrition (de Graaf et al, 2000a; de Graaf et al, 2000b). We therefore believe that our results are not appreciably affected by attrition.
3. MDD was diagnosed with a reliable and validated instrument, the CIDI. However, recently criticism has been raised concerning the use of community-based diagnostic instruments administered by lay interviewers as the CIDI, in stead of a clinical interview by an experienced psychiatrist (Regier et al, 1998). It has been argued that the threshold for a case in the CIDI is too low and especially, there is concern on the clinical significance of cases found with the CIDI. These criticisms have some grounds, but it is unrealistic to equate a diagnostic interview for a population survey with a clinical diagnostic interview as they serve different goals and their results have to be evaluated as such. Furthermore, we do not think that the use of the CIDI invalidates our results. Our focus was on the more severe and prognostic unfavourable MDEs and these are clinically significant. Secondly, the similarities of our results with that of clinical populations strengthen their validity.
4. Strength of our design was that only newly developed MDEs were included (chapter 5,6) thereby avoiding the bias when prevalent cases are included with a predominance of chronic cases.
5. The course of MDE was assessed with a life chart instrument which made it possible to document the course of MDE in detail. However, although NEMESIS

has a prospective design, the duration of depressive episodes during the two years between T_1 and T_2 was assessed retrospectively at T_2, thereby, possibly, introducing recall bias. We believe, however, that this method of assessment of duration, with a combination of prospectively and retrospectively obtained data, is the best feasible for general population surveys.

6. The follow-up of two years was sufficient to investigate the duration of MDE. However, at the same time, the follow-up was a limitation as the long-term course of MDD, in terms of chronicity exceeding the two years and recurrences, could not be observed.
7. A limitation of the design was that only one aspect of poor outcome of MDD was examined i.e. persistence (and chronicity) of MDE; relapses and recurrences of episodes were not studied.
8. The NEMESIS design with three waves was excellent to avoid confounding. Potential determinants of duration were assessed at baseline, before the development of a MDE.
9. A strength of the design was that many potential determinants of duration of MDE (among them many psychosocial variables) were investigated. A limitation is that biological determinants were completely absent in NEMESIS. Our results suggest that this domain might be of particular importance.

Implications

What are the implications of the findings? I will discuss these from different perspectives:1) for the treatment for depressed patients, 2) for mental health policy and 3) from a theoretical perspective.

1) Implications for the treatment of depressed patients

As discussed above, the course of MDE and it's determinants in the general population and in depressed in- and outpatients are much more similar than expected. This implies that our findings from the general population are probably also relevant for clinical populations.

The recommendations are aimed at the improvement of the outcome of care for depression and, in particular, the prevention of chronicity. As the prevalence of major depression is high in primary care and the first contact with professional care in general will take place in primary care, the results of this thesis are especially applicable in primary care.

Primary care The results demonstrated that the course of MDE is heterogeneous. The current guidelines for the diagnosis and treatment of depression lack the specificity to adequately guide day to day clinical practice. More detailed and differentiated guidelines could be helpful and the results of this thesis could be used for that.

For patients with newly developed MDEs, the prognosis seems to be fairly good; 50% recover within three months. But if the duration of an episode exceeds three months the prognosis deteriorates progressively and with a duration of 12 months long-term chronicity has already been reached. A prognostic index could be helpful in discriminating depressed individuals who probably will recover rapidly from those

who will not. The determinants of a longer duration of MDE (illness-related factors, physical illness, lack of social support) are easily to ascertain in depressed patients. For primary care professionals a brief and usable checklist should be devised to assess the presence (and intensity) of these determinants. Illness-related characteristics are the most important items in this checklist, in particular the aspect of duration of the index episode or prior episodes. With such a prognostic index depressed individuals can be discriminated in low, medium and high risk for chronicity.
The following guideline could be formulated: A policy of watchful waiting for three months is recommended for patients with recently developed MDEs and with a low risk for chronicity. Patients with a high risk for chronicity should be referred for specialised mental health care or at least for consultation by a psychiatrist. For those with a medium risk for chronicity primary care treatment with antidepressant medication and/or short-term psychotherapy might be indicated with regular follow-up.
If treatment is indicated, it must be started in time and be aimed at prompt recovery of depressive symptoms. If swift recovery fails to occur, adequate adjustments in treatment have to be made. The diagnostic procedure and treatment for depression should be employed under the pressure of time as any delay of recovery increases the risk for chronicity rapidly. Ideally, recovery of depression should be achieved in a maximum of three months after the initial presentation of the depressed patients. Already chronic depressed individuals in primary care should be detected and referred for specialised mental health care. Diagnostic and treatment protocols should support this way of depression management.

Specialised mental health care For clinicians in specialised mental health care the focus also has to be on the prevention of chronicity of referred patients. Just as in primary care, special attention is needed for patients who do not recover in three months after initiation of treatment. Treatment should be intensified (according tot the existing Dutch protocol for the treatment of depression (de Groot, 1995) (or its coming successor) or diagnosis should be re-evaluated.
For referred chronic depressed patients and for patients who became chronic depressed despite treatment, the adequacy of received treatment has to be assessed. Research in the USA has demonstrated that chronic depressed patients received suboptimal treatment for their depression (Keller, 1994). Treatment should be administered according to the existing guidelines, including Electro Convulsive Therapy (ECT). In addition, the results from Cognitive Behavorial Analysis System of Psychotherapy (CBASP) in combination with antidepressant medication are very promising (Keller et al, 2000). Therapeutic interventions to increase social support with the help of volunteers can also be beneficial as a pioneering study of Harris et al (1999) has shown. The finding of this thesis that even in patients with long-lasting episodes of depression functioning improves after symptomatic recovery, must urge clinicians to treat these depressions aggressively. A defeatist attitude towards patients who have been depressed for such a long period is inappropriate. Nevertheless, a minority of our depressed patients will not profit from any treatment what so ever. They deserve as much professional care but also the support of non-professional activities and groups to help them to cope with this chronic life-long

condition.

2) Implications for mental health policy

Our results suggest that utilisation of care for depression is rather satisfactory in the Netherlands. Most depressed individuals have professional care and at the right level of care. The public campaigns in the Netherlands to destigmatise depression and to educate the people on depression seem to have been successful. However, we do not know whether depressed individuals sought and received professional care in time. If the delay between the development of depression and the initiation of treatment is too long, the prognosis deteriorates (Scott et al, 1992). Future public campaigns should educate the people on the differential prognosis of depression. Again a prognostic index could be devised for the general public to help depressed individuals to decide whether waiting to consult a professional is sensible.

Primary care professionals should be trained and supported in their prognostic skills in order that they are able to make a prognosis and indicate properly for a policy of watchful waiting, treatment or for referral. Possibly, minimal interventions in the form of bibliotherapy (Cuijpers, 1995) or therapy via internet (if efficacy has been established) (de Lange et al, 2001) can fill up the gap between no care and primary care treatment.

The organisation of the treatment for depression should depend on timing and pace. After the initial presentation of a depressed individual, the diagnostic assessment and initiation of treatment should be as fast as possible to prevent the development of chronicity. The care for depressed patients should be organised to facilitate such pace. A waiting time before the first contact with professional care and again before the start of treatment must be avoided. Consultation and referral from primary care to secondary care must also be organised in a way that the pace of treatment will be promoted.

A systematic approach to the treatment of depression as well in primary as in specialised mental health care is needed. Stepped care programs (Tiemens, 1999) are especially suitable for the treatment of depression with initially watchful waiting or minimal interventions and more intensive interventions if recovery of depression fails to occur. However, stepped care programs bear the risk of losing precious time if the prognostic characteristics of the depression are not accounted for and each depression is initially treated with minimal interventions. Further research has to establish whether starting with the more intensive interventions in the event of a prognostic unfavourable depression will lead to better outcome.

In primary care as well as in specialised mental health care more attention is needed for chronic depressed patients. A re-evaluation of the diagnosis and an assessment of the adequacy of treatment should be part of the treatment program. Efficacious treatments for chronic depression (ECT,CBASP (Keller et al, 2000), befriending therapy (Harris et al,1999)) should be amply available in specialised mental health care.

The biggest challenge for the mental health organisation is to improve the outcome of care for MDD. There is a disconcerting gap between efficacy of care and effectiveness of care for major depression. The only way to narrow this gap is by regular and large-scale assessment of the outcomes of care, subsequent analysing the sources for unsatisfactory outcomes and implementing necessary improvements.

Outcome assessment should be aimed not only at symptomatic improvements but also at improvements in social and occupational functioning. For public mental health policy functional outcomes are even more useful than symptomatic outcomes and the introduction of these outcome parameters in standard clinical practice must be supported. Only in this way, potential beneficial effects of treatment-interventions to relieve the burden of disease in terms of improved social functioning and reduced sickness absence days can be measured.
A special remark has to be made on health politics on the workplace as sickness absence and lost productivity was found to be substantial in depressed employees (chapter 7; Laitinen-Krispijn & Bijl, 2000). Actions have to be taken to manage these mental health problems effectively through early recognition and appropriate management (Jenkins, 2001).

3) Theoretical implications
The short-term prognosis of major depression seems to be less pessimistic as previously thought: 50% of those with a depressive episode recover within three months and the one-year outcome for mildly depressed persons without significant limitations in role functioning is favourable. There is now some evidence to adjust the recent clinical notion of MDD as a life-long chronic illness (Keller, 1994; Judd, 1997). However, it must be noted that the long-term prognosis was not investigated and the focus of our studies was on duration and chronicity of a single episode and not on relapses and recurrences. Obviously, relapses and/ or recurrences have occurred in those who initially recovered swiftly.
Knowledge of the natural course of MDE is useful to classify different forms of depression. Efforts to distinguish depressions with different etiologies or pathogenesis (van Praag, 1976) proved to be fruitless. Nevertheless, it is clinical relevant to classify the diversity of the clinical expressions of depression, in order to indicate properly for treatment. Clinical characteristics and course patterns are at present the most likely candidates for such a classification (Keller et al, 1996). At the same time, it is not very likely that different forms represent different disease entities as there is accumulating evidence to consider MDD and it subtypes as different stages or phases of a single clinical illness, which is expressed along a dimensional continuum of symptom severity (Judd et al, 1998).
A remarkable aspect of the natural course of MDE is that recovery is almost coming to a standstill with a duration of 12 months, meaning that those who are still depressed at 12 months are very likely to be depressed at 24 months. It can be argued that the present two-year criterion in the DSM-IV definition of chronicity (APA, 1994) should be replaced by a one-year criterion as this is more in line with the natural course of MDE. A one-year definition might urge clinicians to speed up the management of depression.
Only recently, dysfunctioning was introduced as a criterion in the DSM-classification for MDD (APA, 1994). Theoretically, the relationship between depression and functioning is complex. The results of this thesis suggest that functional disability is not only a consequence of depression but can also be a precursor and possibly even cause a depression. Probably, functional disability is not determined by psychopathology only but by many other determinants.

Recommendations for future research

New research should expand the knowledge on the course of MDD and common mental disorders in general.

- A replication of our findings in another population survey would be important to validate our results. A new general population survey could be improved by the inclusion of ethnic minority groups, longer follow-up and biological and genetic determinants in the design.
- Rates of relapse and recurrence of MDE and their determinants in the general population should be studied. We focussed on one unfavourable outcome (chronicity) but (frequent) relapses or recurrences of MDE are probably as detrimental.
- With the high comorbidity of mood, anxiety and substance use disorders (de Graaf et al, 2002), the question is relevant whether our findings are specific to MDD or if they refer to 'affective disorders' (mood and anxiety disorders) or to an even broader concept of 'common mental disorders' in general.

New research on determinants of the course should be initiated.

- For clinical practice it is of vital importance to investigate the validity and value of a prognostic index in the assessment of MDD.
- From a theoretical perspective, further research on the determinants of illness-related characteristics of a depressive episode is necessary. As these characteristics were found to be the strongest predictors of persistence it is important to understand what affects these characteristics. The dynamic stress-vulnerability model can serve again as a theoretical framework for this kind of research.

New research on outcome of care should have high priority.

- Recommendations for more intensive treatment for those with a greater risk for chronicity should be followed with research on the outcome of such treatments. Is it possible to improve the unfavourable outcome?
- Is it possible to improve the long-term outcome of MDD with systematic treatment programs? And which programs perform best?
- Outcome assessment (including functional outcome) is an important future research task for the mental health care organisation.
- Research on functional disability and depression should address the bi-directional effects of functioning and depression (and comorbid psychopathology) and examine the determinants of dysfunctioning.

Epilogue

The results of our studies have broadened the knowledge on the natural course of MDE and possibly lead to a new paradigm shift on depression and treatment of depression. Since the work of Kraepelin, depression has been considered a disease with a benign course. In recent decennia a paradigm shift has taken place towards a more gloomy view of depression as a lifelong chronic illness (Keller, 1994; Judd, 1997). The results of this thesis suggest that depression is neither of the two but a very heterogeneous condition with a very variable outcome. For some depressed

individuals the prognosis is favourable, even without professional care and for others poor outcome is threatening, despite professional care. The goal of treatment of a depressive episode should be to influence the natural course in a favourable direction and each small step in that direction is of benefit. One of the elements to achieve this, is that clinicians should learn to discriminate between the different clinical expressions and courses of depression and to recognize the relevant prognostic characteristics of the depressive episode in order to indicate properly for treatment.

table: course and determinants of course of major depressive episodes (revised).

	research population (1)	follow-up	classification (2)	N	instruments (3) diagnostic	course	drop out %	course (4)	analysis	lead time bias	median duration (5)	outcome ≥1 yr	outcome ≥2 yr	predictors for persistence/chronicity
Sargeant et al (1990) ECA *[1]	g.p	1 year	DSM-III	423	DIS	DIS	18.7	p + r		yes		23.5% non-recovery		female >30 year, lower education, previous psychiatric history, duration previous episodes, severity depression
Eaton et al (1997) ECA*[1] follow-up	g.p.	15 years	DSM-III-R	71	DIS	life chart	11.4	p	survival	no	3 months		50% non-recovery	
Spijker et al (2001) NEMESIS*[2]	g.p.	1 years	DSM-III-R	305	CIDI	CIDI	23.6	p + r		yes		28.8 % non-recovery		younger age, low mastery, multiple negative life events, duration previous episodes, severity depression, anhedonia/early awakening.
Spijker et al (in press) NEMESIS*[2]	g.p.	2 years	DSM-III-R	250	CIDI	life chart	8.4	p	survival	no	3 months	24% non-recovery	20% non-recovery	chronic physical illness, lack of social support, duration previous episodes, recurrent depression (-), severity of depression
Brown & Moran (1994)	g.p. women	3 years	BCC	89	PSE	PSE	29.2	p	survival	?	6 months	24% non-recovery	6% non-recovery	adverse youth experiences, interpersonal difficulties
Coryell et al (1994)	pts/relatives/ g.p.	6 years	RDC	575	SADS	LIFE	28	p	survival	no	5 months	30% non-recovery	15% non-recovery	no differences in course between patients and others
Ormel et al (1993)	primary care pts	3,5 years	BCC	200	PSE	PSE	20	p + r		yes		21% non-remission	12% non-remission	comorbidity with anxiety disorders
Keller et al (1982; 1984) CDS*[3]	in- and outpts	2 years	RDC	101	SADS	LIFE	6	p	survival	yes	4 months (from entry into the study)	30% non-recovery	19% non-recovery	lower income, being married, previous admissions, secondary depression, duration episode, severity depression
Brown et al (1994)	female in- and outpts	2 years	BCC	125	PSE	PSE	19	p	survival	yes	10 months	41% non-recovery	16% non-recovery	adverse youth experiences, interpersonal difficulties

Furukawa et al (2000)	in- and outpts	2 years	DSM-IV	90	COALA	COALA	4	p	survival	yes	3 months	15% non-recovery	12% non-recovery	severity of depression
Ramana et al (1995); Paykel et al (1996)	in- and outpts	15 mnths	DSM-III-R	70	PSE	PSE	9	p	survival	yes	3.5 months	14% (15 months) non-remission		longer duration of illness,severity of depression
Scott et al (1992)	inpts	2 years	RDC criteria	61	NDI	LIFE	9	p		yes		50% non-recovery	9% non-recovery	neuroticism, time before treatment
Keitner et al (1992)	inpts	1 year	DSM-III	78	DIS	-	10	p + r		yes		51.4% non-recovery		younger age, disturbed family functioning, previous admissions, comorbidity, lenght of hospitalisation

(1) g.p. = general population, pts = patients; (2) DSM = Diagnostic and Statistical Manual, BCC = Bedford College criteria, RDC = Research Diagnostic Criteria; (3) DIS = Diagnostic Interview Schedule, CIDI = Composite International Diagnostic Interview, LIFE = Longitudinal Interval Follow-up Evaluation, PSE = Present State Examination, SADS = Schedule for Affective Disorders and Schizophrenia, COALA = Comprehensive List for Affective Disorders, NDI = Newcastle Diagnostic Instrument; (4) p = persistence, p + r = no distinction was made between persistence and recurrence; (5) estimation of median duration as this information was not always available.
*[1] ECA = Epidemiologic Catchment Area study, *[2]NEMESIS = Netherlands Mental Health and incidence Study, *[3] CDS = Collaborative Study of the Psychobiology of Depression.

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Summary

Chapter 1: Introduction.
Unipolar major depressive disorder (MDD) represents an important and worldwide public health problem among other things because of the high tendency towards relapse, recurrence and chronicity. Knowledge of the development of these unfavourable courses of MDD may guide the development of more effective treatment strategies to prevent them.
The subject of this thesis is chronicity of major depressive disorder (MDD). The main aims of the study were to examine:

4. the duration of a major depressive episode (MDE) and the rate of a chronic duration of MDE in the general population,
5. the determinants of (chronic) duration of MDE,
6. the consequences of a longer duration of MDE on daily functioning.

The DSM-IV definition of chronicity implies full criteria for MDD during two years or more. In this thesis broader definitions of chronicity were employed including one with a one-year criterion and one with non-recovery during two years or more (including comorbid dysthymia).
The studies in the thesis were part of a general population survey amongst adults (18-64 year): the Netherlands Mental Health Survey and Incidence Study (NEMESIS) with three waves in 1996 (T_0), 1997 ($T_1 = T_0 + 12$ months) and 1999 ($T_2 = T_0 + 36$ months). The diagnoses of psychiatric disorders in NEMESIS were based on DSM-III-R. The instrument used to determine the diagnoses was the Composite International Diagnostic Interview (CIDI) Version 1.1 (computerised version). Various determinants of the course of mental disorders were assessed.

Chapter 2: Review of the literature.
A literature review was performed on the determinants of the prognosis of MDD with a special focus on a chronic course of depression. A chronic course develops in 9% to 19% of depressed patients. Illness-related factors were found as the strongest predictors of persistence of depression: severity of the depressive episode, duration of (previous) episodes and comorbidity (with somatic disorders, alcohol addiction, anxiety disorders and possibly dysthymia). However, in most of the reviewed literature selected populations of depressed inpatients or outpatients were employed which leads to an overrepresentation of cases with longer duration of depression. General population studies can avoid this selection bias (or referral filter bias).
Treatment appeared to be another issue in the review. The role of treatment to prevent chronicity is difficult to study in naturalistic designs because of the complex association between clinical characteristics of the depression, care utilisation and outcome of care. An additional aim of the thesis was to examine this association.

Chapter 3: Determinants of poor one-year outcome of DSM-III-R major depression in the general population.

223 individuals with a (six-month prevalence) diagnosis of MDE at T_0, were prospectively assessed at T_1. A broad range of potential risk factors was evaluated. Of those with MDE at baseline, 28.3% were still (or again) depressed one year later. Younger age, severe depression, melancholic symptoms (anhedonia and early morning awakening), longer duration of previous episodes, external locus of control were found as important risk factors for a poor outcome. In addition, the influence of multiple negative life events also appeared considerable.
The results suggest that depressed individuals in the general population are basically subject to the same risk factors of poor outcome as clinically (i.e. identified) depressed patients.
There were some limitations to this study. In the first place it was not possible to differentiate between a relapsing, recurrent or chronic one-year course. Secondly, lead time bias was introduced i.e. depressed persons were not recruited at a similar point in time in the course of the disorder; mostly prevalent cases were included. And thirdly, confouding was introduced as some determinants of the course of MDE (like personality characteristics) were assessed during the depressive episode.

Chapter 4: Care utilisation and outcome of care of DSM-III-R major depression in the general population.
Care utilisation between T_0 and T_1 and outcome of care were evaluated for 223 individuals with a (six-month prevalence) diagnosis of MDE at T_0. Outcome was assessed at T_1 using depression status at T_1 (yes/no) and changes in role functioning between T_0 and T_1 (assessed with the Short Form-36 Health Survey (SF-36).
Of the depressed individuals, 45.3% received professional care and 42.6% of these individuals were treated with antidepressants. Respondents treated within different levels of care (no professional care, primary care only and specialised mental health care), were found to differ on clinical factors and role dysfunctioning, but not on socio-demographic variables. More intensive treatment was found related to more severe or comorbid depression.
Depressed individuals who received treatment were found to improve substantially in functioning, but this progress was not sufficient for many of them (with severe or anxiety comorbid depression) to recover from the depression itself.
The outcome of care was best for those without professional care and worse for those with specialised mental health care.
These findings substantiate the notion of referral filter bias and demonstrate that depressed patients in specialised mental health care are more severly ill than depressed primary care patients who, in turn, are more severly ill than those without treatment.

Chapter 5: Duration of major depressive episodes in the general population.
Duration of MDE was assessed in a cohort of 250 respondents with newly developed episodes (with a diagnosis of two-year prevalence MDD at T_2 but no diagnosis of one-month prevalence MDD at T_1). A Life Chart Interview was

administered at T_2 in order to document the course of MDE between T_1 and T_2 in detail. Duration of MDE was calculated using survival analysis.
The median time to recovery was 3.0 months (95% CI 2.2-3.8 months) and the mean time to recovery with the upper limit of 24 months was 8.4 months (95% CI 7.3-9.5 months). Of the respondents, 50% (95% CI 44- 56%) recovered within 3 months; 63% (95% CI 57-69%) within six months; 76% (95% CI 70-82%) within 12 months and 80% (95% CI 74-86%) within 21 months. This means that half of those with MDE recovered fast but rate of recovery slowed down toward 12 months, virtually coming to a standstill after 12 months. Almost 20% of the depressed subjects had not recovered at 24 months. The risk of a chronic course was the same in treated and in untreated depressed subjects.

Chapter 6: Determinants of persistence of major depressive episodes in the general population.
Several potential determinants of persistence were examined in 250 respondents with newly developed MDE's from the general population, using the 'dynamic stress-vulnerability model' as a conceptual framework. Cox proportional hazards models were used to test the associations between the various determinants and duration of MDE.
Just as in clinical populations, illness-related factors were found as the strongest predictors of episode duration: i.e. severity of the index episode and a longer duration of previous episodes. The index episode being a recurrent episode enhanced the speed of recovery. Lack of social support was also associated with longer duration and (chronic) physical illness had a predictive value on the duration of later depressive episodes. Determinants of duration in the early phase of the episode differed from determinants later on in the episode: in the first three months only illness-related factors predicted duration but if the episode persists personality characteristics, (chronic) physical illness and comorbid dysthymia became important.

Chapter 7: Duration of depression and recovery and functional disability in the general population.
The associations between duration of depression and recovery and functional disability were examined in 250 respondents with newly developed MDE's from the general population. Functional disability was assessed using the Short Form-36 Health Survey (SF-36) at T_1 and T_2 and absence days from work at T_2. Functional disability was not found to be associated with duration of MDE but with severity of depression and comorbid anxiety. After symptomatic recovery, functioning improved to premorbid level, irrespective of the length of MDE. Functioning in daily activities improved with longer duration of recovery but social functioning did not.

Chapter 8: Discussion
The main findings of the studies were:
1. The median duration of MDE in the general population was 3 months and almost 20% of the depressed individuals had not recovered at 24 months.
2. Illness-related factors were found as the strongest predictors of episode duration i.e. severity of the index episode, a longer duration of previous

episodes and the index episode being a recurrent episode. Furthermore, lack of social support and (chronic) physical illness were found to be associated with longer duration.
3. Longer duration of depression was not found to be associated with increased functional disability.
4. Depressed individuals with professional care utilisation were found to be more severely and longer depressed and more functionally impaired than those without care. The one-year outcome for those with professional care utilisation was worse compared to those without care.

The rate of chronicity and the determinants of persistence of depression in the general population were very similar to clinical populations. An important explanation for these unexpected findings were the methodological strengths of the design:
As a general population survey, NEMESIS had the advantage of the non-selection of depressed individuals i.e. referral filter bias was avoided. Furthermore, only newly developed MDEs were included thereby avoiding the bias when prevalent cases are included with a predominance of chronic cases. Course of MDE was documented in detail. And finally, the NEMESIS design with three waves, was excellent to avoid confounding; potential determinants of duration were assessed at baseline, before the development of a MDE.

The results of this thesis suggest that MDD is a heterogeneous condition with a variable outcome. The implications of the results are especially applicable in primary care. A more differentiated guideline for the treatment of MDD could be formulated: A policy of watchful waiting for three months is recommended for patients with recently developed MDEs and with a low risk for chronicity. Depressive patients with a high risk for chronicity should be referred for specialised mental health care or at least for consultation. For those with a medium risk for chronicity primary care treatment might be indicated with regular follow-up. A prognostic index should be devised for the assessment of the risk for chronicity in depressed individuals. Determinants of persistence of MDE, especially illness-related characteristics as severity and duration of the index episode or prior episodes, should be included in this index.

Samenvatting

Hoofdstuk 1: Inleiding.
Unipolaire depressie is wereldwijd een belangrijk volksgezondheidprobleem onder andere vanwege de hoge mate van voorkomen van terugval, recidieven en chroniciteit. Kennis over deze ongunstige belooppatronen is van belang om behandelingsstrategieën te ontwikkelen die het ongunstige beloop kunnen voorkomen.
Het onderwerp van dit proefschrift is het chronisch beloop van de unipolaire depressie in engere zin (DSM-III-R). De belangrijkste onderzoeksvragen waren:

1. Wat is de duur van een depressieve episode in engere zin (verder genoemd depressieve episode) in de algemene bevolking en hoe vaak komt een chronisch beloop van een depressieve episode voor?
2. Wat zijn de determinanten van (een chronische) duur van een depressieve episode?
3. Wat zijn de gevolgen van een langere duur van een depressieve episode op het algemeen functioneren?

De huidige DSM-IV definitie voor een chronisch beloop van depressie stelt dat er minstens twee jaar aan alle criteria voor een depressieve stoornis voldaan moet worden. In dit proefschrift werden minder strikte definities voor chroniciteit gebruikt zoals een één-jaars definitie en een definitie van geen herstel gedurende twee jaar waarbij ook comorbide dysthymie werd meegerekend.
De studies in dit proefschrift maakten deel uit van een algemene bevolkingsstudie onder volwassenen (18-64 jaar): de Netherlands Mental Health and incidence Study (NEMESIS) met drie interviewrondes in 1996 (T_0), 1997 ($T_1 = T_0 + 12$ maanden) en 1999 ($T_2 = T_0 + 36$ maanden). Psychiatrische stoornissen werden vastgesteld met de Composite International Diagnostic Interview (CIDI) Version 1.1 (gecomputeriseerde versie) volgens de DSM-III-R systematiek. Verschillende determinanten voor het beloop van stoornissen werden vastgelegd.

Hoofdstuk 2: Literatuuroverzicht.
Er werd een literatuuronderzoek verricht naar de determinanten van het beloop van unipolaire depressie met het focus op chronisch beloop. Bij 9-19% van de patiënten met een depressieve episode bleek er sprake van een chronisch beloop. Ziektekenmerken bleken de sterkste voorspellers voor het persisteren van depressie: grotere ernst van de depressieve episode, langere duur van (vorige) episode(n), en comorbiditeit met somatische aandoeningen, alcoholverslaving, angststoornissen en mogelijk ook dysthymie. Echter, over het algemeen werden in de gevonden studies vooral behandelde patiënten onderzocht met een oververtegenwoordiging van ernstig en/of langdurig zieke patiënten. Bevolkingsstudies kennen deze vorm van selectie bias (of ‘referrral filter’ bias) niet.
De rol van behandeling bleek gecompliceerd. Effecten van behandeling zijn niet goed te onderzoeken in naturalistische studies gezien de associaties tussen de klinische karakteristieken van depressie en zorggebruik en uitkomsten van zorg.

De relaties tussen deze factoren vormden een extra onderzoeksvraag voor dit proefschrift.

Hoofdstuk 3: Determinanten van een ongunstig 1-jaarsbeloop van de DSM-III-R depressie in engere zin in de algemene bevolking.

223 volwassenen met een (6-maands prevalente) depressieve episode op T_0 werden prospectief gevolgd tot T_1. Een groot aantal mogelijke voorspellers voor ongunstig beloop werd onderzocht.

28.3% van degenen die op T_0 depressief waren, bleek na één jaar nog steeds (of opnieuw) depressief. Jongere leeftijd, ernstige depressie, vitale symptomen (anhedonie, vroeg ontwaken), langere duur van eerdere episoden en een externe 'locus of control' bleken voorspellers voor een ongunstig beloop. Daarnaast was er een invloed van het meemaken van meerdere negatieve life events.

De resultaten wijzen erop dat in de algemene bevolking dezelfde determinanten het beloop van een depressieve episode bepalen als bij behandelde patiënten. Er waren enkele beperkingen aan de studie: In de eerste plaats bleek het niet mogelijk om een onderscheid te maken tussen een één -jaars beloop met terugval, recidief of chroniciteit. Ten tweede waren op T_0 prevalente casus met een depressieve episode geïncludeerd met een verschillende voorafgaande duur van depressie (zgn. 'lead time bias'). En tenslotte was er sprake van 'confounding' omdat sommige determinanten van het beloop (bijv persoonlijkheidstrekken) waren vastgesteld tijdens de depressie.

Hoofstuk 4: Zorggebruik en uitkomsten van zorg voor DSM-III-R depressie in engere zin in de algemene bevolking.

Zorggebruik tussen T_0 en T_1, en uitkomsten van zorg werden vastgesteld voor 223 individuen met een 6-maands prevalente depressie op T_0. Uitkomsten werd vastgesteld op T_1 met behulp van de depressie-status (ja/nee) en de veranderingen in rolfunktioneren tussen T_0 en T_1 (vastgesteld met behulp van de Short Form-36 Health Survey (SF-36)).

Van de respondenten met een depressieve episode bleek 45.3% professionele hulp ontvangen te hebben en bij 42.6% van dezen bleek antidepressieve medicatie voorgeschreven te zijn. Respondenten die in verschillende niveaus van de zorg werden behandeld (geen professionele zorg, alleen zorg in de eerste lijn of ook zorg in de tweede lijn) bleken te verschillen op klinische kenmerken en rolfunctioneren maar niet op sociaaldemografische kenmerken. Meer intensieve zorg was geassocieerd met een meer ernstige depressieve episode of comorbiditeit. Respondenten die behandeling ondergingen verbeterden in hun algemeen functioneren. Deze verbetering was echter niet voldoende voor degenen met een ernstige depressieve episode of een depressieve episode in combinatie met angststoornissen om te herstellen van de depressie. De uitkomsten waren het beste voor diegenen die geen professionele zorg zochten en het slechtst voor diegenen die tweede lijnszorg ontvingen.

De resultaten laten het effect van "referral filter bias' zien en tevens dat depressieve patiënten, die behandeld worden in de tweede lijn, ernstiger ziek zijn dan patiënten die in de eerste lijn worden behandeld, die op hun beurt weer zieker zijn dan respondenten die geen behandeling zochten.

Hoofdstuk 5: Duur van depressieve episoden in de algemene bevolking.
De duur van een depressieve episode werd vastgesteld in een cohort van 250 personen met een nieuw ontstane episode (met een diagnose van twee-jaars prevalente depressieve episode op T_2 maar geen diagnose van één-maands prevalente depressieve episode op T_1). Een Life Chart Interview werd afgenomen op T_2 om het beloop van de depressieve episode tussen T_1 en T_2 in kaart te brengen. Duur van de depressieve episode werd berekend met behulp van survival analyses.
De mediane tijd tot herstel was 3.0 maanden (95% CI 2.2-3.8 maanden) en de gemiddelde duur tot herstel binnen de observatieperiode van 24 maanden was 8.4 maanden (95% CI 7.3-9.5 maanden). 50% (95% CI 44- 56%) van de depressieve personen herstelden binnen 3 maanden; 63% (95% CI 57-69%) binnen 6 maanden; 76% (95% CI 70-82%) binnen 12 maanden en 80% (95% CI 74-86%) binnen 21 maanden. Dit betekent dat de helft van degenen met een depressieve episode snel herstelden (binnen drie maanden). De snelheid van herstel nam af na drie maanden en kwam bijna tot stilstand na 12 maanden. Na 24 maanden was bijna 20% nog niet hersteld. De kans op dit chronische beloop was niet verschillend voor behandelde en onbehandelde respondenten.

Hoofdstuk 6: Determinanten van het voortduren van depressieve episoden in de algemene bevolking.
Verschillende mogelijke determinanten voor het voortduren van een depressieve episode werden onderzocht in een cohort van 250 respondenten met een nieuw ontstane depressieve episode. Het ‘dynamisch stresskwetsbaarheidsmodel’ diende als theoretisch model.
In een Cox regressie model werden de associaties berekenend tussen de verschillende determinanten en de duur van een depressieve episode. Ziektekenmerken bleken de sterkste voorspellers voor de duur: de ernst van de episode en een langere duur van voorafgaande episoden. Als de index episode een recidief bleek te zijn, bleek dit juist een voorspeller voor kortere duur. Gebrek aan sociale steun en eerder vastgestelde (chronisch) somatisch aandoeningen bleken voorspellers voor een langere duur van een depressieve episode.
In het begin van een episode bleken de determinanten voor de duur te verschillen van de determinanten later in de episode. In de eerste drie maanden waren alleen de ziektekenmerken voorspellers voor de duur maar als de episode aanhield bleken ook persoonlijkheidskenmerken, (chronische) somatische aandoeningen en comorbide dysthymie van belang.

Hoofdstuk 7: Duur van depressie en van herstel en functionele beperkingen in de algemene bevolking.
De associaties tussen duur van depressie en duur van herstel en functionele beperkingen werden onderzocht in een cohort van 250 respondenten met nieuw ontstane depressieve episoden. Functionele beperkingen werden vastgesteld met behulp van de Short Form-36 Health Survey (SF-36) op T_1 enT_2 en ziektedagen op T_2 .

Functionele beperkingen bleken niet geassocieerd met de duur van een depressieve episode maar wel met de ernst van depressie en met comorbiditeit met angststoornissen. Na een symptomatisch herstel van de depressieve episode, verbeterde het functioneren ook weer tot een niveau van voor de depressieve episode, ongeacht de duur van de episode. Het functioneren in dagelijkse activiteiten verbeterde bij een langere duur van herstel in tegenstelling tot het sociaal functioneren.

Hoofdstuk 8: Discussie

De belangrijkste uitkomsten van het onderzoek waren:

1. De mediane duur van een depressieve episode in de algemene bevolking was 3 maanden en bijna 20% van de personen met een depressieve episode was nog niet hersteld na 24 maanden.
2. Ziektekenmerken bleken de belangrijkste voorspellers voor de duur van depressieve episode (ernst van de episode, een langere duur van eerdere episoden, een recidief episode). Verder waren ook gebrek aan steun en (chronische) somatische aandoeningen voorspellers voor een langere duur.
3. Een langere duur van een depressieve episode bleek geen verband te houden met een verdere achteruitgang in functioneren.
4. Depressieve personen, die professionele zorg ontvingen voor depressie, bleken ernstiger en langer depressief en hadden meer beperkingen in hun functioneren dan depressieve personen die geen professionele zorg ontvingen. De uitkomst na één jaar was slechter voor diegenen met professionele zorg dan voor diegenen zonder professionele zorg.

De mate van chroniciteit en de determinanten voor het persisteren van depressie in de algemene bevolking kwamen overeen met de resultaten in behandelde groepen.
Methodologische kwaliteiten van het onderzoek vormden de belangrijkste verklaring voor deze onverwachte bevindingen. In NEMESIS heeft geen selectie van depressieve personen plaatsgevonden m.a.w. van ‘referral filter bias’ was geen sprake. Verder werden alleen casus met nieuw ontstane depressieve episoden geïncludeerd, in plaats van prevalente casus, waardoor een oververtegenwoordiging van depressies met een langere duur ontstaat. Het beloop van depressieve episoden werd gedetailleerd in kaart gebracht. Tenslotte was het NEMESIS design met drie interviewrondes zeer geschikt om ‘confounding’ te vermijden: potentiële determinanten konden worden vastgesteld voor het ontstaan van depressieve episoden.

De resultaten van het onderzoek wijzen erop dat de unipolaire depressie in engere zin een heterogene aandoening is met een variabel beloop. De resultaten zijn vooral van belang voor de eerste lijn. Een meer gedifferentieerde richtlijn voor de behandeling van depressie is nodig. Bij nieuw ontstane depressieve episoden met een laag risico op chroniciteit lijkt een afwachtend beleid gerechtvaardigd. Als de verwachte duur langer wordt ingeschat dient behandeling plaats te vinden. Bij een hoog risico op chroniciteit is een verwijzing naar de tweede lijn op zijn plaats of er zou consultatie aangevraagd kunnen worden. Verder onderzoek is nodig om een prognostische index te

ontwikkelen om bij mensen die zich met een depressie presenteren de risico's voor chroniciteit vast te stellen. Determinanten voor het persisteren van een depressieve episode en met name de ziekte kenmerken zoals ernst en duur van de index episode en eerdere episoden moeten in zo'n prognostische index opgenomen worden.

Dankwoord

Dankwoorden van proefschriften zijn over het algemeen weinig origineel en dat zal deze ook niet worden. Eén van de redenen voor dit gebrek aan originaliteit is dat een promotietraject zich toch meer volgens vaste patronen voltrekt dan je zou verwachten. Een standaardopmerking in dankwoorden is dat de promovendus niet alleen promoveert maar met velen. En zo is het mij ook vergaan, zonder de mensen die aan de promotie hebben bijgedragen was het er niet van gekomen.
Ik wil daarom hier de mensen bedanken die voor de promotie belangrijk geweest zijn en tegelijk de chronologie van het traject beschrijven.
Het begon in 1995 met de opmerking van Frank Kortman, toen directeur van het APZ Wolfheze en nu hoogleraar psychiatrie te Nijmegen dat ik maar eens moest gaan praten bij het Trimbos-instituut toen ik me tot hem wendde met een plannetje voor onderzoek. Dat bleek een gouden greep want mijn eerste gesprek was daar met Giel Hutschemakers, nu bijzonder hoogleraar Academisch Centrum Sociale Wetenschappen KUN en directeur Gelderse Roos Instituut voor Professionalisering. Giel opende vele deuren met zijn grote bevlogenheid: alles was mogelijk! Na enkele omzwervingen bracht hij me op het spoor van Rob Bijl en het NEMESIS onderzoek. Mijn belangstelling ging uit naar depressie en, door de praktijkervaringen, met name naar het chronisch beloop van depressie. Na vele gesprekken met Rob, waarbij ik me steeds weer verbaasde met hoeveel gemak hij belangstelling, deskundigheid en zakelijkheid combineerde, kwamen we uiteindelijk tot een globaal onderzoeksplan. Rob was bereid copromotor te worden.
Vervolgens zocht ik een promotor en die bleek geografisch heel dichtbij, slechts het Wilhelminapark in Utrecht overstekend. Willem Nolen, hoogleraar psychiatrie UMC Utrecht, bleek ook op andere manieren zich zeer nauw bij het project betrokken te voelen. Zijn zorgvuldig en uitvoerig commentaar op de toegestuurde stukken kwam soms per kerende mail (!!) terug. Met zijn grote inzet en enthousiasme gedurende het gehele onderzoek ontkrachtte Willem de mythe dat promotoren ontoegankelijk zouden zijn.
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Om het eigenlijke onderzoekswerk te kunnen doen hebben vele collegae op het Trimbos mij geholpen om de beginselen van methodologie, statistiek en schrijven van artikelen onder de knie te krijgen waaronder Lea Jabaaij, Anneloes Ravelli, Margreet ten Have, Filip Smit, Casper Schoemaker, Saara Laitinen, Saskia van Dorsselaer, Bea Tiemens en Wilma Vollebergh. Maar het meest toch Ron de Graaf die met veel geduld mij de mysteriën van SSPS onthulde en ook kritisch bleef meelezen aan de artikelen.
Geleidelijk aan ging het onderzoek steeds meer beslag op me leggen en kwamen andere werkzaamheden in de knel. Mijn Gelderse Roos collegae van

de deeltijdbehandeling in Tiel en later de ambulante teams persoonlijkheidsstoornissen en stemmingsstoornissen in Arnhem hebben hier vooral mee te maken gehad maar ik kan me niet herinneren dat er ooit een onvertogen woord is gevallen (maar misschien wel eens gedacht?).
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Een promotieonderzoek hoort met ups en downs te gaan. De downs lieten aanvankelijk even op zich wachten maar toen halverwege de analyses niet wilden vlotten was het toch zover. Nieuwe inbreng was nodig en Hans Ormel, hoogleraar sociale psychiatrie te Groningen en Aartjan Beekman, psychiater GGZ Buitenamstel te Amsterdam, waren gelukkig bereid hun vele kwaliteiten voor het onderzoek in te zetten; Hans met een scherp oog voor de methodologische aspecten en Aartjan met een groot talent voor schrijven.
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En tenslotte Robert, jij maakte de omslag van het boek maar jouw bijdrage is veel groter. De chronologie van het verhaal klopt hier ook niet meer. Jij was er al heel lang voor dit promotietraject en ik hoop dat je er ook nog heel lang zult zijn hierna.
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Curriculum vitae

Jan Spijker werd geboren op 20 januari 1960 te Dedemsvaart. Hij behaalde in 1978 zijn VWO-diploma aan het Menso Altingh College te Hoogeveen en studeerde daarna Geneeskunde aan de Rijksuniversiteit Utrecht tot het arts-examen op 30 augustus 1985.
Hij werkte daarna een half jaar als AGNIO bij de GG& GD te Amsterdam. Vanaf 1986 vervulde hij zijn militaire dienstplicht als arts-assistent op de afdeling psychiatrie van het Militair Geneeskundig Hospitaal te Utrecht. Hierna volgde een AGNIO-schap bij de afdeling neurologie van het Bleuland ziekenhuis te Gouda. Vervolgens werkte hij bij Zon & Schild te Amersfoort waar hij per 1 december 1988 zijn opleiding tot psychiater startte met als opleider dr. G. Hellinga. Het keuzejaar psychotherapie deed hij bij de RIAGG RNO Rotterdam (opleider H. van den Berg) en sociale psychiatrie bij de RIAGG Westelijk Utrecht (opleider mevr. M. de Pater).
Vanaf 1993 werkt hij als psychiater bij APZ Wolfheze, nu de Gelderse Roos; de eerste jaren bij de psychiatrische deeltijdbehandeling in Tiel en sinds 1999 bij de ambulante afdeling volwassenzorg in Arnhem en tevens als plaatsvervangend A-opleider. Hij volgde de opleiding tot groepspsychotherapeut van 1993 tot 1998.
Zijn eerste werkzaamheden bij het Trimbos-instituut dateren vanaf 1995; deze leidden tot een detachering voor een dag in de week en dit proefschrift.
Hij woont, met zijn partner, in Utrecht.