Epidemiology of late life depression

Longitudinal findings
from the Amsterdam study of the elderly

The study presented in this thesis was conducted at the Institute for Research in Extramural Medicine (EMGO Institute), the department of Psychiatry (VU Medical Center Amsterdam) and the department of Sociology and Social Gerontology (Vrije Universiteit Amsterdam). The EMGO Institute participates in the Netherlands School of Primary Care Research (CaRe), which was acknowledged in 1995 by the Royal Netherlands Academy of Arts and Sciences (KNAW). The study was funded by grants of the Netherlands Health Research Promotion Programma (Stimuleringsprogramma Gezondheidsonderzoek) and the Netherlands Foundation of Mental Health (Nationaal Fonds Geestelijke Volksgezondheid).

NFGV
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The printing of this thesis was financially supported by:
Vrije Universiteit afdeling Psychiatrie.
Lundbeck BV.
Wyeth Pharmaceuticals.
Janssen-Cilag BV.
Pfizer BV.
Eli Lilly Nederland BV.
Organon Nederland BV.

Cover design: Annelies Frölke
Lay-out: Lydia Funneman
Printed in the Netherlands by Ridderprint Offsetdrukkerij BV.

ISBN: 90-9019430-4

VRIJE UNIVERSITEIT

EPIDEMIOLOGY OF LATE LIFE DEPRESSION

LONGITUDINAL FINDINGS FROM THE AMSTERDAM STUDY OF THE ELDERLY

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. T. Sminia,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op woensdag 6 juli 2005 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

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geboren te Lagos, Nigeria

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Introduction

1.1 Introduction

In this first chapter, a brief overview will be presented of the background, primary aims and the clinical and theoretical notions that have lead to the research on which this thesis is based.

1.2 Background

In the year 2000, unipolar major depression was the fourth leading cause of disease burden worldwide in terms of Disability Adjusted Life Years, causing the largest amount of non-fatal burden and accounting for almost 12% of all years lived with disability worldwide (Ustun et al. 2004). A growing body of literature has shown that, at a later age as well as in younger adults, depression is associated with a diminished quality of life, significantly higher levels of disability, functional decline, demands on caregivers and service utilization (Charney et al. 2003;Hays et al. 1995;Katon et al. 2003;Wells et al. 1989). With a prevalence of depression requiring clinical attention in community dwelling older persons of around 13.5 % (Beekman, Copeland, & Prince 1999), the importance of depression in terms of both individual suffering and public health is uncontested. As the population in western countries is rapidly ageing, adequate recognition and, if possible, prevention of the negative consequences of late-life depression is becoming a major public health issue. It is estimated that in the Netherlands, the percentage of the population over the age of 65 years will increase from 13.8% in 2003 to 23.3% in 2040 (Centraal Bureau voor de Statistiek 2004).

In spite of these facts, only 15 years ago little systematic research had been performed on prevalence and natural history of geriatric depression (Blazer 1989;Cole 1990). Studies in the community were relatively rare, and the issue of late-life psychopathology had not yet received the amount of attention from policy makers and researchers that it is currently experiencing. Research in old age psychiatry mainly focused on patients in secondary care facilities, and both recognition and adequate treatment of late-life depression in primary care settings were poor. The study of late-life psychopathology thus mimicked an earlier description by David Goldberg and Peter Huxley in their book 'Mental Illness in the Community' (1980). They pointed out that psychiatry urgently needed more extensive knowledge on prevalence, course and risk profiles of types of psychopathology that do not reach through the consecutive filters in health care up to the specialist level of psychiatry (Goldberg & Huxley 1980).

Since then, a number of epidemiological studies have been initiated to study late-life psychopathology in the community. The Amsterdam Study of the Elderly (AMSTEL) was initiated in 1988 by the Department of Psychiatry of the Vrije Universiteit Amsterdam. In light of the demographic changes and the increase of age-related physical and mental problems, an urgent need was felt for research in geriatrics and psychogeriatrics. AMSTEL was designed to study incidence and course of dementia or cognitive impairment, depression and generalised anxiety disorder in elderly peo-

ple living in the community. The study also aimed to investigate diagnostic instruments that would differentiate between early stages of dementia, age-related cognitive impairment and other forms of somatic or psychiatric pathology in later life. The study was supervised by Prof.dr.W. van Tilburg. The project was directed by Prof.dr.C.Jonker and Dr.C.Hooijer. AMSTEL was supported by the Netherlands Health Research Promotion Programme (Stimuleringsprogramma Gezondheids Onderzoek, SGO).
This thesis is based on data from the AMSTEL study, collected from 1990 until 2001.

1.3 Aims of this thesis

The primary aims of this thesis were to study late-life depression and its longitudinal associations with a comprehensive set of risk factors in a large community sample. This general topic was subdivided into the following research domains;

1 The onset of depression in later life and the factors associated with onset.
2 The natural course of depression in later life, and the associations of risk factors with course types.
3 Comorbidity patterns and temporal associations between depression and generalised anxiety disorder, and between depression and cognitive decline
4 The associations of depression with excess mortality
5 A research agenda for prevention of depression in primary care according to vulnerability characteristics of community living older persons.

Specific research questions originating from these aims will be addressed in the subsequent chapters of this thesis.

1.4 Depression as a clinical concept; from black bile to bio-psycho-social disorder

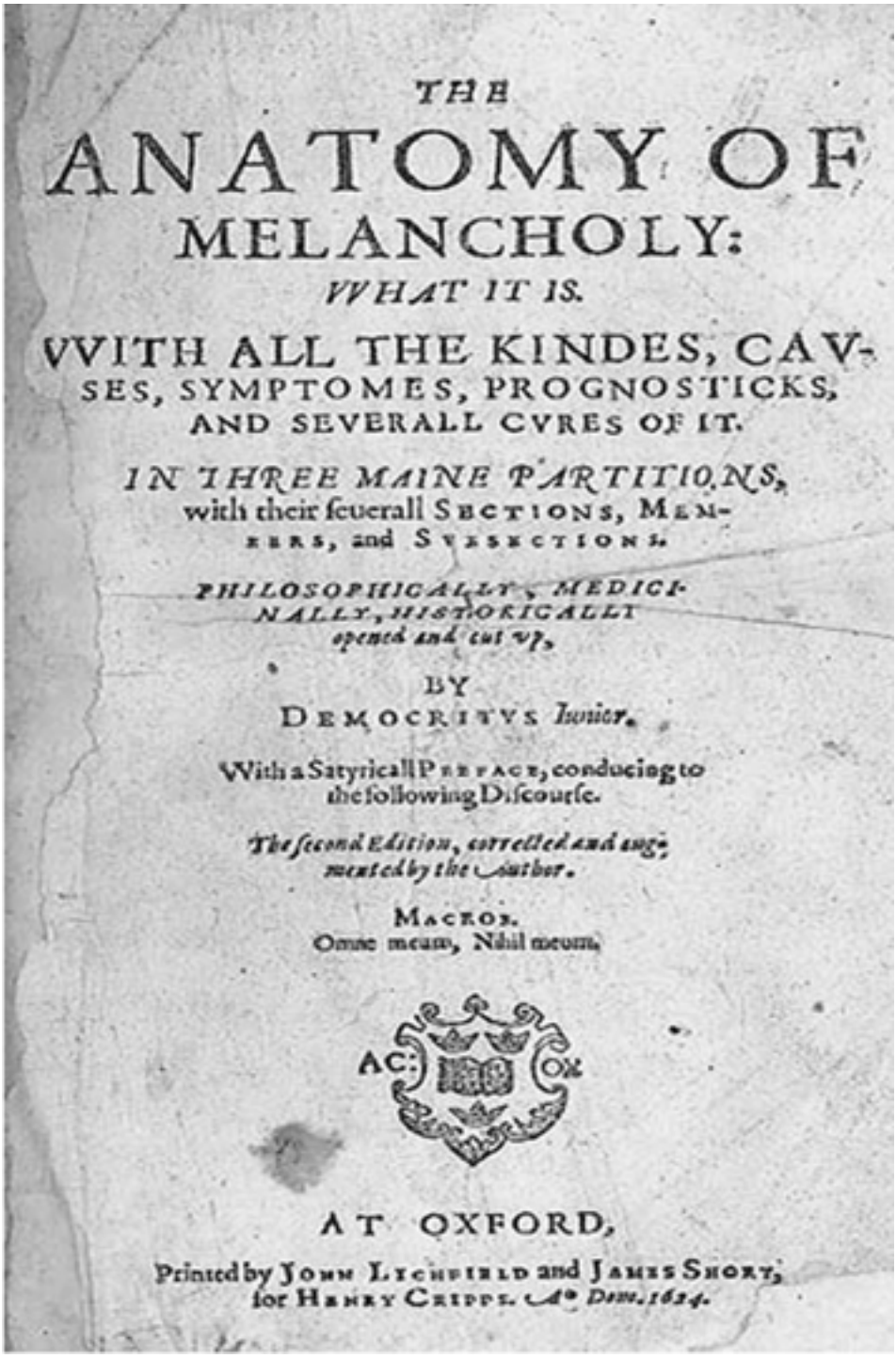
In his comprehensive work on the history of the depression concept, 'Melancholia and depression', Stanley W. Jackson has demonstrated how descriptions of the core symptoms of depression have remained remarkably stable over more than 2500 years of medical writings (Jackson 1986). Another consistent factor is that throughout history depression has been considered to be the result of an interaction between internal (personal) and external causes, the shape and meaning of which were determined by the dominant beliefs of the different eras. In the works of Hippocrates (460-357 BC), melancholia is characterised as a chronic condition with 'aversion to food, despondency, sleeplessness, irritability and restlessness'. According to the humoral theory, diseases were the result of a disturbance of the equilibrium between the four humours, and melancholia was believed to be associated with a pathological excess of black bile, a 'cold and dry' condition that affected the brain. A link between depression and anxiety was already noted, and the Roman Galen (131-201 AD) stated that melancholia manifested itself in 'fear and depression, discontent with life, and hatred of all people'. Almost fifteen hundred years later, in

1621, Burton published his 'Anatomy of Melancholy' in which he referred to the ideas of the ancient Greeks and Romans. Burton also described different pathways to depression. He distinguished 'congenite or inward causes of depression' such as inheritance and temperament, but also exogenous causes that could either be supernatural ('from God or the devil immediately, or mediated by magicians or witches') or natural (e.g. diet, alcohol, sleeping and other biological rythms, and 'passions and perturbations of the mind' due to factors such as 'intense love'). Amongst others, Burton specifically mentioned the risk of 'love of learning, and study in excess', responsible for the 'misery of scholars' and the melancholy of the muses [Figure 1].

Today, we define depression as a result of the interplay between stress factors such as loss events and a wide array of endogenous/genetic, social and personality characteristics. In their milestone work "social origins of depression" (1978) Brown and Harris described the results of their research on the onset of depression in women of different social classes and 'life-stages' (Brown & Harris 1978). They were especially interested in the position of women with young children who did, or did not, have an outside job, and the level of depressive symptomatology they experienced. The "vulnerability-stress model", that clusters variables according to their role in a causal model of the development of depression, is the underlying concept for the studies presented in this thesis [figure 2].

Provoking agents A great number of authors have stressed the importance of loss events, most often the death of a loved one, as precursor to depression. In 'Mourning and Melancholia', Freud made clear that the object of love need not have died to cause such a reaction, but merely has been lost as an object of love (Freud S. 1917). He stated that the difference between grief and depression is that the melancholic patient feels a profound loss of self-esteem, accompanied by self-reproach and guilt, while the mourner maintains a reasonably stable sense of self-esteem after the actual loss of a significant figure. Brown and Harris defined loss events as the deprivation of sources of value or reward. Apart from loss, also (perceived) threat of loss, and long-term difficulties (household, health or other) qualified as provoking agents. It was found that such difficulties were much more prevalent in lower social classes, which was seen as an explanation for the differences in morbidity depending on socio-economic status. The importance of these provoking agents in the genesis of depression is that it 'leads to an inability to hold good thoughts about ourselves, our lives, and those close to us' (Brown & Harris 1978). It causes 'loss of faith in ones ability to attain an important and valued goal' and may generalise to a state of hopelessness, a crucial factor in the development of depression (Melges & Bowlby 1969). Still, similar circumstances may cause entirely different reactions in different people. Therefore a second crucial aspect is introduced; that of the interpretation of events by the individual.

Vulnerability or protective factors In line with the work of Beck (Beck 1971;Kovacs & Beck 1978) and others, Brown and Harris stressed the importance of the cognitive interpretation of events as a necessary mediator in developing or not developing hopelessness and depression. Phrased otherwise; if a person experiences loss or long term difficulties but believes that he or she is able to face it, or will find the resources to overcome some of these difficulties, the chances of becoming depressed are limited. It is here that self-esteem, and a sense of mastery may exert



THE
ANATOMY OF
MELANCHOLY:
VVHAT IT IS.
VVITH ALL THE KINDES, CAVSES, SYMPTOMES, PROGNOSTICKS, AND SEVERALL CVRES OF IT.
IN THREE MAINE PARTITIONS,
with their seuerall SECTIONS, MEMBERS, and SVBSECTIONS.
PHILOSOPHICALLY, MEDICINALLY, HISTORICALLY opened and cut vp,
BY
DEMOCRITVS *Iunior.*
With a Satyricall PREFACE, conducing to the following Discourse.
The second Edition, corrected and augmented by the Author.
MACRO.
Omne meum, Nihil meum.
AC:
OX
AT OXFORD,
Printed by IOHN LICHFIELD and IAMES SHORT, for HENRY CRIPPS. *Anno Dom. 1624.*

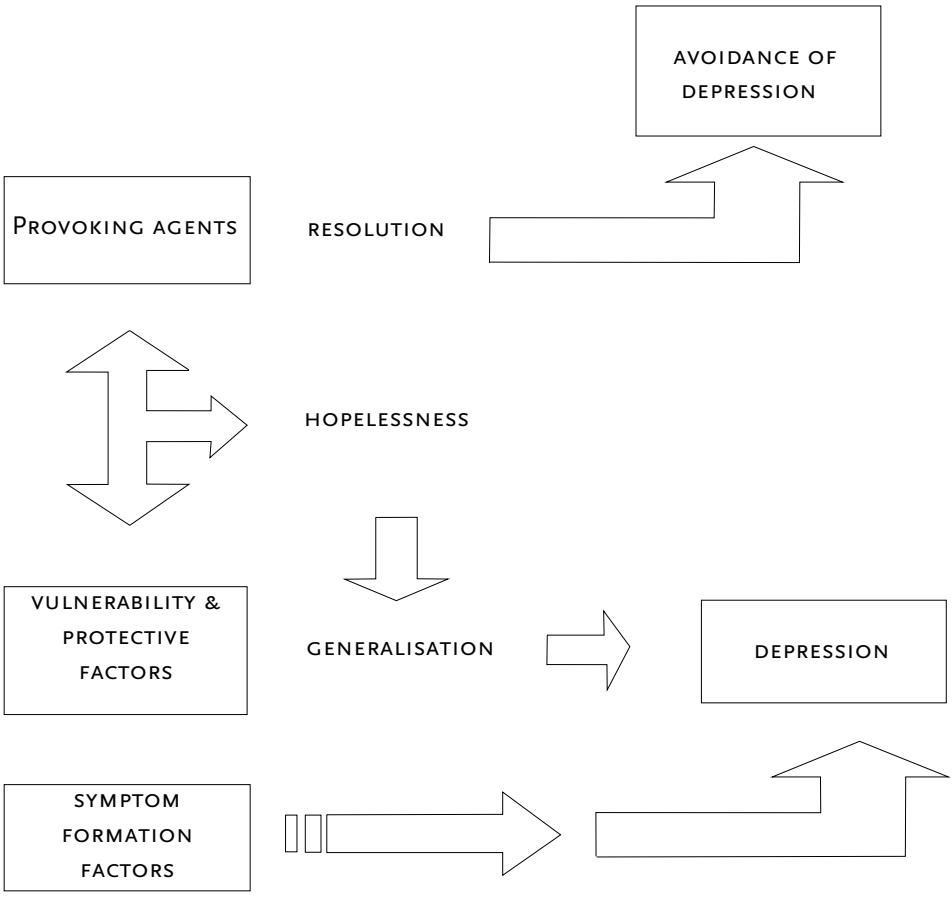
Figure 1: Burtons Anatomy of Melancholy (1621)

their influence. Although such features may in part be an aspect of personality, and thus relatively stable characteristics, it is stressed that concurrent (and preferably less negative) experiences in other social roles may play an important part in limiting vulnerability. As an example of this, Brown and Harris found that for women lack of a full- or part-time job, and/or having three or more children under 14 at home, were associated with higher vulnerability. Evidence-based forms of psychotherapy such as Interpersonal Psychotherapy, have acknowledged the importance of these phenomena and explicitly focus on the restoration of role functioning in different interpersonal relationships after a loss event that has lead to depression (Weissman & Klerman 1977). Another factor determining vulnerability in the Brown and Harris studies was loss of mother before the age of 11. This most probably affects a child's learning of mastery of the environment and self reliance, for the development of which a secure attachment with a principal (mother) figure is essential(Bowlby 1969). Early loss events may thus create a heightened vulnerability to subsequent stressors. An interpersonal determinant of vulnerability is the absence of a confiding relationship. Having an intimate relationship may reduce the risk of depression in several ways. It may help provide a basic sense of self-worth, especially in the context of major losses, when the individual may be inclined to completely loose his of her self-esteem. A confiding relation may also facilitate the working through of grief, and counteract defense mechanisms such as denial that may result in prolonged and dysfunctional mourning (Brown & Harris 1978).

Symptom formation factors were believed to determine the nature and severity of the depressive disorder that may result from the interplay of the above influences. It was argued that earlier losses would 'affect the way an individual looks at the world, and particularly the way one reacts to losses'. Loss by death would, irreversible as it is, be associated with feelings of uselessness, reactions of denial and possible development of psychotic depression in the future. Other types of separation would result in 'neurotic' feelings of rejection and possibly result in 'neurotic depression' as a reaction to new life stresses (Brown & Harris 1978).

Over the years, other authors have elaborated and refined the model proposed by Brown and Harris. Genetic influences have received much more attention (Kendler et al. 1993;Kendler et al. 2001). In the dynamic stress-vulnerability model proposed by Ormel and Neeleman, vulnerability is further subdivided into psychobiological vulnerability, consisting of genetic factors and temperamental style, physiological dysfunctions and cognitive deficits, and social vulnerability consisting of socio-economic factors, urbanisation and familial surroundings (Ormel & Neeleman 2000). Still, the essential idea of a stress-buffer interaction has remained the dominant concept in understanding the etiology of depression. The studies described in this thesis pay tribute to this underlying concept of the pathogenesis of disease. It is however important at this stage to define in what way epidemiological studies may contribute to a better understanding of depression, and hopefully also to more effective preventative or treatment strategies of depression.

Figure 2; Vulnerability-Stress model (adapted from Brown&Harris)



1.5 Epidemiology

In general, longitudinal epidemiological studies offer an opportunity to study both determinants of onset and course, and public health aspects of disease (Bouter & Van Dongen 2000;Rothman & Greenland 1998).

First of all, the importance of a variety of potential risk factors and their mutual interaction on the outcome measure can be studied, thus shedding light on their importance in both the development and course of disease. As the large number of subjects, both predictors of depression, significant interactions or comorbidity patterns with other disorders, and the consequences of these in terms of prognosis filter out individual variation, disability and survival may be detected. Such associations may serve as a starting point for further research of underlying psychological or pathophysiological mechanisms.

Another characteristic of epidemiology is, that it is relatively unbiased by any of the dominant theoretical frameworks in psychiatry. Both biological/genetic, psychological and social determinants of disease can be studied in comprehensive and combined models for onset and course of illness. Epidemiological studies thus offer an opportunity to incorporate and study a wide variety of potential determinants and their associations with depression, regardless of the bio-psycho-social background (Beekman & Ormel 1999).

Thirdly, epidemiological studies can determine the contribution of specific risk factors to the total amount of disease in the population. The increasing costs of health care are a major public concern, and rational choices may have to be made regarding the allocation of resources. Risk factors identified in epidemiological studies can be targeted in naturalistic and randomised trials to assess the potential preventative effects (Beekman 2004). The epidemiological approach may thus be helpful in generating valuable information on the effectiveness and scale of different types of intervention, on the corresponding demands on the health care services, and importantly, also on the associated costs.

Still, one has to bear in mind that, although epidemiology can uncover overall patterns and determinants that may be relevant to the understanding of depression as a disorder, these can by definition not be rigidly applied to the individual patient. It remains the task of the clinician, in dialogue with his or her patient, to translate and apply scientific data from these and other sources to a meaningful and effective treatment.

1.6 Depression in later life

Considering the negative influence of late-life depression on various aspects of daily life, a number of which will be discussed in more detail in this thesis, there may be more similarities than differences in comparison to depression in younger adults. In line with this, theoretical models seeking to explain the etiology of depression often do not make clear distinctions between these age groups. Still, the distribution of potential risk factors for depression in old age is considerably different from the situation in younger adulthood. Specific life events and changes in both physical and social functioning are common in later life, and relatively rare in younger age groups.

In the third phase of life, at least in western countries, people have less (professional) obligations, children are often living separate lives, friends are becoming more sparse, and people are more likely to lose partners and acquire physical illnesses or cognitive decline. If depression is defined as a prolonged, more severe and dysfunctional response to a loss event, later life offers an amalgamation of these; losses of dear ones, losses of social roles, and loss of physical and cognitive abilities. All of these may be risk factors for the onset of depression. In addition, many older persons in western societies live in large cities in which the social framework is less tightly knit. Social interaction and support have become less available, and people of a later age may be limited in their abilities to circulate and interact with others. As has been stated earlier, 'successful ageing' is an attractive but rather fragile concept (Deeg et al. 2002).

Perhaps the most prominent difference characterising later life is the high prevalence of chronic physical illnesses. In the age group from 65 to 74 years, 64 % of Dutch older persons have one or more chronic illnesses, and over 75 years only 29% of older adults do not have any chronic illnesses (Kriegsman et al. 1998). Poor health may be the principal risk factor for depression in old age (Kennedy et al. 1989;Prince et al. 1998). Apart from psychological/emotional reactions to these phenomena, there may also be biological links between physical illnesses and depression. The most important biological dysregulations associated with depression will be discussed in this thesis. Recently, syndromes that are most probably specific to old age psychiatry, such as 'vascular depression' (Alexopoulos et al. 2002;Thomas, Kalaria, & O'Brien 2004) have also received growing attention.

Dementia is another form of comorbidity that is prominent in later life. Alzheimer's disease and other forms of cognitive deterioration range from approximately 1% at age 65 to as much as 30% at age 90 (Hofman et al. 1991;Lobo et al. 2000). The co-occurrence, or subsequent occurrence of depression and cognitive decline has attracted the attention of many researchers, and may be explained by biological as well as psychological mechanisms (Bassuk, Berkman, & Wypij 1998;Yaffe et al. 1999). Depression itself may lead to impaired cognition through attention deficits. The so-called 'pseudo-dementia' concept reflected the idea that cognitive deterioration may in part be due to depression, and may recover when depression remits. However, the validity of this concept has often been questioned, and other mechanisms, either psychological or biological, appear more convincing in explaining the association between depression and cognitive decline (Nussbaum 1994). It is currently stated that depression may be an emotional reaction to subjective (perceived) cognitive decline in the individual, that it may be caused by the neurodegenerative process of Alzheimer's disease, and that it may be associated with subcortical white matter hyperintensities found in 'vascular depression' (Raskind 1998;Steffens, Taylor, & Krishnan 2003). Lastly, the co-occurrence of cognitive decline and depression may also be due to recurrence in later life of earlier and midlife depressive disorder. Community-based studies may provide more information on predictors of cognitive decline and depression, and on their temporal associations, and may thus be helpful to further disentangle these two phenomena.

Another form of comorbidity is that between depression and anxiety disorders. Studies in younger age groups have shown considerable overlap between depression

and anxiety disorders, the latter of which may either antedate, or co-occur with the onset of depression (de Graaf et al. 2003;Kessler et al. 1996;Liebowitz et al. 1990). Until recently, the idea was that this type of comorbidity was less pronounced in later life when compared with younger adulthood. It was stated that in the elderly, anxiety disorders are less common than in younger adults, with generalized anxiety disorder and phobias accounting for most anxiety in late life and panic disorder being relatively rare (Flint 1994). Lately however, this view has been questioned (Lenze et al. 2000;Lenze et al. 2001). Also in older adults, comorbidity of depression and anxiety may frequently occur and may be associated with an untoward course and less optimal response to treatment. The question whether these are specific disorders, or whether they represent different dimensions of a single disorder, has been subject to considerable debate in the literature (Tyrer 1996). Apart from studying differences and similarities in course patterns, this aspect may also be elucidated by investigating risk profiles for either disorder (Beekman et al. 2000). Although community-based studies may provide valuable information in this respect, only a limited number of studies have investigated late life anxiety disorders and the overlap with depression.

There has also been growing attention for the association between major depressive disorder and an increased risk of death, especially in clinical and general hospital populations (Frasure-Smith, Lesperance, & Talajic 1995;Lesperance et al. 2000;Tsuang & Woolson 1978). Much less is known about these associations in more prevalent minor, or 'mild' depressive syndromes that frequently occur in community living older persons. This issue is relevant to clinical practice, but also underlines the growing interest in depression from a public health perspective. The high prevalence of depression and the different types of comorbid conditions merit further study of the prognostic implications. The relatively wide array of possible mechanisms that may be associated with the depression – medical illness – mortality triangle are also intriguing from a scientific angle. If an association between late-life depression and excess mortality can be established, how can it be explained?

Considering the enormous adverse individual and public health consequences of late-life depression, the potential health gains could be substantial if depression could be prevented. The fact that even optimal evidence-based treatment of all depressed patients could reduce the burden of depressive illness by only one third (Andrews et al. 2004), warrants a more thorough study of preventative options. Still, preventive strategies aimed at reducing the incidence of late life depression in community living older persons have only very recently come into focus in mainstream psychiatry (Smit et al. 2004b;Smit et al. 2004a). For reasons of cost-effectiveness, studies on preventative measures should be targeted at subjects with a high a priori risk of developing depression through exposure to multiple risk factors (Cuijpers 2003). As a large number of depressed patients go unnoticed by the health services, community based studies may provide necessary information on both risk profiles and on the potential costs and benefits of preventative action.

1.7 Classification of psychopathology

One of the crucial issues in diagnosing psychopathology is the decision whether a patient's complaints are of sufficient severity to be classified as a psychiatric disorder. For clinicians, a dichotomy is a useful basis for the decision whether or not to intervene, and treatment protocols have been developed and validated according to pragmatic diagnostic criteria. Still, it is doubtful whether in nature such thresholds of psychopathology exist, especially when the diagnosis is based on a syndrome or a cluster of symptoms rather than on an etiologically defined disease entity. Epidemiological data suggest that psychiatric symptoms may have a much wider distribution in the population than those included in the official classifications of a disorder (Beekman, Copeland, & Prince 1999;Blazer et al. 1988;van Os 2003). Furthermore, the negative effects of depression in terms of human suffering and disability appear to be directly related to the number of depressive symptoms, and not to diagnostic threshold levels (Hays, Wells, Sherbourne, Rogers, & Spritzer 1995;Ormel et al. 1998). When investigating depression in a population sample, it is therefore vital to use a research instrument that generates both a clinical diagnosis according to standardised criteria and a continuous assessment of depressive symptoms. This enables the comparison of psychopathology in clinical patients and in community living persons, a considerable number of whom may never reach the health services. Even more importantly, the whole array of symptoms occurring in community samples can thus be determined.

The DSM (Diagnostic Statistical Manual of Mental Disorders) (American Psychiatric Association, American Psychiatric Association, & Task Force on DSM-IV 1994) and ICD (WHO) classification systems have been extremely helpful in distinguishing psychiatric disorders according to clear-cut diagnostic criteria, and enabling international and cross-cultural comparisons and research. Both for clinical purposes and for treatment evaluation in Evidence-Based Medicine, the value of these diagnostic standards cannot be underestimated. Still, the recent history of the development of subsequent DSM-versions shows that, although the core symptoms of depression have remained relatively stable, even these diagnostic reference or 'gold-standard' categories and thresholds have sometimes been somewhat arbitrarily chosen on the basis of consensus, and were subsequently adapted according to both dominant concepts of psychopathology and clinical and epidemiological evidence that was available at that moment (Spitzer 1991;Spitzer 2001;Wilson 1993). The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) distinguishes several types of unipolar affective disorders, the criteria of which are given in table 1 (American Psychiatric Association 2000). The most severe type of depression according to DSM-IV criteria is Major Depressive Disorder or Major Depression. Dysthymic disorder is characterized by the presence of symptoms that are less severe than the symptoms of major depressive disorder, but with a duration of over two years. A relatively new concept is that of 'minor depression', listed as a proposed (research) category, in which a lower number of depressive symptoms allows the diagnosis. This new category reflects the growing interest in the so-called subthreshold depression (Pincus, Davis, & McQueen 1999) that is clinically relevant

but does not meet all of the criteria for major depressive episode (Tannock & Katona 1995). Apart from these categories of mood disorder, DSM-IV also recognises Adjustment disorder with depressed mood, and Depression due to a General Medical Condition.

When considering symptomatology of geriatric depression, it has been argued that this may differ somewhat from that of depression earlier in life. A so-called 'depletion syndrome' characterised by 'negative symptoms' such as loss of interest or pleasure, loss of appetite and hopelessness may predominate over 'positive' emotional and cognitive symptoms such as sadness and inappropriate feelings of guilt (Gallo & Rabins 1999;Gottfries 1998;Newmann, Engel, & Jensen 1991). As geriatric depression often co-occurs with other psychiatric and/or somatic disorders, this may further complicate its assessment. This can be seen as an argument favouring the use of research instruments that specifically recognize late-life depressive symptomatology.

Apart from severity, diagnostic thresholds and symptomatology, the issue of etiology also merits discussion in the context of the classification of psychiatric disorders. Reflective of the fact that the etiology of psychopathology is probably multicausal and largely unclear for most disorders, classification systems such as DSM and ICD strive to be etiologically neutral. An exception to this is made for the category of 'mood disorder due to a general medical condition' and 'substance-induced mood disorder', as the causal mechanisms are better understood in these categories. Still, it is only recently that depression was subdivided into and endogenous and an exogenous form. Especially in the Anglo-Sacksan tradition, psychotic (endogenous) depression was described as a more severe form of depression with a course type including both relapses and remittances, a biologically / genetically determined etiology, and a relatively good response to biological treatments such as antidepressant medication. Neurotic depression was considered to be of mild to moderate severity depending on co-occurring external circumstances, with a predominantly chronic course and a strong association with (neurotic) personality characteristics (Andrews et al. 1990;Kiloh & Garside 1963;Lewis 1938). The Geriatric Mental State schedule (GMS), the diagnostic instrument that formed the basis for the assessment of psychopathology in the study on which this thesis is based, reflects this tradition and generates both a general depression diagnosis and a subdivision into neurotic and psychotic depression (Copeland et al. 1976;Copeland, Dewey, & Griffiths-Jones 1986;Gurland et al. 1976). It also distinguishes both individual depression symptoms and so-called case-levels according to the severity of depression. These properties are especially attractive when studying the depression concept in the general population. In contrast with other diagnostic instruments, GMS-AGECAT provides both a diagnosis of clinically relevant depression, an assessment of severity, and the whole array of subsyndromal depression symptoms. It thus combines the properties of frequently used screening instruments such as the CES-D (Radloff 1977) that measure symptoms but do not provide diagnoses, and diagnostic criterion instruments that are often more time and personnel consuming, and not so easily applicable to study depression in large samples such as the AMSTEL study.

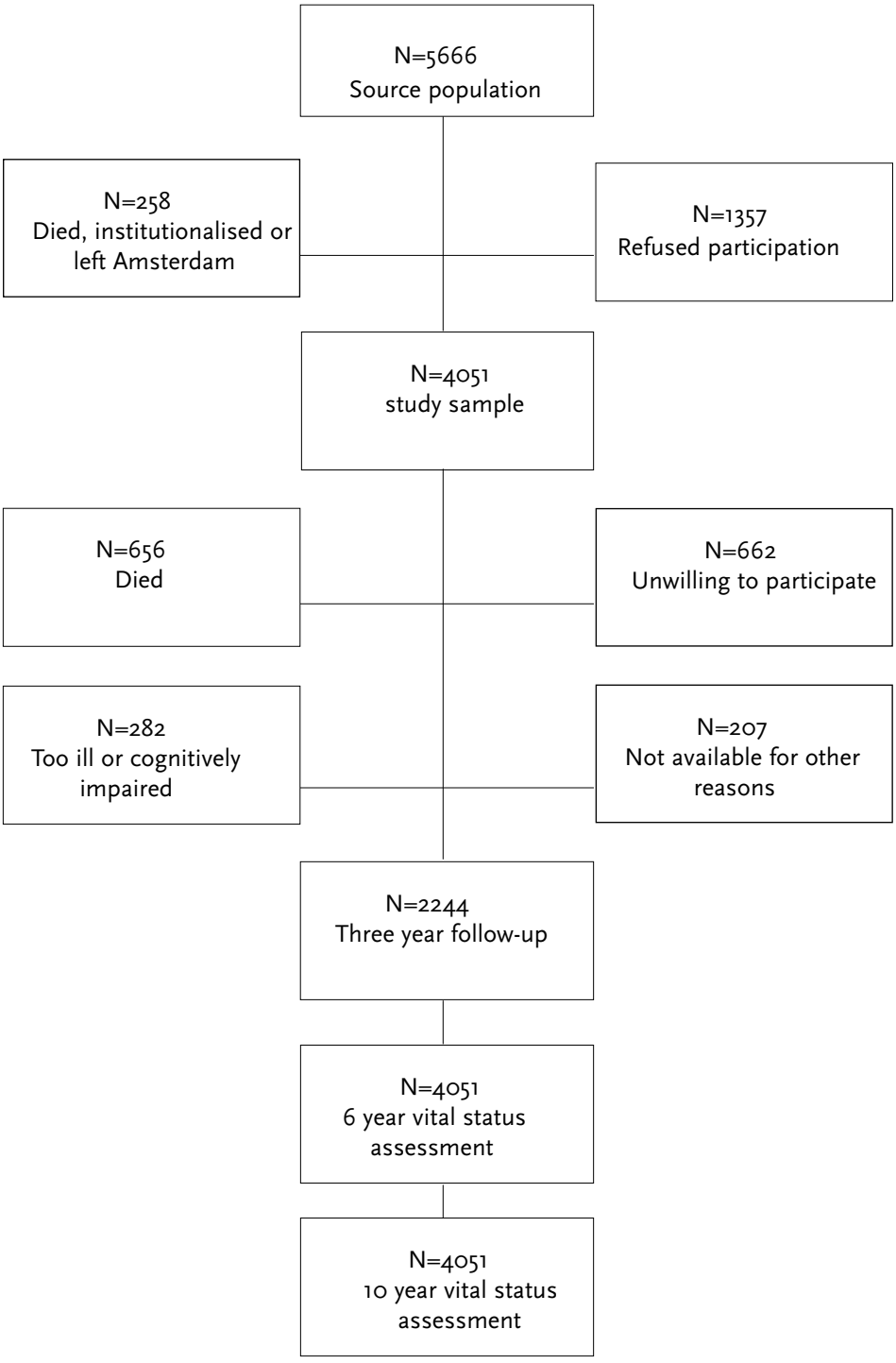
1.8 The Amsterdam Study of the Elderly

The population base for AMSTEL included all non-institutional individuals in the 65-84 age bracket who lived in the city of Amsterdam and were registered with a general practitioner at baseline. The study was actively supported by the general practitioners, whose lists were used as the sampling frame. In the Netherlands, general practitioners are the gate-keepers to the health care system and almost every citizen is enlisted by a general practitioner. In this role, general practitioners in the Netherlands generally provide social support and have a long-standing personal relationship with their patients. Thus, the source population consisted of almost all of the non-institutionalised population. The sample was drawn from a list of 30 general practices spread throughout the city; practices were selected from all practices registered within the city of Amsterdam, 22 randomly and 8 by convenience from a network of general practitioners participating in medical research. The mean proportion of elderly individuals (15%), and the profile of the over-65 general practice-population in terms of age and gender, correspond to the non-institutionalised Amsterdam population (Launer et al. 1993;Launer, Wind, & Deeg 1994)(Launer et al., 1993). Within each practice, respondents were randomly selected from four age strata spanning five years each (65-69 to 80-84). In order to obtain equally sized age-strata at follow-up, the older old were oversampled. Out of a sampled total of 5666, 4051 (71,5%) responded and formed the baseline sample (Figure 3).

At follow-up three years later, 2244 (55,4%) subjects were reinterviewed (median 38 months). By then, 656 (16, 2%) people had died, 662 (16,3%) persons refused further co-operation, 282 (7,0%) were too ill or cognitively impaired to respond, and 207 (5,1%) were not available for interview due to a variety of other reasons.

Both in 1996 and in 2001, data on vital status were obtained from the community registers. This enabled studying the association between depression and mortality, both in the 4051 subjects who attended the baseline assessment and in the 2244 subjects who also attended the follow-up measurement.

Figure 3. AMSTEL: Flow Chart



1.9 Measures

A one-hour interview was developed to gather information on psychiatric symptoms, demographic and medical status, previous history and family history. The interview consisted of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), all Geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland, Dewey, & Griffiths-Jones 1986;Hooijer, Jonker, & Dewey 1991), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969), and part of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth et al. 1986). Included from the CAMDEX were years of education, marital status and living status. Socio-economic status was assessed by asking respondents about the highest level of professional occupation they had reached, and the highest level their partner had reached. The highest occupational level of respondent or partner was taken as the socio-economic status. Social support was ascertained by the question: 'Do you get help from children or neighbours?'. Respondents were then asked to specify whom they received support from. A personal history of psychiatric disorder was ascertained by the relevant CAMDEX-question, asking subjects whether they had ever experienced depression and/or anxiety of such severity that treatment had been sought. The question was considered affirmative if treatment had been requested and if treatment had been prescribed this was interpreted as an indicator of the severity of the illness. Age at first onset was recorded. Also translated from the CAMDEX-questionnaire was a family history of psychiatric illnesses.

Diagnoses of dementia, depression and generalised anxiety were made according to the GMS-AGECAT system (Copeland et al. 1988;Copeland, Dewey, & Griffiths-Jones 1986). Diagnostic levels 3-5 correspond reliably to cases of depression requiring clinical attention in both the community (Copeland, Dewey, & Griffith-Jones 1990) and in elderly hospital patients (Ames & Tuckwell 1994). GMS-AGECAT has proven reliability for epidemiological work in replication studies (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988). The Dutch language version has also proved to be reliable (Hooijer, Jonker, & Dewey 1991). Depression caseness at baseline and follow-up was defined as a GMS-AGECAT level 3 or higher. GMS-AGECAT generates both a non-hierarchical syndrome level and a more narrowly defined diagnostic level. The diagnostic case level is calculated from the syndrome level using a hierarchy from organic to depression to anxiety disorder.

The interview was administered during home visits by lay interviewers who were specially trained using video sessions and regularly supervised. The same GMS-AGECAT package with an identical algorithm was used in the second wave of the study. When re-interviewing, raters were unaware of previous data and diagnoses.

1.10 Contents of this thesis

The primary research aim of this thesis is to model onset and course of late life depression, in view of the specific characteristics of later life and the vulnerability-stress paradigm. This is then further developed into studies of depression and comorbidity with other psychiatric disorders in later life, studies on prognosis and excess mortality associated with depression, and an exploration of the possible use of these epidemiological data to develop a research agenda for prevention of depression in primary care.

In *Chapter 2* the question is put forward whether, in line with the Brown and Harris concept, different etiologic pathways for the onset of late-life depression (through genetic/familial vulnerability, organic vulnerability or environmental vulnerability) can be demonstrated in a longitudinal study of community-living older persons. *Chapter 3* assesses whether risk factors related to incidence of late-life depression are also related to prognosis, and whether a vulnerability-stress model can also be established for the course of late-life depression.

Subsequently, comorbidity patterns of late-life depression with generalised anxiety disorder and cognitive decline are investigated, as both of these disorders frequently either overlap with depression, may affect the prognosis of depression, and may also be difficult to distinguish from depression due to overlapping symptoms. *Chapter 4* reports on a cross-sectional study of risk patterns and comorbidity of depression and generalised anxiety disorder, and in *Chapter 5* the course types of pure depression, pure generalised anxiety disorder and mixed anxiety-depression are described. *Chapter 6* examines whether depression may be indicative of subsequent cognitive decline and Alzheimer's Disease in older adults with normal cognition.

The section on associations between depression and mortality starts with a study examining the overall pattern in a community population of older persons. *Chapter 7* examines this association according to different severity levels of depression and according to gender, controlling for potential confounders. *Chapter 8* provides a review article examining mechanisms that may theoretically be responsible for the excess mortality associated with depression. Subsequently, *Chapter 9* then examines whether specific characteristics of depression may be specifically related to excess mortality.

The final study, described in *Chapter 10* of this thesis, presents an attempt to determine which older individuals are at high risk to develop depression, and proposes a rational model to guide preventative measures to reduce the incidence of depression.

Chapter 11 presents a brief summary of findings, their relevance is commented on and the merits and limitations of the studies are discussed.

The work described in the thesis is the result of the combined efforts of a large number of people. Their contributions are gratefully acknowledged here, and in the final section of this thesis.

Table 1: DIAGNOSES OF DEPRESSIVE DISORDERS (DSM IV-TR, APA 2000)

Diagnostic Criteria Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the last 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1 Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).
2 Markedly diminished interest or pleasure in all, or almost all, most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3 Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight
in a month), or decrease or increase in appetite nearly every day.
4 Insomnia or hypersomnia nearly every day.
5 Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6 Fatigue or loss of energy nearly every day.
7 Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8 Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9 Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specifi plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).
E. The symptoms are not better accounted for by Bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psy chomotor retardation.

Diagnostic Criteria for Major Depressive Disorder

A. Presence of a Major Depressive Episode
B. The Major Depressive Disorder is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

Research Criteria for Minor Depressive Disorder

A. A mood disturbance, defined as follows:
1 at least two (but less than five) of the nine symptoms mentioned above have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (a) or (b):
2 The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3 The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).
(4) The symptoms are not better accounted for by Bereavement, i.e. after the loss of a loved one

B. There has never been a Major Depressive Episode, and criteria are not met for Dysthymic Disorder
C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode, and criteria are not met for Cycisorder, delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Diagnostic Criteria Dysthymic Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years.
B. Presence, while depressed, of two (or more) of the following:

1 Poor appetite or overeating
2 Insomnia or hypersomnia
3 Low energy or fatigue
4 Low self-esteem
5 Poor concentration or difficulty making decisions
6 Feelings of hopelessness

C. During the 2-year period of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.
D. No Major Depressive Episode has been present during the 2 first years of the disturbance; i.e. the dis turbance is not better accounted for by chronic Major Depressive Disorder, or Major Depressive Disorder, in Partial Remission.
E. There has never been a manic episode, a Mixed Episode, or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder.
F. The disturbance does not occur exclusively during the course of a Chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.
G. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).
H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Diagnostic Criteria Adjustment Disorder with Depressed Mood

The predominant manifestations are symptoms such as depressed mood, tearfulness, or feelings of hopelessness.

A. The development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s).
B. These symptoms or behaviours are clinically significant as evidenced by either of the following:
Marked distress that is in excess of what would be expected from exposure to the stressor
Significant impairment in social or occupational (academic) functioning

C. The stress-related disturbance does not meet the criteria for another specific Axis I disorder (clinical disorder) and is not merely an exacerbation of a pre-existing Axis I or Axis II disorder (Personality Disorder or Mental Retardation).
D. The symptoms do not represent Bereavement.
E. Once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 months.

Diagnostic Criteria Mood Disorder due to a General Medical Condition, with depressive features.

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is charac terized by a depressed mood or markedly diminished interest or pleasure in all, or almost all, activi ties.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.
C. The disturbance is not better accounted for by another mental disorder (e.g. Adjustment Disorder with Depressed Mood in response to the stress of having a general medical condition).
D. The disorder does not occur exclusively during the course of a Delirium.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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Risk factors for depression in later life; results of a prospective community based study (AMSTEL)

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Journal of Affective Disorders (2000) 59: 127-137

Abstract

Background

Depression in the elderly was found to be associated with a variety of risk-factors in cross sectional designs. Based on the vulnerability-stress model, etiologic pathways for depression have been suggested, with vulnerability modifying the effect of stress factors. The current prospective study tests an etiologic model for depression incidence, by assessing modifying effects of three types of vulnerability: genetic/familial vulnerability, organic vulnerability, and environmental vulnerability.

Methods

1940 non-depressed community-living elderly were interviewed at baseline, and at follow-up three years later. Bivariate and multivariate relationships between risk factors and incident depression (GMS-AGECAT) were studied.

Results

Higher age, personal history of depression, death of spouse, health related factors and comorbid organic or anxiety syndrome showed significant bivariate associations with depression incidence. In multivariate analysis, the effect of stress factors on incident depression was not modified by a genetic/familial vulnerability, nor by an organic vulnerability. Effect modification by environmental factors was however evident; having a marital partner, and if unmarried having social support, significantly reduced the impact of functional disabilities on the incidence of depression.

Limitations

The study consisted of two measurements with a three years interval, depressive episodes with a short duration may be underrepresented.

Conclusions

In the elderly, the effect of stress on incident depression is modified by environmental vulnerability. No evidence was found of effect modification by either genetic/familial or organic vulnerability. The results have implications for both recognition and treatment of late-life depression.

2.1 Introduction

Current knowledge about risk factors of late-life depression is largely derived from either clinical populations, or from cross-sectional studies in the community. Studies of clinical patients have the disadvantage of not being representative of the vast majority of depressive subjects in the community. Cross-sectional studies in the community suffer from methodological limitations such as recall and report bias in depressed subjects (Raphael & Cloitre 1994), and contamination of the results as risk factors are not measured independently from depression. Temporal relations remain unclear since a characteristic found to be associated with depression may have antedated (or caused) the disorder, but it may also be its consequence. Likewise, cross-sectional designs cannot distinguish whether a characteristic has prognostic value for the course of depression once depression is present, or is actually associated with its aetiology. Finally, in cross-sectional designs chronic depression is overrepresented, which may bias findings with regard to aetiology.

Prospective studies of the incidence of depression among the elderly are relatively scarce and have used different sets of risk factors and research methods. Green et al. (Green et al. 1992) found lack of satisfaction with life, feelings of loneliness and smoking to be significantly associated with the development of depression as measured by GMS-AGECAT three years later in a cohort of community living elderly. Multivariate analysis yielded two more factors; female gender, and bereavement of a close person within six months of the third-year diagnosis. Phifer et al. (Phifer & Murrell 1986) found the incidence of significant depression in a six months period to be closely associated with changes in physical health. Kennedy et al. (Kennedy, Kelman, & Thomas 1990) also found aspects of physical health to be closely related to incidence of depression in a large sample of community-dwelling elderly in a two year follow-up. In a one year follow-up study with 3-monthly assessment of depressive symptomatology by Beekman et al. (Beekman et al. 1995a), depression incidence was also found to be associated with health related variables. A recent publication by Prince et al. (Prince et al. 1998) revealed disablement, and more specifically handicap, to be the chief cause of onsets of depression in late-life in a one-year follow-up of community living elderly.

According to the Brown and Harris (Brown & Harris 1978) etiologic model, depression in adults may be the result of 'social stress' factors such as life events (loss) or long term difficulties, combined with vulnerability/protective factors such as social disadvantage, lack of intimate relationships, early traumatic life events, lower intelligence/education, personal history of depressive illness and family history. Earlier cross-sectional work from the Amsterdam Study of the Elderly (AMSTEL) (van Ojen et al. 1995c;van Ojen et al. 1995a;van Ojen et al. 1995b) was inspired by the work of Brown and Harris. The AMSTEL data suggested three different subtypes of geriatric depression based on etiologic determinants. Early-onset depression was found to be associated with long-standing inborn susceptibility (Kendler et al. 1993b) and vulnerability due to previous episodes: "sensitization" or "kindling" (Post 1992). Late-onset depression with cognitive impairment was mainly associated with the presence of organic vulnerability factors. Late-onset depression without cognitive

impairment was found to be associated with factors related to current life-stresses. The primary aim of the present study was to further investigate the aetiology of late life depression, studying incident cases in the community in a prospective longitudinal design using a comprehensive set of risk factors generally believed to be associated with depression. In this way we hoped to avoid the above-mentioned methodological pitfalls and develop more insight into the temporal and causal relations between risk factors and late-life depression. Secondly we wanted to investigate whether the differential etiologic pathways of late-life depression suggested by earlier cross-sectional data are confirmed using a longitudinal design.

2.2 Methods

2.2.1 Sampling and non-response

The population base for the study included all non-institutional individuals in the 65-84 age bracket who lived in the city of Amsterdam and were registered with a general practitioner at baseline (van Ojen, Hooijer, Jonker, Lindeboom, & Van Tilburg 1995c). The sample was drawn from a list of 30 general practices spread throughout the city. The mean proportion of elderly individuals (15%), and the profile of the over-65 general practice-population in terms of age and gender, correspond to the non-institutionalised Amsterdam population (Launer et al. 1993). Within each practice, respondents were randomly selected from four age strata spanning five years each (65-69 to 80-84). In order to obtain equally sized age-strata at follow-up, the older old were oversampled. Out of a sampled total of 5666, 4051 (71,5%) responded. A study of non-response patterns (Launer, Wind, & Deeg 1994) revealed that non-response in the younger old (<75) was associated with poor performance on cognitive tests and with health problems. In the older old no correlates of non-response were found.

Of the 4051 subjects who initially responded 2244 (55,4%) were reinterviewed three years later (median 38 months). Data from community death certificates were used to cross-check our data on non-response and confirmed that 656 (16,2%) people had died before follow-up. Another 662 (16,3%) persons refused further co-operation, 282 (7,0%) were too ill or cognitively impaired to respond, and 207 (5,1%) were not available for interview due to a variety of other reasons. The study sample for this study consisted of all responders at follow-up who were neither depressed nor demented at baseline (GMS-AGECAT levels of less than three for both depression and organicity; N=1940).

2.2.2 Measures

A one hour interview was developed to gather information on psychiatric symptoms, demographic and medical status, previous history and family history. The interview consisted of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), all Geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland, Dewey, & Griffiths-Jones 1986;Hooijer, van Ojen, & Jonker 1994), the Instrumental Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale

(Lawton & Brody 1969), and part of the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and regularly supervised. The same GMS-AGECAT package with an identical algorithm was used in the second wave of the study. When re-interviewing, raters were unaware of previous data and diagnoses.

Psychiatric syndromes. Diagnoses of dementia, depression and anxiety were made according to the GMS-AGECAT system (Copeland et al. 1988;Copeland, Dewey, & Griffiths-Jones 1986). Diagnostic levels 3-5 correspond reliably to cases of depression requiring clinical attention in both the community (Copeland et al. 1992;Copeland, Dewey, & Griffith-Jones 1990) and in elderly hospital patients (Ames & Tuckwell 1994). GMS-AGECAT has proven reliability for epidemiological work in replication studies (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988). The Dutch language version has also proved to be reliable (Hooijer, Jonker, & Dewey 1991). Depression caseness at baseline and follow-up was defined as a GMS-AGECAT level 3 or higher. Subjects not depressed at baseline who were depressed at follow-up were considered to be incident cases. GMS-AGECAT generates both a non-hierarchical syndrome level and a more narrowly defined diagnostic level. The diagnostic case level is calculated from the syndrome level using a hierarchy from organic to depression to anxiety disorder. In order to be able to also assess overlapping comorbidity influences, we have used syndrome levels in our analyses since otherwise the diagnostic hierarchy would bias the results.

Vulnerability factors. As stressors may have a different impact in the older old than in the younger old, age was conceived as a vulnerability factor. The same applies for sex, as females have been found to be more vulnerable to depression (Weissman & Klerman 1977). Educational status was dichotomised into lower (primary school or less) and higher (more than primary school) education. Socio-economic status was assessed by asking respondents about the highest level of professional occupation they had reached, and the highest level their partner had reached. The highest level of respondent or partner was taken as the socio-economic status. Marital status was assessed with the associated questions in GMS-AGECAT. Social support was ascertained by the question: 'Do you get help from children or neighbours?'. Respondents were then asked to specify whom they received support from. A personal history of psychiatric disorder was ascertained by the relevant CAMDEX-question. The question was considered affirmative if treatment had been requested and if treatment had been prescribed this was interpreted as an indicator of the severity of the illness. Age at first onset was recorded. Onset before the age of 60 was classified as early history, onset at age 60 or after as late history. Also translated from the CAMDEX-questionnaire was a family history of mental handicaps.

Stress factors. In order to test the vulnerability-stress hypothesis 'change' variables were derived from differences that had occurred between baseline and follow-up. Stressors thus defined were personal life events (partner loss, relocation), changes in physical health (the emergence of chronic diseases), a substantial decrease in ADL or IADL functioning (a difference of two points or more), and cognitive decline (incident organic syndrome; GMS-AGECAT organic level three or more at follow-up).

Genetic/familial vulnerability was defined as the presence of a personal or family

history of mental disorders, organic vulnerability was defined as a baseline score on the MMSE of less than 26 points, or a GMS-AGECAT organic syndrome level higher than two at follow-up, and environmental vulnerability was defined by lack of social support and being unmarried.

2.2.3 Data analysis

Baseline characteristics and response rate were calculated using bivariate and multivariate statistics. Bivariate associations of depression incidence at follow-up (T1) with independent variables at baseline (T0) were assessed by calculating relative risks. When the 95% confidence interval of the latter did not include one, the association was regarded to be statistically significant. Stepwise logistic regression modelling was used to achieve independent predictive ability.

In subjects with either a genetic/familial or environmental vulnerability, the association between stress factors and incident depression is expected to be stronger than in subjects without these types of vulnerability (Brown & Harris 1978;Kendler et al. 1993a;Post 1992). Similarly, organic vulnerability characteristics are expected to reduce the impact of life events on incident depression (Cervilla & Prince 1997;van Ojen, Hooijer, Jonker, Lindeboom, & Van Tilburg 1995c;van Ojen, Hooijer, Bezemer, Jonker, Lindeboom, & Van Tilburg 1995a;van Ojen, Hooijer, Bezemer, Jonker, Lindeboom, & Van Tilburg 1995b). In order to detect effect modification, interactions were therefore investigated between either an environmental, a genetic/familial or an organic vulnerability on the one hand, and stress factors that were found to be significantly associated with incident depression on the other hand.

2.3 Results

2.3.1 Sample characteristics and response pattern

In multivariate logistic regression, age, sex, level of education, chronic disease(s), ADL and IADL impairment and organic syndrome differed significantly between responders and non-responders ($p<0.05$). Marital status, personal history and both anxiety and depression syndrome did not. When the deceased were excluded from the sample, only educational level, marital status and organic syndrome remained as significant predictors of other types of non-response. Importantly, controlling for other factors both depression and anxiety at baseline did not significantly affect response-rate.

At follow-up 309 subjects (15,9% of the study sample) had become depressed. The following analyses investigate associations of risk factors with incident depression.

2.3.2 Bivariate associations with depression incidence

Vulnerability factors. In bivariate analysis [table 2A], older age (>74 yrs) showed a significant association with depression. The level of incident depression was higher in each consecutive five year age stratum, ranging from 12.8% in subjects aged 65-69 to 19.5% in subjects aged 80-86 (chi-square: 8.26, $p<0.05$). Sex, level of education, family history, marital status and social support did not show an effect, but personal history of mental disorders did predict incident depression. In order to further investigate the influence of a personal history, this variable was dichotomised in several ways (history vs. no history, early vs. all, late vs. all, early vs. no history, late vs. no history). All analyses showed a significant association between personal history and incident depression, with a similar impact on incident depression of either early or late history. Family history did not attain statistical significance as a separate vulnerability factor.

TABLE 1: ASSOCIATIONS OF PARTICIPATION AT T1 WITH SAMPLE CHARACTERISTICS AT To (*= p<0,05, **= p<0,01, ***= p<0,001)

VARIABLES (Value at TO)	T0 (%)	T1 (% T0)	Resp vs Nonresp Chi-2/df/p	Resp vs Nonresp excl. deceased Chi-2/df/p
N	4051	2244 (55,4)		
AGE 65-69	836 (20,6)	544 (65,1)	89,2/3/***	17,2/3/**
70-74	974 (24,0)	581 (59,7		
75-79	1050 (25,9)	581 (55,3)		
80-86	1191 (29,4)	538 (45,2)		
SEX Male	1523 (37,6)	817 (53,6)	3,02/1/ns	6,8/1/**
Female	2528 (62,4)	1427 (56,4)		
EDUCATION				
Higher than PS	2335 (57,6)	1394 (59,7)	41,4/1/***	29,2/1/***
Primary school or less	1716 (42,4)	850 (49,5)		
SOCIO-ECON STATUS			21,1/2/***	11,9/2/**
High	182 (4,5)	121 (66,5)		
Middle	1803 (44,7)	1045 (58,0)		
Low	2050 (50,8)	1075 (52,4)		
MARITAL STATUS			0,02/1/ns	0,2/1/ns
Married	1970 (48,6)	1093 (55,5)		
Not/no longer	2078 (51,3)	1149 (55,3)		
SOCIAL SUPPORT			24,4/1/***	4,4/1/*
No/little social support	3209 (79,2)	1841 (57,4)		
Help from others	842 (20,8)	403 (47.9)		
CHRONIC DISEASES			24,95/2/***	0,4/1/ns
None	1894 (46,8)	1128 (59,6)		
One or more	2157 (53,2)	1116 (51,7)		

TABLE 1: ASSOCIATIONS OF PARTICIPATION AT T1 WITH SAMPLE CHARACTERISTICS AT To (*= p<0,05, **= p<0,01, ***= p<0,001)

VARIABLES (Value at TO)	T0 (%)	T1 (% T0)	Resp vs Nonresp Chi-2/df/p	Resp vs Nonresp excl. deceased Chi-2/df/p
PSYCHIATRIC HISTORY			1,81/2/ns	1,6/2/ns
None				
Early history	438 (10,8)	251 (57,3)	early/other:ns	early/other:ns
Late history	164 (4,0)	84 (51,2)	late/other: ns	late/other: ns
ADL FUNCTION			40,7/1/***	5,4/1/*
Able	3183 (78,6)	1846 (58,0)		
Disabled	868 (21,4)	398 (45,9)		
IADL FUNCTION			92,3/1/***	13.9/1/***
Able	2585 (63,8)	1578 (61,0)		
Disabled	1466 (36,2)	666 (45,4)		
MMSE SCORE			161,3/2/***	84.8/2/***
26-30	3281 (81,0)	1969 (60,0)		
22-25	522 (12,9)	209 (40,0)		
0-21	248 (6,1)	66 (26,6)		
ORGANIC			89.7/1/***	35,5/2/***
None	3790 (93,6)	2173 (57,3)		
Case	261 (6,4)	71 (27,2)		
ANXIETY			1,56/1/ns	4,1/1/*
None	3923 (96,8)	2180 (55,6)		
Case	128 (3,2)	64 (50,0)		
DEPRESSION			18,2/2/***	7.3/2/*
None	3528 (87,1)	1996 (56,6)		
Neurotic	441 (10,9)	216 (49,0)		
Psychotic	82 (2,0)	32 (39,0)		

TABLE 2: BIVARIATE ANALYSYES OF FACTORS PREDICTING DEPRESSION INCIDENCE
(N=1940; subjects with baseline organic and depression levels<Agecat level 3)

RISK FACTORS (N)	DEPRESSION Relative Risk (95% c.i.)
A: VULNERABILITY	
AGE >74 yrs (941)	1.30 (1.06-1.60)
SEX female (1173)	1.20 (0.97-1.49)
EDUCATION Primary School&less (694)	1.11 (0.90-1.37)
MARITAL STATUS Unm/div/wid (950)	1.02 (0.83-1.25)
SOCIAL SUPPORT Help relat/friends (311)	1.16 (0.89-1.51)
PERSONAL HISTORY (253)	1.61 (1.25-2.06)
FAMILY HISTORY psych (214)	1.23 (0.92-1.66)
B: STRESS	
Chronic (baseline)	
CHRONIC DISEASE(S) (928)	1.46 (1.19-1.80)
ADL DISABILITY (290)	1.49 (1.16-1.90)
IADL DISABILITY (493)	1.55 (1.26-1.92)
Changes between TO-T1	
PARTNER DIED (134)	2.30 (1.77-2.99)
RELOCATION (233)	1.15 (0.86-1.55)
ALL ADL DECREASE >1pt (102)	1.59 (1.11-2.27)
ALL IADL DECREASE > 1 pt (392)	1.73 (1.39-2.14)
NEW CHRONIC DISEASE(s) (366)	1.40 (1.11-1.77)
C: PSYCHIATRIC COMORBIDITY	
Comorbidity at baseline	
MMSE <26 (181)	1.12 (0.81-1.57)
ANXIETY SYNDROME (25)	2.56 (1.57-4.19)
New (incident) comorbidity To-T1	
ORGANIC SYNDROME (129)	1.57 (1.13-2.17)
ANXIETY SYNDROME (73)	4.82 (3.96-5.87)

Stressors (table 2B). All of the stressors that were already present at baseline (chronic disease, ADL/IADL disability) predicted depression at follow-up. New stressors (changes T0-T1) that attained significance were death of spouse, a substantial decrease in ADL or IADL function, and the occurrence of new chronic disease(s).

Comorbidity. Assessment of psychiatric comorbidity (table 2C) showed baseline anxiety and incident anxiety to be associated with depression at T1. Impaired cognitive function at baseline (a Mini Mental State Examination of less than 26 points; N=181, RR 1.13: 95% C.I. 0.62-2.07), did not predict depression at follow-up. We also investigated whether enlarging the sample to include all baseline organic cases would affect this result, but found this was not the case. There was also no significant association between baseline organic syndrome and incident depression. In the study sample, the development of a new organic syndrome did however show an association with incident depression. In order to establish whether psychiatric comorbidity would confound the results, all bivariate analyses were repeated excluding also baseline anxiety cases (baseline organic cases were already excluded). This yielded essentially the same results.

2.3.3 Multivariate analysis

Table 3 shows the relative risks of risk factors that remained significant using stepwise logistic regression. Loss of spouse retained the highest relative risk, followed by personal history, IADL decrease, incident chronic disease, baseline IADL disability and baseline chronic disease.

Interactions between either a personal or a family history and risk factors were not found. The association between stress and incident depression was thus unaffected by a difference in genetic or acquired vulnerability. Likewise, no interaction was found between organic vulnerability and the same risk factors. When examining effect modification by environmental vulnerability, we found a strong interaction between marital status (not/no longer married) and baseline ADL-disability (RR 3.60; 1.79-7.20). Social support status did not show interactions with any of the stress factors. As these variables are related, and subjects who were married had significantly less social support (chi-square: 58.20, p<0,0001), the multivariate analysis was repeated excluding the married subjects. A buffering effect of social support could then be established in unmarried subjects in the presence of a substantial decrease in ADL-functioning (RR 0.23; 0.06-0.92).

TABLE 3: LOGISTIC REGRESSION; REMAINING SIGNIFICANT VARIABLES (backward stepwise logistic regression, Pout <0.05).

VARIABLE	RR (95% c.i.)
Loss of spouse	3.11 (2.10-4.60)
Personal history	1.75 (1.26-2.43)
IADL decrease (>1pt)	1.71 (1.28-2.27)
Baseline IADL disability	1.44 (1.10-1.90)
New chronic disease	1.41 (1.05-1.90)
Baseline chronic disease	1.40 (1.08-1.80)

2.4 Discussion

The aim of the present study was to model the aetiology of late life depression, studying incident cases in the community in a three-year prospective design. Of the subjects without depression at baseline, 15.9% had developed a GMS-AGECAT depressive syndrome at follow-up. Compared to previous studies of depression incidence in the elderly this is relatively high. Phifer et al. (Phifer & Murrell 1986) noted an incidence of 10.7% after only six months, using a Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977) score of 16 or higher as cut-off. Kennedy et al. (Kennedy, Kelman, & Thomas 1990) found an incidence of 11% with CES-D after two years, but excluded those cases who already showed subthreshold levels of depression at baseline and only developed a mild increase in depressive symptoms to reach the cut-off level of 16 points, thus underestimating the number of emergent cases as compared to our definition. The Liverpool study (Copeland, Davidson, Dewey, Gilmore, Larkin, McWilliam, Saunders, Scott, Sharma, & Sullivan 1992;Green, Copeland, Dewey, Sharma, Saunders, Davidson, Sullivan, & McWilliam 1992) revealed 44 incident cases of depression after three years in a population at risk of 619 (7,1%), using also GMS-AGECAT, but following the diagnostic hierarchy which does not recognise depressive syndrome levels when a comorbid organic syndrome is also present. The only other Dutch study (Beekman, Deeg, Smit, & Van Tilburg 1995a) used five assessments of depressive symptomatology in a period of one year and revealed a CES-D (16 points or more) depression incidence of in total 26%; composed of 11% incident cases that remained depressed during the study, 11% that remitted, and 4% showing a variable course. Prince et al. (Prince, Harwood, Thomas, & Mann 1998) found a one year onset rate for pervasive depression of 12.0% using SHORT-CARE, with a one year maintenance rate of 63.2%.
These data suggest that, due to the development of chronicity, longer follow-up periods tend to show somewhat higher overall incidence rates of depression. Still, as is the case in studies of depression prevalence (Beekman et al. 1995b), there appears to be considerable variation in the levels of depression incidence found. This may be partly be explained by different study intervals, but also by differences in assessment methods and sample characteristics.

In a first, bivariate assessment of risk factors and depression, we found that all except one of the stress factors predicted depression incidence. Only relocation, known to be an important life-event, did not attain statistical significance. Loss of spouse appeared to be the strongest predictor of incident depression, which is consistent with other community-based studies of late-life depression (Beekman et al. 1997). Physical and functional parameters also showed a relation with depression, with both baseline measures and indicators of declining physical health predicting new episodes of depression. These findings are concordant with those of other community based studies, and with studies comparing the relative impact of physical health on late-life depression (Kennedy et al. 1989;Kennedy, Kelman, & Thomas 1990;Prince, Harwood, Thomas, & Mann 1998).

Among the vulnerability factors, higher age showed a statistically significant main effect. The level of incident depression was higher in each consecutive five year age

stratum. This would suggest that ageing itself may be a risk factor for depression in the elderly. However, after controlling for the confounding influence of other potentially relevant factors, the effect of age disappeared. This is similar to what was found in previous, cross-sectional studies (Beekman, Penninx, Deeg, Ormel, Braam, & Van Tilburg 1997;Blazer & Burchett 1991).

Other vulnerability factors such as gender, level of education (and social economic status), marital status and social support did not attain significance as separate risk factors. Many cross-sectional studies have however found women to be significantly more at risk to be depressed than men (Wolk & Weissman 1995). This is not replicated in our sample of incident cases, and may be due to the fact that we have left out all baseline prevalent cases from the analyses. Among the prevalent cases at baseline 79.9% were women, whereas among the non-depressed 59.8% were women (chi-square 78.6, $p<0.0001$). A higher tendency of chronicity in women may explain the higher prevalence in cross-sectional designs. This issue will be addressed when studying the course of late-life depression.

Contrary to our expectation, a family history of psychiatric disorder was not significantly associated with incident depression in our study sample. This is surprising since others have found correlations of a family history and depression in cross-sectional studies (Kendler, Kessler, Neale, Heath, & Eaves 1993a). Family history was also associated with depression prevalence in our own baseline study (van Ojen, Hooijer, Bezemer, Jonker, Lindeboom, & Van Tilburg 1995b), and in another community-based study of elderly in the Netherlands (Beekman, Deeg, van Tilburg, Smit, Hooijer, & Van Tilburg 1995b). As in the above discussion of sex-differences, it may be that, in later life, family history acts as a prognostic factor rather than an etiologic factor. Family history would then be associated with a longer duration of episodes, increasing prevalence but not affecting incidence.

In comorbidity analyses, newly emerging organic syndromes correlated with incident depression, but baseline organic vulnerability did not. Also when enlarging the sample to include all baseline organic cases, there was no significant association between long-standing organic symptoms and incident depression. This finding fits the clinical impression that the onset of cognitive decline is often accompanied or even preceded by depressive symptoms. Our data also suggest that the effect of cognitive decline as a risk factor for depression appears to wane with the passing of time. Subjects may have had more time to adapt to their condition, or dementia symptoms have progressed to a state where depressive symptomatology is less pronounced. With regard to anxiety, both baseline and new anxiety syndromes predicted depression incidence. The impressive relative risks of depression in subjects with anxiety syndrome may very well be due to overlapping symptoms of comorbid disorders, but may also be taken to indicate that depression and anxiety are different manifestations of the same underlying condition (Tyrer 1996).

We hypothesised that three types of vulnerability would modify the effect of stress factors: a genetic or familial vulnerability, indicated by a personal or family history of mental disorder, an organic vulnerability indicated by cognitive/organic symptoms at baseline or follow-up, and an environmental vulnerability defined as being unmarried and lack of social support. Contrary to our expectations, both indicators of a genetic/familial vulnerability did not act as effect modifiers. Although subjects

with a personal history had a significantly higher chance of becoming depressed, increased vulnerability when confronted with similar life-stresses could not be shown. Both with and without stress factors, individuals with a previous history tend to relapse. One is tempted to suggest that spontaneous relapse forms proof of the 'kindling' phenomenon. However, according to the kindling theory, subjects with a previous history are expected to be more vulnerable than others, when confronted with stress factors (Atre-Vaidya & Taylor 1997). Our data do not support this expectation. One explanation may be that the stress factors we have used in our study are too strong to be able to detect more subtle, threshold-lowering effects that one would expect in individuals who have become sensitised through earlier experiences. Furthermore, in our study 80.6% of those with incident depression did not report a personal history and were 'true' old-age depressions. The decrease of vulnerability in older age samples, due to the association between personal history and excess mortality (van Ojen, Hooijer, Jonker, Lindeboom, & Van Tilburg 1995c), may also have influenced these findings. Younger age samples, such as formed the basis of the Brown and Harris Studies (Brown & Harris 1978), may therefore show significantly higher associations between stress-factors and incident depression in subjects with a personal or family history.

The second vulnerability type, organic vulnerability, also did not modify the association between stress and depression. Subjects who already had mild cognitive symptoms at baseline or who had developed an incident organic syndrome at follow-up, were no more, and no less vulnerable to other (non-organic) stress-factors. Although others have found some support for a differential pathway to late-life depression mediated by cerebral deterioration in cross-sectional analysis (Cervilla & Prince 1997), we have not been able to reproduce this in a prospective design.

With regard to environmental vulnerability, subjects without a marital partner were more vulnerable to depression in the presence of baseline functional disabilities. As marital status did not attain significance as an independent risk factor for depression, this points to a protective modifying or buffering effect of being married. Social support could not be shown to influence subject's vulnerability to depression in the study sample. Since marital status and social support are related, further analysis in the unmarried showed that social support did have the hypothesised buffering effect when these subjects were confronted with a decrease in functional abilities. We need to point out that our assessment of social support has been rather crude compared with more commonly used instruments. According to Cohen and Wills (Cohen & Wills 1985) a detailed assessment of the availability of interpersonal resources that are responsive to the needs elicited by specific stressful events is required to demonstrate a stress-buffering effect. Our question of whether a person receives 'help from family and/or others' points mainly to instrumental support, which seems especially appropriate when faced with invalidating circumstances such as a decrease in functional abilities. Although instrumental support and emotional support are generally not mutually independent, measures of emotional support may show more pronounced buffering effects with respect to psychological distress (Oxman et al. 1992;Tijhuis et al. 1995). Nevertheless, both indicators of environmental vulnerability in our study do show modifying effects that fit the vulnerability-stress model.

Although the design of the study is an improvement over previous designs (a prospective study, incident cases, large numbers, community based, established measurement instruments and risk factors), there remain some limitations. There were two measurements of symptomatology covering three years. Therefore, it is possible that subjects without depression at baseline have been depressed between measurements and remitted before T1. Episodes with a shorter duration may be underrepresented in the study. We have also been unable to assess the exact temporal relations between life events and depression. Studies with more frequent measurements are needed to explore this in more detail.

In conclusion, we were able to investigate differential etiologic pathways to geriatric depression that have been put forward by other authors. Our findings partially support the vulnerability-stress model. In the presence of changes in subject's lives that lead to a heightened dependency on others, being married, and if unmarried having social support served as buffers against incident depression. Although both a personal history of mental disorders and organic vulnerability were predictive of incident depression in bivariate analysis, we could not show a differential impact of stress factors in subjects with or without these specific vulnerability characteristics. Further analysis with a wider set of more detailed stress variables may still show such effects. It is also possible that, at a later age, these vulnerability characteristics are more influential on the course of depression than on its incidence. Further studies on both incidence and course of geriatric depression are therefore needed. If replicated, these findings may both support and further differentiate our appreciation of etiologic pathways of depression in later life.

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3

The natural history of late life depression

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Journal of Affective Disorders (2003) 76: 5-14.

Abstract

Background

This study examines whether risk factors related to incidence of depression are also related to prognosis, and whether a vulnerability-stress model can be established for prognosis.

Methods

A prospective model for prognosis of depression (chronic or remitted course) in later life was studied in 236 depressed community-living elderly. Subjects were interviewed at baseline, and at follow-up three years later. Bivariate and multivariate relationships between risk factors and chronic depression (GMS-AGECAT) were assessed. Effect modification was studied between stressors and two types of vulnerability: vulnerability through a personal history of depression, and gender.

Results

A personal history of depression, baseline functional limitations and incident anxiety syndrome predicted chronic depression, whereas life-events occurring between assessments, and changes in physical, functional or cognitive status did not. In subjects without a previous history, functional disabilities, male gender and receiving instrumental support correlated with a poor prognosis. The prognosis for subjects with a personal history of depression was not affected by other factors. In women, the development of chronicity was more strongly associated with a personal history than in men, whereas in men recent psychosocial and health related characteristics were more important than in women.

Limitations

Because the study consisted of two measurements with a three-year interval, depressive episodes with a short duration may be underrepresented.

Conclusions

In the elderly, the impact of risk factors on the course of depression is modified by longstanding vulnerability characteristics, such as a personal history of depression and gender. More recent life stresses are related to prognosis in subjects without a personal history, and in men.

3.1 Introduction

Depression, and especially chronic depression, has a profound negative influence for late-life physical and social adjustment (Vaillant et al. 1996), health service use (Beekman et al. 1997;Unutzer et al. 1997) and well-being (Hays et al. 1995;Ormel et al. 1998;Wells et al. 1989). Still, the majority of depressive elderly in primary care remain either unrecognised or undertreated (Cole, Bellavance, & Mansour 1999;Henderson et al. 1997;Livingston et al. 1997). Both for clinical and theoretical purposes, understanding the process that leads to chronicity is of major importance. Identifying vulnerability factors associated with an untoward course may result in both a better understanding of the natural history, and in more accurate therapeutic interventions.

Findings regarding prognostic factors are mainly inconclusive (Cole, Bellavance, & Mansour 1999). This may be due to methodological differences and limitations of available studies. Factors potentially associated with chronicity and remittance can be grouped as depression-related (length and severity of index episode, personal history), genetic (family history), socio-demographic (age, gender, socio-economic status, marital status, availability of support), physical (medical illness) and cognitive (mental status, neuroradiological abnormalities) (Alexopoulos & Chester 1992). Earlier research shows that both length and severity of the index episode and an early onset of depression are predictive of an unfavourable course, as do comorbid cognitive symptoms and health-related variables (Beekman et al. 1995;Cole, Bellavance, & Mansour 1999;Henderson, Korten, Jacomb, Mackinnon, Jorm, Christensen, & Rodgers 1997;Kennedy, Kelman, & Thomas 1991). Demographic variables do not appear to influence the course of depression. Life-events and social support show contradictory effects.

According to the Brown and Harris etiologic model (Brown & Harris 1978), depression may be the result of 'social stress' factors such as life events (loss) or long term difficulties, in addition to vulnerability or protective factors. Earlier work on the AMSTEL cohort (Amsterdam Study on the Elderly) confirmed a higher incidence of depression in subjects with longstanding (a personal history of depression) and more recent risk factors such as loss of spouse, higher age, untoward health and comorbid organic and anxiety symptoms (Schoevers et al. 2000a). It was hypothesised that three types of vulnerability would modify the effect of stressors: genetic or familial vulnerability, indicated by a personal or family history of mental disorder, organic vulnerability indicated by cognitive/organic symptoms at baseline or follow-up, and environmental vulnerability defined as being unmarried and/or not having social support. Neither a genetic/familial nor organic vulnerability acted as effect modifiers. Effect modification was apparent only for environmental vulnerability. Having a partner, and, if unmarried, having social support, significantly reduced the association between functional disabilities and the emergence of depression.

The present study seeks to investigate whether similar risk patterns can be found for the prognosis of late-life depression. A personal history of depression, a family history, dependence on social and/or professional support, functional limitations, chronic medical conditions, and comorbid cognitive or anxiety symptoms are there-

fore hypothesised to predict the development of chronicity. It is also postulated that stress factors occurring between assessments, such as life events, or changes in physical, functional or psychiatric comorbidity status, may influence the course of depression. Prognostic factors may have different predictive power, depending on specific vulnerability characteristics that may modify its effects. A personal history is a key variable in many studies on the course of depression. Depression is known to relapse more easily after each new episode, regardless of the presence of psychosocial stressors (Brown, Harris, & Hepworth 1994). We therefore postulated that prognostic factors have a stronger impact on chronicity in depressed subjects without a previous history. Likewise, women are consistently found to have higher depression prevalence levels (Beekman, Copeland, & Prince 1999), and suggestions have been made about a differential impact of risk factors for depression in men and women (Sonnenberg et al. 2000;Wolk & Weissman 1995). The sample was therefore stratified according to the presence or absence of a personal history, and according to gender.

The present study was performed in a large representative sample of community-dwelling elderly with a three-year follow-up, incorporating a wide set of risk factors generally considered to be related to late-life depression.

3.2 Methods

3.2.1 Sampling and non-response

The study was designed as a part of the Amsterdam Study of the Elderly (AMSTEL) which has been described in more detail elsewhere (Launer, Wind, & Deeg 1994;Schoevers, Beekman, Deeg, Geerlings, Jonker, & Van Tilburg 2000a;van Ojen et al. 1995). The population base for AMSTEL included all non-institutional individuals in the 65-84 age bracket who lived in the city of Amsterdam. Of the 4051 subjects who initially responded 2244 (55,4%) were reinterviewed three years later (median 38 months). In total, 656 (16,2%) persons had died before follow-up, 662 (16,3%) persons refused further participation, 282 (7,0%) were too ill or cognitively impaired to respond, and 207 (5,1%) were not available for interview due to a variety of reasons. The study sample consisted of all responders at follow-up who were depressed at baseline (236 cases).

3.2.2 Measures

A one hour interview was conducted consisting of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), all Geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland, Dewey, & Griffiths-Jones 1986), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969), and the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and regularly supervised. The same GMS-AGECAT package with an identical algorithm was used in the second wave of the study. When re-interviewing,

raters were unaware of previous data and diagnoses.

Psychiatric syndromes. Diagnoses of depression, organic caseness and anxiety were reached using the GMS-AGECAT system (Copeland et al. 1988;Copeland, Dewey, & Griffiths-Jones 1986). Diagnostic levels 1 and 2 are classified as subcases. Diagnostic levels 3-5 have been proven valid to detect cases of depression requiring clinical attention in both the community (Copeland et al. 1992;Copeland, Dewey, & Griffith-Jones 1990) and in elderly hospital patients (Ames & Tuckwell 1994). AGECAT has proven reliability for epidemiological work (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988). The Dutch language version has been proven reliable (Hooijer, Jonker, & Dewey 1991). In the analyses the diagnostic level depressive disorder was used, with a distinction between neurotic and psychotic depression. When assessing the impact of comorbidity, syndrome levels were used, as the diagnostic hierarchy in GMS-AGECAT would otherwise bias the results. Depression caseness at baseline (T0) and follow-up (T1) was defined as a GMS-AGECAT level 3 or higher. Subjects who were depressed at both T0 and T1 were classified as having 'chronic or relapsing depression'. Subjects who were depressed at T0 but not at T1 were considered remitted.

Prognostic factors. Educational status was dichotomised as lower (primary school or less) and higher (more than primary school) education. Socio-economic status was assessed by asking respondents about the highest level of professional occupation they had reached, and the highest level their partner had reached. The highest level reached by either the respondent or the partner was taken as the socio-economic status. Marital status was assessed using the appropriate questions in GMS-AGECAT. Instrumental support was ascertained by the question: 'Do you get help from your children, neighbours or other aquintances?' If so, respondents were asked to specify whom they received support from. Professional support was ascertained by the question: 'Do you get help from home-care institutions (such as Humanitas, home-care), or do you get day-care (outpatient care) in a nursing home on a regular basis?'. Subjects where then asked to specify the kind of home-care or day-care they received. A personal history of depression was ascertained by the relevant CAMDEX-question. Onset before the age of 60 was classified as early onset, at age 60 or after as late onset. For functional disability a cut-off was used of 1 (ADL), or 3 (IADL) points below the maximum score (ADL 12 and IADL 16 points), following the standard deviations of 0.98 and 2.77, respectively.

Change variables Changes that occurred between baseline and follow-up were included separately in the analyses. Change variables were made for social status (partner loss, relocation), physical health (one or more new chronic diseases) and functional status (impairment or improvement in ADL/IADL functioning with one S.D.) or psychiatric comorbidity (incident organic syndrome, incident anxiety syndrome).

3.2.3 Data analysis

Response pattern was analysed using chi-square tests, with depression or no depression at baseline. To assess stability of diagnostic subcategories over time, wave 1 values were cross-tabulated against wave 2 values. Bivariate associations of chronicity with independent variables were assessed calculating relative risks. When the 95% confidence interval did not include 1, the association was regarded to be statistically significant. Subjects were then stratified according to the presence of a personal history of depression and according to gender. A statistically significant difference between two opposite strata was concluded when the confidence intervals of both strata mutually excluded the opposite relative risk value. Logistic regression modelling was used to assess the effect of comorbidity. Backward stepwise analysis was used to reach the most parsimonious model. Interaction terms were included for variables that remained after this procedure, and for variables that were believed to be of key importance based on a priori notions.

3.3 Results

3.3.1 Sample characteristics, response pattern

The total non-response has been described earlier (Launer, Wind, & Deeg 1994). At baseline, 487 subjects had a depression diagnosis (12.0% of the total sample). Of these, 236 participated in the follow-up study. Attrition consisted of 99 subjects who had died at follow-up (20.3%), 80 who refused further participation (16,4%), 46 subjects who were ineligible due to illness (9,5%), and 26 who were otherwise unavailable (5,3%). Mortality was significantly higher in depressed subjects (Schoevers et al. 2000b), and depressed subjects were also more likely to be ineligible for follow-up interview due to illness. This pattern remained when excluding subjects with comorbid organic syndromes at baseline. There were no significant differences between depressed and non-depressed subjects with respect to refusal and lack of availability for other reasons. More detailed bivariate analyses of non-response showed that, among depressed subjects, nonresponse was associated with higher age, male sex, ADL and IADL disability, and both lower MMSE and organic syndrome at baseline. When non-response due to death was excluded from the analysis, only initial IADL disability and cognitive impairment retained a statistically significant relationship with response-rate: depressed subjects with these characteristics were at increased risk to be ineligible at follow-up.

3.3.2 Course of depression

Of the 236 subjects who participated in the follow-up study, 114 (48,3%) had remitted and 122 (51,7%) were again found to be depressed [Table 1]. The prognosis of neurotic depression (51% chronic or relapsing course) and psychotic depression (56.3% chronic or relapsing course) was very similar ($chi2=0.31$, $df=1$, $p=0.58$).

TABLE 1: CHRONICITY AND REMITTANCE; STABILITY OF DIAGNOSTIC CATEGORIES (all responders, N=2244, % of baseline category)

DIAGNOSIS at baseline:		T1: No depression		Depressed	
		Well	Subcase	Neurotic	Psychotic
No depression	Well (1589)	1026 (64,6)	380 (23,9)	150 (9,4)	33 (2,1)
	Subcase (419)	172 (41,1)	35 (32,2)	86 (20,5)	26 (6,2)
Depressed	Neurotic (204)	60 (29,4)	40 (19,6)	16 (7,8)	88 (43,1)
	Psychotic (32)	9 (28,1)	5 (15,6))	12 (37,5)	6 (18,8

3.3.3 Prognostic factors

Bivariate associations. [Table 2] shows relative risks derived from bivariate analyses of chronicity with prognostic factors. A personal history of depression, and baseline functional (ADL) limitations predicted chronicity of depression. Among the changes occurring between assessments (change variables), only incident comorbid anxiety syndrome was associated with chronicity of depression.

Stratification according to personal history of depression. In subjects with a personal history, only incident anxiety was associated with chronicity [Table 3], first column). In subjects without a personal history of depression, chronicity was associated with male gender, with receiving instrumental support, with baseline ADL or IADL disabilities and with incident anxiety (Table 3, second column). A statistically significant difference between the opposite strata was found for two variables: a family history of psychiatric disorder and gender. Both a family history and male gender showed significantly higher relative risks for developing chronic or relapsing depression in subjects without a personal history.

Stratification according to gender. Stratification for gender revealed that a personal history of depression, baseline functional (ADL) limitations, and incident anxiety syndrome had a significant impact in women (Table 3, third column), whereas receiving instrumental support, IADL disability, loss of spouse, new IADL disabilities and both incident organic and anxiety syndrome were predictive of chronicity in men (Table 3, fourth column). Statistically significant differences between these two strata were found for a number of variables. A personal history of depression was a significantly stronger predictor of chronicity in women than in men, whereas higher age, less education, being unmarried, IADL disabilities, loss of spouse, IADL impairment between assessments, and incident organic syndrome were stronger predictors in men than in women.

Logistic regression. Logistic regression analysis of chronicity was performed on the following baseline variables; age, gender, educational status, marital status, functional limitations (ADL/IADL), instrumental support, professional support, personal history of depression, family history, chronic diseases, organic syndrome and anxiety syndrome. Three variables were significantly associated with chronic or relapsing depression ($p<0.05$). Stepwise logistic regression revealed the same variables: personal history (OR 1.86; $p=0.037$), ADL disability (OR 2.20; $p=0.007$) and lower education (OR 0.56; $p=0.030$). Since we also expected gender to be significantly associated with the course of depression, this factor was added to the model to determine whether there were any significant interactions that influenced these findings. This yielded an interaction between personal history and gender ($p=0.046$), and none between any of the other variables (personal history, gender, ADL impairment, educational status). These results confirm the earlier stratification along these lines that was based on a priori notions.

TABLE 2: FACTORS PREDICTING CHRONICITY
bivariate analyses with Relative Risks (95% c.i.) (N=236)

PROGNOSTIC FACTORS	N (exposed)	CHRONIC / RELAPSING DEPRESSION (122)
1: VULNERABILITY		
Personal history of depression	75	1.35 (1.06-1.71)
Family history of psych disorder	44	1.07 (0.79-1.45)
2. DEMOGRAPHIC VARIABLES		
Age >74 yrs	126	0.96 (0.75-1.23)
Sex: Female	200	0.92 (0.67-1.27)
Education; Primary School & less	111	0.84 (0.65-1.08)
Socio-economic status: Low	131	1.04 (0.81-1.34)
Unmarried/divorced/widowed	152	0.90 (0.70-1.16)
Instrumental Support	65	1.24 (0.96-1.59)
Profess. Support	67	1.23 (0.96-1.58)
3: PHYSICAL/FUNCTIONAL STRESS		
Chronic (baseline)		
Chronic diseases	147	1.07 (0.83-1.39)
ADL disability	82	1.44 (1.14-1.83)
IADL disability	60	1.28 (0.99-1.64)
4: CHANGES TO-T1; LIFE EVENTS		
Partner died	21	0.91 (0.57-1.46)
Relocation	47	0.93 (0.68-1.29)
New ADL disability	69	0.94 (0.71-1.24)
New IADL disability	35	1.06 (0.76-1.48)
New chronic diseases	56	1.14 (0.87-1.50)
Positive changes To-T1		
ADL functional improvement	26	1.30 (0.96-1.78)
IADL functional improvement	11	0.87 (0.45-1.69)
5: PSYCHIATRIC COMORBIDITY		
Comorbidity at baseline		
Organic syndrome	15	1.02 (0.67-1.56)
Low MMSE (<24)	18	1.04 (0.71-1.53)
Anxiety syndrome	35	1.20 (0.93-1.54)
New (emergent) comorbidity		
New Organic syndrome	29	1.13 (0.85-1.51)
New Anxiety syndrome	35	1.64 (1.38-1.95)

TABLE 3: STRATIFIED ANALYSES OF CHRONICITY Relative risks (95% c.i.)

RISK FACTORS (n)	Chronic / relapsing depression with personal history (47)	Chronic / relapsing depression no personal history (75)	Chronic / relapsing depression women (102)	Chronic / relaps. depression men (20)
1: VULNERABILITY				
Personal history			1.55 (1.20-2.00)	0.57 (0.25-1.31)
Family history	0.75 (0.46-1.23)	1.30(0.89-1.90)	1.01 (0.71-1.44)	1.29(0.71-2.31)
2: DEMOGRAPHICS				
Age >74 yrs	1.01 (0.71-1.43)	0.98 (0.70-1.37)	0.85(0.65-1.12)	1.86 (0.97-3.54)
Sex: Female	1.85 (0.83-4.11)	0.68 (0.48-0.96)		
Lower Education	0.75 (0.51-1.09)	0.91 (0.65-1.26)	0.77(0.59-1.02)	1.40 (0.80-2.45)
S.E.S.Low	0.90(0.64-1.27)	1.11 (0.79-1.55)	0.96(0.73-1.26)	1.66 (0.84-2.71)
Unmarried	0.99(0.70-1.41)	0.91 (0.64-1.29)	0.81(0.62-1.07)	1.53 (0.85-2.75)
Instrumental Support	0.97 (0.64-1.47)	1.44 (1.05-1.99)	1.13 (0.84-1.51)	1.86 (1.10-3.14)
Professional Support	1.09 (0.75-1.58)	1.33 (0.95-1.85)	1.19 (0.91-1.58)	1.50 (0.87-2.59)
3: PHYSICAL/ FUNCTIONAL STRESS				
Chronic diseases	1.03 (0.71-1.49)	1.08 (0.76-1.52)	1.05 (0.79-1.40)	1.17 (0.60-2.26)
ADL disability	1.28 (0.91-1.79)	1.56 (1.13-2.14)	1.41 (1.08-1.83)	1.64 (0.95-2.82)
IADL disability	1.13 (0.76-1.66)	1.41 (1.02-1.95)	1.16 (0.87-1.55)	2.00 (1.24-3.23)
4: CHANGES TO-T1				
Partner died	1.07 (0.65-1.77)	0.70 (0.31-1.58)	0.81 (0.47-1.40)	1.89 (1.38-2.60)
Relocation	1.04 (0.70-1.56)	0.83 (0.52-1.33)	0.89(0.63-1.27)	1.25 (0.65-2.41)
New ADL disability	0.97 (0.67-1.41)	0.87 (0.58-1.29)	0.90(0.66-1.24)	1.08 (0.59-1.97)
New IADL disability	0.85 (0.48-1.50)	1.20 (0.79-1.81)	0.94(0.64-1.39)	2.00 (1.41-2.83)
New chronic diseases	0.94 (0.63-1.42)	1.26 (0.89-1.80)	0.89(0.63-1.27)	0.88 (0.41-1.88)
Positive changes To-T1				
ADL improvement	1.30 (0.81-2.10)	1.40 (0.95-2.05)	1.29 (0.91-1.82)	1.41 (0.74-2.71)
IADL improvement	0.62 (0.21-1.85)	1.08 (0.48-2.44)	0.87(0.41-1.82)	0.89 (0.22-3.70)
5: PSYCHIATRC COMORBIDITY				
Comorbidity at baseline				
Organic syndrome	0.47 (0.10-2.37)	1.25 (0.82-1.91)	1.01 (0.62-1.65)	1.03 (0.45-2.38)
Low MMSE (<24)	0.56 (0.19-1.67)	1.30 (0.88-1.93)	0.99(0.62-1.58)	1.18 (0.63-2.19)
Anxiety syndrome	1.10 (0.79-1.51)	1.17 (0.78-1.75)	1.21(0.92-1.59)	1.18 (0.63-2.19)
New comorbidity				
Organic	0.96 (0.59-1.57)	1.23 (0.86-1.75)	1.07(0.77-1.49)	1.62 (1.24-2.11)
Anxiety	1.62 (1.33-1.96)	1.60 (1.23-2.07)	1.67 (1.38-2.02)	1.49 (1.00-2.2

3.4 Discussion

In this study of a large sample of community-dwelling elderly, depression was found to have an unfavourable, chronic or relapsing course in approximately half of the cases.

Only a limited number of variables shown to be relevant for the incidence of depression were found to predict a chronic course. Stratified analysis showed important differences in the likelihood to develop chronic depression between men and women, and between subjects with or without a personal history of depression.

Different risk patterns for incident and chronic depression

In our earlier study on the emergence of depression, a substantial influence was demonstrated not only of a personal history, but also of baseline health related factors, negative life events and a decline of physical health and functional status prior to the onset of depression (Schoevers, Beekman, Deeg, Geerlings, Jonker, & Van Tilburg 2000a). The current study shows that, once a depression is present, such recent life events and changes in health appear to have less influence with regard to prognosis, which is mainly depending on long-standing vulnerability. Kraepelin (Kraepelin 1913) already described the phenomenon of sensitisation and kindling-effects in mental disorders. Depression is considered to be a recurrent disease, that after each new episode tends to relapse more easily regardless of the presence of psychosocial stressors (Brown, Harris, & Hepworth 1994;Dolan et al. 1985;Ezquiaga, Ayuso Gutierrez, & Garcia 1987;Zis & Goodwin 1979). In this study, depressed subjects were stratified according to the presence or absence of a personal history, and it was expected that prognostic factors would have a stronger impact on chronicity in subjects without a previous history. This proved to be the case. In subjects with a previous history, none of the prognostic factors showed a statistically significant predictive effect, except for incident anxiety, which was associated with chronicity in all strata. In subjects without a previous history however, baseline functional (ADL and IADL) disabilities, male gender and receiving instrumental support correlated with chronicity. As having instrumental support was associated with IADL disabilities ($P<0.001$), it may be fair to conclude that, in the elderly, a first onset depression is more likely to become chronic in the context of circumstances that make people more dependent on others. Depressed subjects with longstanding vulnerability however develop chronic depression regardless of co-occurring risk-factors.

Gender differences

Women are consistently found to have higher prevalence levels of depression than men. As we did not find a higher incidence of depression in elderly women in an earlier study on this subject (Schoevers, Beekman, Deeg, Geerlings, Jonker, & Van Tilburg 2000a), the prognosis of depression was expected to be worse in females. In the current study, this was not confirmed. Women with a depression at baseline did not develop a chronic course more often than depressed men. Stratification for gender however did show differences between the sexes. In men, the development of chronicity is associated with a number of demographic (higher age, lower educa-

tion), social (without marital partner, receiving instrumental support) and health related characteristics (functional disability, cognitive decline) or loss events (of spouse). These characteristics appear to undermine their ability to cope, and may be of a recent origin. In women, only a personal history of depression and functional disabilities were associated with chronicity. This suggests that the risk profile in females is more longstanding and possibly endogenous, with a much lower impact of recent psychosocial stressors or changes in health. Gender differences are also apparent in the consequences of late-life depression, such as excess mortality. Depressed men are more likely to die, even when experiencing relatively mild levels of depression (Penninx et al. 1999;Schoevers, Geerlings, Beekman, Penninx, Deeg, Jonker, & Van Tilburg 2000b). The higher prevalence levels of depression in women may therefore be the result of both an interaction between personal history of depression and gender, and of the fact that depressed elderly women are more likely to survive than depressed elderly men.

Depression and anxiety

The only risk factor that showed a stable and statistically significant association with chronicity in all strata was incident anxiety syndrome. This is of interest, as it has been suggested that anxiety and depression may both be manifestations of a communal underlying condition (Tyrer 1996). Earlier studies in adults have shown high correlations between anxiety and depression (Goldberg & Huxley 1992;Kessler et al. 1994;van Balkom et al. 2000), and recent cross-sectional research in the elderly confirmed such symptom overlap in the age group under study (Beekman et al. 2000). Our prospective data show that co-occurring anxiety symptoms are also associated with an untoward course of depression. More detailed analysis of the exact symptoms of anxiety that are associated with chronic depression may further our insight into this relatively new area of research.

Severity of depression and chronicity

Interestingly, the development of chronicity did not depend on the severity of the index episode. In our study, more severe psychotic depressions had a chronic or relapsing course a little more often than neurotic depressions (56% vs. 51%), but this difference was not statistically significant. This finding once more underlines the clinical importance of so-called minor levels of depression identified in community based studies, which often do not meet the criteria for major depressive disorder (Pincus, Davis, & McQueen 1999).

Limitations

A limitation of the current study is the fact that levels of symptomatology were assessed with a three-year interval. An unknown number of subjects may have experienced both remittance and relapse in the meantime. This may influence our results and lead to an overestimation of the importance of chronic depression. Hoewever, an extensive review and meta-analysis by Cole et al. (Cole, Bellavance, & Mansour 1999) also showed the level of chronicity at 24 months follow-up to be almost 50% of those still alive. Recent studies with more frequent measurements (Geerlings et al. 2000;Sharma et al. 1998) suggest that the majority of these subjects indeed has a

chronic course.
Another potential limitation is the fact that this study is a naturalistic follow-up in the community, not controlling for ongoing treatment that may have affected the results. Literature shows that recognition of depression in comparable samples of community living elderly is generally poor, with the majority of depressed subjects not receiving any specific treatment for their depressive complaints (Beekman, Copeland, & Prince 1999;German et al. 1987). The current study is no exception to this. Only 12% of the depressed subjects were using any 'medication for nervous complaints', and the majority of these subjects no doubt were not using antidepressant medication but other pharmacological agents such as benzodiazepines. There was no relationship between such medication use and the outcome measure of this study. According to this study it appears fair to conclude that in community dwelling elderly treatment for depression is usually not given at all, and if given, it is often inadequate.

Thirdly, selective attrition to the follow-up assessment of the study has probably occurred among the very frail. Depressed subjects were more likely to die, and depressed subjects with functional disabilities or cognitive impairment were more likely to be too ill to respond at follow-up. Most probably, the prognosis of depression in these subjects is worse than in those that were included in the study.

Conclusions

The main finding of the current study is that risk profiles for emerging depressive syndromes and for the development of chronicity are distinctly different and considerably affected by both longstanding vulnerability and gender. In women, a personal history of depression, which probably is largely biologically determined, is most influential when predicting chronicity. In men however, chronicity may also be the consequence of a number of demographic, social and physical circumstances that can be of a more recent origin. This interaction between gender and longstanding vulnerability has not previously been described in a community based study such as ours, and may, if replicated, further our insight into the natural history of late-life depression.

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4

Comorbidity and risk-patterns of depression, generalised anxiety disorder and mixed anxiety-depression

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International Journal of Geriatric Psychiatry (2003) 18: 994-1001.

Abstract

Background

Depression and generalised anxiety disorder frequently overlap. The question remains unresolved whether these are specific disorders, or that they represent different dimensions of a single disorder. Although both are highly prevalent disorders in this age group, studies on this issue in the elderly are scarce. Research is needed that investigates patterns of comorbidity and possibly different risk profiles for pure depression, pure generalised anxiety and mixed anxiety-depression in older people.

Methods

GMS-AGECAT diagnoses were obtained from 4051 community living older persons. Comorbidity was studied along a severity gradient for men and women separately. Multivariate analysis of risk factors included demographic variables, environmental vulnerability, longstanding vulnerability, physical/functional stresses and gender.

Results

The prevalence of pure depression was 12.2%, pure generalised anxiety 2.9%, mixed anxiety-depression 1.8%. Comorbidity increased with higher severity levels of both depression and generalised anxiety. Comorbidity was twice as likely in women than in men. Different risk profiles for diagnostic categories were not demonstrated for concurrent risk factors. Longstanding vulnerability was associated significantly stronger with mixed anxiety-depression than with pure anxiety and pure depression. Mixed anxiety-depression was overrepresented in women.

Conclusions

Both lines of investigation suggest that, in the elderly, a dimensional classification is more appropriate than a categorical classification of depression and generalised anxiety. Mixed anxiety-depression is a more severe form of psychopathology that is almost specific to women in this age group.

4.1 Introduction

Co-occurrence of depression and anxiety is a consistent finding across the life cycle, and is associated with a poorer prognosis (Regier et al. 1998). Patients suffering from both depression and anxiety disorders experience greater functional disability (Bijl & Ravelli 2000) and utilise services more heavily than persons with a single disorder (Kessler et al. 1994). Comorbidity is also associated with a more persistent illness course, in adults (Liebowitz et al. 1990) as well as in the elderly (Schoevers et al. 2003).

Classification of depression and anxiety as distinct forms of psychopathology has been disputed (Tyrer 1996). Generalised anxiety disorder in particular may lie on a continuum with depression (Liebowitz, Hollander, Schneier, Campeas, Fallon, Welkowitz, Cloitre, & Davies 1990). Diagnostic thresholds may differentiate categories of 'pure' depression, 'pure' generalised anxiety or mixed anxiety-depression that represent the same disorder but at a different level of severity or at a different stage of development.

A second possibility is that depression and anxiety are different entities, associated with different sets of risk factors. Earlier research in adults confirmed shared genetic factors associated with both depression and generalised anxiety disorder, but suggested that environmental experiences determine the actual development of either condition (Kendler 1996).

Although generalised anxiety appears to be the most prevalent anxiety disorder in the elderly (Beekman et al. 1998;Flint 1994), studies comparing severity levels and risk factors with geriatric depression are scarce (Beekman et al. 2000). The current study first investigates the diagnostic threshold hypothesis, and then assesses whether 'pure' depression, 'pure' generalised anxiety disorder, and mixed anxiety-depression have similar or different risk profiles. A distinction was made between long-term vulnerability factors, concurrent environmental vulnerability and stress. As gender differences have been described with regard to both depression and anxiety disorders in the elderly (Schaub & Linden 2000;Schoevers et al. 2000b;Sonnenberg et al. 2000), gender specific patterns were assessed.

4.2 Methods

4.2.1 Sampling and non-response

The Amsterdam Study of the Elderly (AMSTEL) is a longitudinal study of a large and representative sample of non-institutionalised community living older persons on mental health problems, medical diagnoses and demographic characteristics. The sampling and data collection procedures have been described elsewhere (Launer et al. 1993;Schoevers et al. 2000a). In short, the population base for AMSTEL included all non-institutional individuals in the 65-84 age bracket who lived in the city of Amsterdam. The profile of the study sample corresponded to the non-institutionalised Amsterdam population in terms of age and gender. An age-stratified sample was drawn. All 4051 subjects (71.5%) who responded and gave their informed consent were interviewed at baseline. Non-response in the younger old (<75) was associated with poor performance on cognitive tests and with health problems. In the older old no correlates of non-response were found (Launer, Wind, & Deeg 1994). The study sample for this study consisted of all subjects not meeting criteria for organic caseness.

4.2.2 Measures

A one hour interview was conducted consisting of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), Geriatric Mental State Examination (GMS) items related to organic, affective and anxiety syndromes (Copeland, Dewey, & Griffiths-Jones 1986), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969), and the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and regularly supervised.

Psychiatric syndromes. Diagnoses of depression, organic caseness and generalised anxiety were reached using the GMS-AGECAT system (Copeland et al. 1988;Copeland, Dewey, & Griffiths-Jones 1986). GMS-AGECAT generates both syndrome levels and hierarchically defined diagnostic levels. In the analyses syndrome levels were used, as comorbidity was the specific interest of this study. GMS-AGECAT case levels represent levels of increasing severity of the disorder, with case level 5 indicating the most severe end of the spectrum (Copeland et al. 1987;Copeland et al. 1992;Copeland, Dewey, & Griffith-Jones 1990). Case levels 1 and 2 are classified as subcases. Levels 3-5 have been proven valid to detect cases requiring clinical attention in the community. AGECAT has proven reliability for epidemiological work (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988), as has its Dutch language version (Hooijer, Jonker, & Dewey 1991). Depression and generalised anxiety caseness were defined as a GMS-AGECAT level 3 or higher. Subjects meeting GMS criteria for depression and not meeting GMS criteria for generalised anxiety were classified as 'pure depression' (DEP). Subjects with GMS generalised anxiety without depression caseness were classified as 'pure gener-

alised anxiety' (ANX). Subjects meeting GMS criteria for both depression and anxiety (with GMS-AGECAT levels higher than 2 for both conditions) were labelled 'mixed anxiety-depression' (ANXDEP).

Demographic variables. Potentially confounding covariates were age, level of education and socio-economic status. Educational status was dichotomised as lower (primary school or less) and higher (more than primary school) education.

Vulnerability factors. Marital status was assessed using the appropriate questions in GMS-AGECAT. Social support was ascertained by the question: 'Do you get help from your children, neighbours or other acquaintances?' If so, respondents were asked to specify whom they received support from. Professional support was ascertained by the question: 'Do you get help from home-care institutions, or do you get day-care (outpatient care) in a nursing home on a regular basis?' Subjects where then asked to specify the kind of home-care or day-care they received. A personal history of depression and/or generalised anxiety disorder was ascertained by the relevant CAMDEX-question. The question was considered affirmative if treatment had been requested. Age at first onset was recorded. A personal history of depression or anxiety was treated as longstanding vulnerability with possible biological origins, whereas marital status, social support and professional support were considered as more concurrent, environmental vulnerability characteristics.

Stress factors. The presence of chronic diseases was assessed with the pertinent Camdex questions on cardiovascular diseases, cancer, lung disease, diabetes, Parkinson's disease, arthritis and epilepsy. Cognitive status was assessed by MMSE-score. Subjects were considered to have functional disability if their ADL or IADL scores were two or more points below the maximum score on the respective scales (ADL 12 and IADL 16 points). This signifies that subjects were 'in need of help' to perform at least two of the tasks in the respective domains.

4.2.3 Data analysis

Baseline sample characteristics were assessed, including prevalence levels of depression, generalised anxiety and organic caseness. In the study sample, excluding organic cases, comorbidity of depression and generalised anxiety was directly calculated form GMS data using the Mantel-Haenszel chi-square test for linear association, with specification of GMS-AGECAT severity levels. This procedure was then repeated after stratification for gender, in order to determine whether comorbidity patterns differed in men and women. Bivariate associations of DEP, ANX and ANXDEP with independent variables were assessed calculating relative risks (results not shown). In order to control for confounding due to associations among risk factors, multivariate analyses, using logistic regression modelling, were carried out in each of the diagnostic categories using the same set of risk factors. The control group for these analyses was composed of all subjects without either depression or anxiety. Backward stepwise analysis was used to reach the most parsimonious model for each diagnostic category.

TABLE 1: SAMPLE CHARACTERISTICS

VARIABLES		N (%)	Mean	Standard deviation
Full sample		4051		
AGE	65-69	836 (20,6)	74.35	5.73
	70-74	974 (24,0)		
	75-79	1050 (25,9)		
	80-86	1191 (29,4)		
SEX	Male	1523 (37,6)		
	Female	2528 (62,4)		
EDUCATION	Higher than PS	2335 (57,6)		
	P.S. or less	1716 (42,4)		
MARITAL STATUS	Married	1970 (48,6)		
	Not/no longer	2078 (51,3)		
SOCIAL SUPPORT	No/little	3209 (79,2)		
	Help from others	842 (20,8)		
PROFESSIONAL	None	3351 (82.7)		
SUPPORT	Receiving P.S.	700 (17.3)		
PERSONAL	None	3449 (85,1)		
HISTORY	Yes	602 (14.9)		
CHRONIC	One	1894 (46,8)		
DISEASES	None	1390 (34.3)		
	Two or more	767 (18.9)		
ADL FUNCTION	Able	3726 (92.0)	11.63	0.98
	Disabled	325 (8.0)		
IADL FUNCTION	Able	3012 (74.4)	14.60	2.77
	Disabled	1039 (25.6)		
MMSE SCORE	26-30	3281 (81,0)	26.94	3.81
	22-25	522 (12,9)		
	0-21	248 (6,1)		
ORGANIC	None	3790 (93,6)		
SYNDROME	Case	261 (6,4)		
DEPRESSION	None	3528 (87,1)		
	Case	523 (12,9)		
GENERALISED	None	3923 (96,8)		
ANXIETY	Case	128 (3,2)		
MIXED ANXIETY-	None	3975 (98.1)		
DEPRESSION	Case	76 (1.9)		

4.3 Results

4.3.1 Sample characteristics

The demographic and functional profiles of the full sample are presented in [Table 1]. Depression was present in 523 subjects (12.9%), generalised anxiety in 128 (3.2%) subjects, and 261 (6.4%) were organic cases. For this study, subjects with organic disorder were omitted, yielding a study sample size of 3790. Cross tabulation of depression with generalised anxiety in the study sample showed that 14.5% of the depressed subjects also met criteria for generalised anxiety, as opposed to 1.3% in non-depressed subjects. Subjects with generalised anxiety were concurrently depressed in 60.4%, whereas depression prevalence was 10.8% in subjects not meeting criteria for generalised anxiety (chi-square 247.2, df 1, $p<0.0001$). 463 subjects were classified as DEP (12.2%), 111 had ANX (2.9%), and 67 (1.8%) had ANXDEP.

4.3.2 Comorbidity associated with severity of psychopathology

Cross tabulation of overlapping symptoms and severity levels [table 2] shows that comorbidity levels of generalised anxiety in depression at D1 and D2 (subcase levels) are low, and then steeply increase across severity levels from 11.1% in DN3 (neurotic depression) to 40% in DP4 (psychotic depression). Conversely, depression is a comorbid condition in 25% and 17.6% of anxiety subcases, but rises from 56% to a 100% with increasing severity levels in generalised anxiety cases. Thus, a parallel and highly statistically significant increase in comorbidity is found along a gradient of severity in both depression and generalised anxiety (Mantel-Haenszel test for linear association 577.7, $p<0.0001$).

Repeating the analysis after stratification for gender showed that this pattern of increasing severity in both disorders was reproduced and remained statistically highly significant in both men and women. However, women showed levels of comorbidity that were 50 to 100% higher than those in men at all severity levels of both depression and generalised anxiety.

TABLE 2: COMORBIDITY OF DEPRESSION AND GENERALISED ANXIETY DISORDER (GMS caselevels with increasing severity of disorder, n=3790)

Generalised anxiety in depression

Depression diagnostic levels (n)	Percentage with comorbid generalised anxiety		
	All	Men	Women
D0; no depression (2537)	0.4 %	0.1 %	0.7 %
D1; subcase level (410)	3.2 %	} 30 %	} 4.7 %
D2; subcase level (380)	5.3 %		
DN3; neurotic depression (349)	11.1 %	} 7.7 %	} 14.1 %
DN4; neurotic depression (62)	23 %		
DP3; psychotic depression (37)	22 %	} —	} 33.3 %
DP4; psychotic depression (15)	40 %		

Depression in generalised anxiety disorder

Generalised anxiety diagnostic levels (n)	Percentage with comorbid depression		
	All	Men	Women
A0 no anxiety (1916)	2.5 %	1.4 %	3.6 %
A1 subcase level (513)	25 %	} 14.1 %	} 21.9 %
A2 subcase (1250)	17.6 %		
A3 case (70)	56 %	} 42.9 %	} 62.9 %
A4 case (36)	64 %		
A5 case (5)	100 %		

4.3.3 Risk factor analyses

Logistic regression modelling, with backward stepwise analysis, was used to reach the most parsimonious model in each diagnostic category using the same set of risk factors. The control group consisted of all subjects without either depression or anxiety [Table 3]. Odds ratios were calculated for the remaining variables in the best fitting model for each of the diagnoses.

Overall, there was a trend towards higher odds ratios in ANX and ANXDEP than in DEP. Among the demographic variables, higher age was negatively associated with ANXDEP. Being unmarried was associated with the presence of DEP, but was inversely related to ANX. As being unmarried has been suggested to affect men and women differently (Wolk & Weissman 1995), we have also assessed whether stratification for gender and repeating the multivariate analyses in men and women separately would yield differences in this domain. Being unmarried remained associated with pure depression in both men and women, but the negative association of being unmarried with pure anxiety was no longer apparent in either sex. Of the other environmental vulnerability characteristics, having professional support was associated with ANXDEP. Social support was not associated with any of the diagnostic categories.

Longstanding vulnerability effects, as indicated by a personal history of depression or anxiety disorder, was highly statistically significant, with a steep increase of the impact of this type of vulnerability going from DEP to ANX to ANXDEP. The confidence intervals of the odds ratios for a personal history and gender in ANXDEP and DEP mutually excluded the opposite value, indicating a statistically significant difference between strata on these domains.

Stress factors were significantly and similarly associated with all three diagnostic categories. Although chronic diseases were not related to ANXDEP, and IADL disability was not associated with ANX, a clear pattern of differences between strata could not be demonstrated. Physical and functional stresses thus appeared to have a similar impact in all three diagnostic categories.

Gender differences were rather pronounced, and the pattern of increasing odds ratios across categories paralleled that of a personal history. The association between being female and the presence of ANXDEP was the strongest, and significantly different from the odds ratio of gender with DEP. The value in ANX was exactly between these extremes, suggesting a stepwise increase in the impact of this factor across categories.

TABLE 3: MULTIVARIATE ANALYSIS; BEST FITTING MODEL FOR EACH DIAGNOSTIC CATEGORY
Control group without depression and anxiety (O.R. with 95 % C.I., stepwise logistic regression, backstep, P out < 0.05)

RF	Depression	Anxiety	Mix
Age > 74			0.53 (0.30-0.91)
Ed; Primary or less			
Unmarried	1.47 (1.16-1.87)	0.51 (0.27-0.97)	
Social support			
Professional support			1.84 (1.03-3.28)
Personal history	2.47 (1.91-3.19)	4.11 (2.16-7.81)	5.94 (3.54-9.96)
Chronic diseases	1.51 (1.20-1.89)	2.39 (1.18-4.83)	
ADL disability	2.27 (1.62-3.18)	3.50 (1.64-7.48)	2.48 (1.27-4.87)
IADL disability	1.74 (1.36-2.23)		2.67 (1.49-4.81)
MMSE < 26	1.49 (1.13-1.96)	2.66 (1.34-5.26)	2.26 (1.24-4.11)
Sex: female	2.06 (1.57-2.72)	3.73 (1.65-8.46)	5.53 (2.36-13.00)

4.4 Discussion

The present study sought to investigate whether, in a large epidemiological sample of community living elderly, generalised anxiety disorder and depression are best described as distinct diagnostic entities or whether a dimensional classification is more appropriate. To do so, two hypotheses were studied. The first hypothesis was that depression and generalised anxiety are on a continuum, with diagnostic thresholds differentiating categories of 'pure' depression, 'pure' generalised anxiety or mixed anxiety-depression that essentially represent the same disorder. Different levels of severity, or different stages of development, may thereby be responsible for classification as different nosological entities. The second hypothesis was, that depression and anxiety are in effect different entities, likely to be associated with different sets of risk factors that for both clinical and theoretical reasons should be discerned form each other. Lastly, gender differences were studied, as a large body of research suggests not only different prevalence levels but also distinct risk profiles for men and women.

The current study is the first community based study among the elderly that we know of that uses GMS-AGECAT data on prevalence of depression and generalised anxiety disorder to compare both severity levels and risk profiles for these conditions. It is important to note that case finding of elderly subjects with depression and/or anxiety disorders by the health services is generally poor. Notwithstanding the considerable amount of suffering that is associated with these conditions, the majority do not receive any treatment at all (German et al. 1987). Previous research has shown that a substantial number of primary care patients have a non-specific pattern of both anxious and depressed symptoms not meeting current definitional thresholds, but associated with significant distress or impairment (Zinbarg et al. 1994). These 'subthreshold mental disorders' (Pincus, Davis, & McQueen 1999) as they are found in the community are identified with instruments such as GMS-AGECAT.

In contrast with other diagnostic instruments, GMS-AGECAT not only allows to validly diagnose large numbers of community living elderly, but it also attributes levels of caseness signifying increasing severity levels of psychopathology with a clear distinction between cases and subcases. Screening instruments that measure symptoms allow comparisons of severity, but do not make valid diagnoses. Diagnostic criterion instruments are often more time and personnel consuming, and do not usually attribute severity- or caselevels to subjects with valid diagnoses. These rather unique diagnostic properties of GMS-AGECAT are well tailored to compare severity levels of comorbid psychiatric conditions in large samples such as ours.

Severity levels of depression and generalised anxiety disorder in mixed anxiety-depression

The first hypothesis, on a dimensional classification of depression and generalised anxiety, appears to be largely supported by the data of this study. In this sample of community living elderly, higher severity levels of both disorders were associated with higher co-occurrence of the comorbid condition. More severely depressed subjects are more liable to have more severe generalised anxiety symptoms and vice versa. This parallel trend suggests a solid common ground for the two conditions, and can be seen a strong argument favouring a dimensional instead of a categorical diagnostic classification. As mixed anxiety-depression is on the most severe end of both the depression and the generalised anxiety spectrum, this underlines the importance of including both symptom clusters when studying late life psychiatric disorders. Most studies so far have not done this (Beekman, de Beurs, van Balkom, Deeg, Van Dyck, & Van Tilburg 2000), and data on overlap between generalised anxiety disorder and depression in the elderly are relatively scarce (Flint 1994). A study by Lindesay et al. (Lindesay, Briggs, & Murphy 1989) found that 91% of persons with generalised anxiety disorder also had 'depressive symptoms', whereas a community study by Beekman et al. (Beekman, de Beurs, van Balkom, Deeg, Van Dyck, & Van Tilburg 2000) showed that among elderly subjects with anxiety disorders 26.5% also met stricter criteria for major depression. The current study underlines the high co-occurrence of these disorders also in the elderly, as 60.4% of subjects with clinically relevant generalised anxiety symptoms were also having a depression diagnosis. The prevalence rate of 12.9% for GMS depression found in the current study, is well within what has been found in a larger number of community based studies on depression in the elderly. Prevalence levels of depressive syndromes requiring clinical attention generally range around 13.5% (Beekman, Copeland, & Prince 1999). Prevalence rates of generalised anxiety in the same age group are much less frequently described, and vary from 0.7% to 7.1%, (Flint 1994). The percentage of 3.2% in the current study thus appears to be well within the range of earlier findings also. Although more studies in the age group are needed to confirm the patterns of increasing comorbidity along severity lines found in this study, the prevalence levels found for depression and generalised anxiety suggest that these findings may very well be reproduced in future work.

Risk profiles in different diagnostic categories

Our second research question was to determine whether pure depression, pure generalised anxiety disorder, and mixed anxiety-depression may have different risk profiles. If differential risk patterns are found this could be important for clinical reasons, but it may also further our understanding of the nosology of both conditions. Following the findings by Kendler et al (1996), it was hypothesised that long-term vulnerability factors would be associated with both depression and anxiety symptoms, whereas more recent stress and vulnerability characteristics would be specifically associated with either category of psychopathology.

In this study longstanding vulnerability, exemplified by a personal history, was found to be associated with both depression and generalised anxiety. As may be expected in more severe psychopathology, the associations were much stronger in

mixed anxiety-depression than in pure depression. However, also in pure generalised anxiety disorder longstanding vulnerability was considerably higher than in pure depression. Longitudinal research is needed to assess whether generalised anxiety indeed has a more chronic course than pure depression in the elderly, or whether subjects with this diagnosis have a higher change of developing mixed anxiety-depression.
Differences in concurrent risk profiles for each of the diagnostic categories were rather limited in the current study. Pure depression was significantly associated with being unmarried. Environmental vulnerability has been described to be related to depression in both adults (Brown & Harris 1978) and in older persons (Beekman et al. 1995). The current data suggest that this type of vulnerability is specific for pure depression in the elderly when compared with the other diagnostic categories. Professional support was also analysed as environmental vulnerability, and was associated with mixed anxiety-depression specifically. In our view, this factor can also be taken as an indication of severity of both psychiatric and other handicaps in these subjects. This is in line with the trend towards higher odds-ratios for both functional disabilities and cognitive decline in mixed anxiety-depression. Also specific to mixed anxiety-depression was its predominant occurrence in the younger old. With longstanding vulnerability being very high in mixed anxiety-depression, this finding fits the idea of a decrease of this type of vulnerability at a higher age, as the most vulnerable subjects selectively leave the population (van Ojen et al. 1995).

No differences between strata were demonstrated for physical and/or functional stress factors, which were largely associated to the three categories in a similar manner. We therefore conclude that our second hypothesis, suggesting different risk profiles in 'pure' depression, 'pure' anxiety and mixed anxiety-depression, is not supported by the data. Although environmental vulnerability was apparent in pure depression and not in the other categories, there were much more similarities than differences in the overall risk profile of the three diagnostic categories. The rather steep increase in longstanding vulnerability across diagnoses and the trend towards higher odds ratios very well fits the idea of increasing severity of psychopathology that was also apparent in the assessment of comorbidity. This is another argument favouring dimensional rather than categorical classification of depression and generalised anxiety in this age group.

Gender differences

The distribution of both pure generalised anxiety disorder and mixed anxiety-depression was very skewed, with women being 6 times as liable to have the combined disorder than men. Although higher prevalence of anxiety disorders in women has previously been described in the same age group (Schaub & Linden 2000), the overrepresentation of women in mixed anxiety-depression is striking for several reasons. Firstly, earlier research in the AMSTEL study has shown that among all depressive subjects, regardless of comorbid anxiety, the gender distribution becomes more equal when higher severity levels are assessed. Women have 2.7 times more neurotic depression than men, but only 1.4 times more psychotic depression (Schoevers, Geerlings, Beekman, Penninx, Deeg, Jonker, & Van Tilburg 2000b). The gender distribution of mixed anxiety depression does not follow this pattern, as the overrepre-

sentation of women in this specific type of severe psychopathology became more pronounced rather than less. Secondly, the current data not only show that levels of comorbidity increase along severity lines in both depression and generalised anxiety, but also underline that this association of severity with comorbidity is twice as strong in women than in men.

One may therefore conclude that mixed anxiety-depression is a subtype of severe psychopathology that is strongly associated with longstanding, possibly biologically determined vulnerability, and almost specific to women.

Limitations

The current study was performed among a large and representative sample of community living elderly using a well-established diagnostic instrument, including a large set of risk factors generally believed to be associated with late-life psychiatric disorders. However, there are several limitations.

First of all, the cross-sectional design does not allow a distinction between risk factors associated with aetiology and with prognosis of the disorders under study. Similarly, temporal associations between depression and generalised anxiety can not be addressed in cross-sectional analysis. Prospective designs are needed to clarify the issue of possible temporal sequencing, as depression and generalised anxiety may occur in the same person at different times and different stages of the development of the disorder. If this is found to be the case, it is another argument favouring a dimensional classification of depression and generalised anxiety. A second limitation is the fact that cross-sectional studies tend to overrepresent subjects with chronic disorders and longstanding vulnerability. Thirdly, the current study did not assess other types of anxiety disorders. Although generalised anxiety is the most prevalent anxiety disorder at a later age, and probably most closely related to depression, studies are needed that also investigate the associations between depression and other types of anxiety disorder in the age group under study.

Conclusions

The present study shows that in the elderly, mixed anxiety-depression is on the most severe end of both the depression and generalised anxiety spectrum. High co-occurrence and parallel increase in severity suggest a continuum rather than distinct diagnostic categories. Pure depression, pure anxiety and mixed anxiety-depression were significantly associated with longstanding vulnerability, with a stepwise increase in strength of the association across categories. Searching for possible differential risk profiles demonstrated that these were very similar in the different diagnostic categories, and higher odds ratios in mixed anxiety depression most probably also reflect more severe psychopathology. Comorbidity was markedly higher in women and in men, and mixed anxiety-depression appears to be a form of severe psychopathology that is almost specific for women in this age group.

The findings have implications for clinical work, as comorbidity of generalised anxiety or depression may often indicate a more severe form of psychopathology. Longitudinal studies are needed to assess natural course and treatment response of pure depression, pure generalised anxiety and mixed anxiety-depression in the elderly.

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5

Depression and generalized anxiety disorder; co-occurrence and longitudinal patterns in elderly patients

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American Journal of Geriatric Psychiatry (2005) 13: 31-39

Abstract

Objective

To establish the natural course and risk profile of pure depression, pure generalized anxiety disorder and depression with co-existing generalized anxiety disorder in later life.

Method

2173 community living elderly were interviewed at baseline, and at 3-year follow-up. The course of pure depression, pure generalized anxiety disorder and depression with co-existing generalized anxiety disorder (GMS-AGECAT) was studied in 258 subjects with baseline psychopathology. Bivariate and multivariate relationships between risk factors and course types were assessed. The risk profile for onset of pure depression, pure generalized anxiety disorder and the mixed condition at follow-up was studied in 1915 subjects without baseline psychopathology.

Results

Remission rate at follow up was 41% for subjects with pure depression, 48% in pure generalized anxiety, and significantly lower (27%) in depression with coexisting generalized anxiety disorder. A pattern of temporal sequencing was established, with anxiety often progressing to depression or depression with generalized anxiety disorder. Onset of pure depression and depression with co-existing generalized anxiety disorder was predicted by loss events, ill health and functional disability. Onset of pure generalized anxiety disorder, and more strongly that of depression with co-existing generalized anxiety disorder, was associated with longstanding, possibly genetic vulnerability.

Conclusions

In comparison with either pure depression or pure anxiety, the co-occurrence of these represents more severe and more chronic psychopathology, associated with longstanding vulnerability. In the elderly, generalized anxiety disorder often progresses to depression or to the mixed condition. These findings mostly favor a dimensional versus a categorical classification of anxiety and depression.

5.1 Introduction

Co-occurrence of depression and generalized anxiety disorder is a consistent finding across different age groups (Beekman et al. 2000;Kessler et al. 1996;Regier et al. 1998). In adults, comorbidity is associated with a poorer prognosis (Liebowitz et al. 1990;Regier, Rae, Narrow, Kaelber, & Schatzberg 1998), greater functional disability (Bijl & Ravelli 2000) and higher service utilization than in persons with a single disorder (Kessler et al. 1994). In the elderly, much less is known about the course and consequences of depression with co-existing generalized anxiety disorder (Flint 1994). Available data however suggest that also in the elderly, comorbidity of depression and generalized anxiety disorder may represent a group with unfavorable characteristics in terms of severity and prognosis of psychopathology (Lenze et al. 2001). Cross-sectional findings from the Amsterdam Study of the Elderly (AMSTEL) showed that the combined condition differs from both single disorder conditions in the sense that comorbidity increases with higher severity levels of both depression and generalized anxiety (Schoevers et al. 2003). Given the high prevalence and potential adverse consequences of this type of comorbidity in the elderly, there is an urgent need for longitudinal research in this domain (Charney et al. 2003).

Apart from its clinical implications, the frequent co-occurrence of depression and anxiety has also fuelled the discussion concerning the validity of current categorical classifications of mental disorders, with critics suggesting a dimensional approach is more appropriate (Goldberg & Huxley 1992;Tyrer 1996;Zinbarg et al. 1994). Generalized anxiety disorder in particular may be on a continuum with depression (Liebowitz, Hollander, Schneier, Campeas, Fallon, Welkowitz, Cloitre, & Davies 1990). It has also been suggested that, although the same genetic factors appear to predispose to both generalized anxiety and depression, specific environmental factors may be differentially associated with the development of either anxiety or depression (Kendler et al. 1987;Kendler 1996). Studies on the association of risk factors with each of these disorders in the elderly are however sparse and showed contradictory results in cross-sectional analyses (Beekman, de Beurs, van Balkom, Deeg, Van Dyck, & Van Tilburg 2000;Lenze, Mulsant, Shear, Alexopoulos, Frank, & Reynolds, III 2001;Schoevers, Beekman, Deeg, Jonker, & Van Tilburg 2003). This may be a result of differences in study designs. It may also be due to the fact that a cross-sectional design is unsuited to differentiate between factors that co-occur with or result from psychopathology, and factors that actually antedate and may be etiologically related to the occurrence of a condition. Thirdly, anxiety, depression and the mixed condition may also represent subsequent stages of disorder. Although temporal sequencing has been described in younger adults, with anxiety often occurring prior to the onset of depression, very little is known about longitudinal patterns in the elderly (Kessler, Nelson, McGonagle, Liu, Swartz, & Blazer 1996;Merikangas et al. 1996).

The current study describes the natural course and risk profile of pure depression, pure generalized anxiety disorder and depression with co-existing generalized anxiety disorder in later life. It seeks to establish patterns of temporal sequencing, and investigates whether comorbidity in fact represents a more severe and more

chronic condition in comparison with 'single' disorders. It also investigates the hypotheses on the specificity of risk factors for onset of these disorders, in light of the debate on dimensional versus categorical classification of depression and anxiety. The study was performed in a large cohort of community living elderly using a prospective design with a three-year interval.

5.2 Methods

5.2.1 Sampling and non-response

The Amsterdam Study of the Elderly (AMSTEL) is a longitudinal study of a large and representative sample of community dwelling elderly concerning mental health problems, medical diagnoses and demographic characteristics. The sampling and data collection procedures have been described elsewhere (Launer et al. 1993;Schoevers et al. 2000a). In short, the population base for AMSTEL included all non-institutional individuals in the 65-84 age bracket who lived in the city of Amsterdam. The profile of the study sample corresponded to the non-institutionalized Amsterdam population in terms of age and gender. An age-stratified sample was drawn. All 4051 subjects (71.5%) who responded and gave their informed consent were interviewed at baseline. Non-response in the younger old (<75) was associated with poor performance on cognitive tests and with health problems. In the older old no correlates of non-response were found (Launer, Wind, & Deeg 1994).

Of the 4051 subjects who initially responded, 2244 (55,4%) were reinterviewed three years later (median 38 months). Nonresponse consisted of 656 (16,2%) subjects who had died, 662 (16,3%) persons who refused further co-operation, 282 (7,0%) who were too ill or cognitively impaired to respond, and 207 (5,1%) who were not available for interview due to other reasons. Subjects with an organic diagnosis at baseline (GMS-AGECAT case levels for organicity higher than two, N=71) were excluded, yielding a total sample of 2173 subjects.

The study sample for the investigation of course types of psychopathology consisted of subjects with baseline GMS-AGECAT case levels of depression, anxiety or both, who attended follow-up assessment. The sample for these assessments thus consisted of 258 subjects.

The analyses on the association between risk factors and incidence of depression, anxiety and depression with co-existing generalized anxiety disorder at follow-up, were performed in a sample consisting of all responders who did not have depression, generalized anxiety disorder or dementia at baseline (GMS-AGECAT levels of less than three for depression, anxiety and organicity; N=1915).

5.2.2 Measures

A one hour interview was conducted consisting of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), Geriatric Mental State Examination (GMS) items related to organic, affective and generalized anxiety syndromes (Copeland, Dewey, & Griffiths-Jones 1986), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale

(Lawton & Brody 1969), and the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and regularly supervised.

Psychiatric syndromes. Diagnoses of depression, organic caseness and generalized anxiety were reached using the GMS-AGECAT system (Copeland et al. 1988;Copeland, Dewey, & Griffiths-Jones 1986). AGECAT has proven reliability for epidemiological work (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988). The Dutch language version has been validated (Hooijer, Jonker, & Dewey 1991). In the analyses syndrome levels were used for psychopathology, as the diagnostic hierarchy in GMS-AGECAT would otherwise bias the results. Diagnostic levels 1 and 2 are classified as subcases. Levels 3-5 have been proven valid to detect cases requiring clinical attention in the community (Copeland et al. 1987;Copeland et al. 1992;Copeland, Dewey, & Griffith-Jones 1990). Depression, generalized anxiety and organic caseness were defined as a GMS-AGECAT level 3 or higher. Subjects meeting GMS criteria for depression and not meeting GMS criteria for anxiety were classified as 'pure depression' (DEP). Subjects with GMS generalized anxiety disorder without depression caseness were classified as 'pure generalized anxiety disorder' (GAD). Subjects meeting GMS criteria for both depression and anxiety were labeled 'depression with co-existing generalized anxiety disorder' (DEPGAD). GMS-AGECAT case levels also represent levels of increasing severity of the disorder, with case level 5 indicating the most severe end of the spectrum. To determine the prognostic value of different severity levels at baseline, a dichotomous variable was constructed for severity of psychopathology. GAD case levels 4 and 5 were classified as higher severity, and level 3 as less severe illness. Depressed subjects are subdivided into neurotic and psychotic depression. Psychotic depression was classified as more severe than neurotic depression. In subjects with any of these three types of psychopathology at baseline, remission was defined as no longer having any of these diagnoses at follow-up.

Risk factors. Educational status was dichotomized as lower (primary school or less) and higher (more than primary school) education. Marital status was assessed using the appropriate questions in GMS-AGECAT. Social support was ascertained by the question: 'Do you get help from your children, neighbors or other acquaintances?' A personal history was ascertained by the relevant CAMDEX-question, asking subjects whether they had ever experienced depression and/or anxiety of such severity that treatment had been sought. Age at first onset was recorded. Also translated from the CAMDEX-questionnaire was a family history of psychiatric illnesses. The presence of chronic diseases was assessed with the pertinent Camdex questions on cardiovascular diseases, cancer, lung disease, diabetes, Parkinson's disease, arthritis and epilepsy. A dichotomous variable indicates whether or not subjects had any chronic illnesses. Cognitive status was assessed by MMSE-score. Subjects were considered to have functional disability if their ADL or IADL scores were two or more points below the maximum score on the respective scales (ADL 12 and IADL 16 points). This means that subjects were 'in need of help' to perform at least two of the tasks in the respective domains.

Differences that had occurred between baseline and follow-up were also noted. Stressors thus defined were personal life events (partner loss), changes in physical

health (the emergence of one or more chronic diseases), a substantial decrease in ADL or IADL functioning (two scale points or more), and cognitive decline (incident organic syndrome; GMS-AGECAT organic level three or more at follow-up).

5.2.3 Data analysis

Characteristics at baseline and follow-up were described, and response rate according to baseline characteristics were calculated using bivariate and multivariate statistics.

In the baseline case sample, possible patterns of temporal sequencing across both assessments of DEP, GAD and DEPGAD were calculated in cross-tabulation with chi-square analysis. The probability of different course types was tested by dichotomizing outcome as 'remission vs. persistence', and 'developing DEPGAD vs. not' and drawing up two by two cross tabulations. In this way the courses of baseline GAD and DEP were compared, as were the courses of subjects with either DEP or GAD and subjects who had DEPGAD.

In the non-case baseline sample, associations of independent variables with the incidence of either DEP, GAD and DEPGAD at follow-up were assessed calculating odds ratios, using the subjects without depression and anxiety at follow-up as reference category. When the 95% confidence interval did not include 1, the association was regarded to be statistically significant. Multinominal logistic regression analysis was used to achieve independent predictive ability for each diagnostic category using the full model of potential risk factors. Differences between strata were considered statistically significant according to the criterion that the confidence intervals of a risk factor mutually exclude the point estimates in one or both of the other diagnostic categories (Gardner & Altman 1986). Backward stepwise analysis was subsequently used to reach the most parsimonious model for each diagnostic category.

5.3 Results

5.3.1 Sample characteristics and response pattern

Non-response at the follow-up assessment was predicted by higher age, male gender, lower education, chronic disease(s), ADL and IADL impairment and organic caseness (Schoevers, Beekman, Deeg, Geerlings, Jonker, & Van Tilburg 2000a). After subjects with dementia at baseline and those who died between measurements were excluded from the sample, only lower education, not having a marital partner and baseline cognitive deficits (MMSE < 26) remained as significant predictors of non-response. Importantly, controlling for other factors in multivariate logistic regression analysis, neither DEP (RR 0.87, 95% c.i. 0.68-1.12), GAD (RR 0.97, 59% c.i. 0.50-1.88), nor DEPGAD (RR 0.85, 95% c.i. 0.48-1.48) were significantly associated with the risk of attrition (overall likelihood Chi2 test for full model 85.29, df 16, P<0.001). [Table 1] shows the sample characteristics and the associations with GAD, DEP and DEPGAD at follow-up.

TABLE 1: SAMPLE CHARACTERISTICS
(baseline sample excluding subjects with dementia, dichotomised variables, N=2173, with psychopathology at follow-up, Chisq= Pearson chi-square test with two sided p-value; *= p<0.05, **=p<0.01, ***=p<0.001)

RISK FACTORS		FOLLOW-UP:				
	BASELINE (%)	NO DEP OR GAD (1695)	GAD (32)	DEP (351)	DEP GAD (95)	Chisq/df/p
Age >74 yrs at baseline	1066(49.1)	808 (47.7)	13 (40.6)	202 (57.5)	43 (45.3)	12.9 / 3 / **
Sex: female	1372(63.1)	1033(60.9)	24 (75.0)	244 (69.5)	71 (74.7)	17.1 / 3 / **
Lower education	803(37.0)	612 (36.1)	16 (50.0)	137 (39.0)	38 (40.0)	3.9 / 3 / 0.27
Unmarried	1100(50.6)	848 (50.1)	13 (40.6)	192 (54.7)	47 (49.5)	3.8 / 3/ 0.28
Social Support	373(17.2)	273 (16.1)	4 (12.5)	78 (22.2)	18 (18.9)	8.4 / 3 / *
Pers. hist. dep.	327(15.0)	207 (12.2)	8 (25.0)	72 (20.5)	40 (42.1)	75.7 / 3 / ***
Family history	258(11.9)	185 (10.9)	3 (9.4)	50 (14.2)	20 (21.1)	11.2 / 3 / *
Baseline chron. dis.	1073(49.4)	792 (46.7)	18 (56.3)	205 (58.4)	58 (61.1)	22.0 / 3 /***
Baseline ADL disability	103(4.7)	61 (3.6)	3 (9.4)	27 (7.7)	12 (12.6)	26.3 / 3 /***
Baseline IADL disability	393(18.1)	255 (15.0)	7 (21.9)	104 (29.6)	27 (28.4)	49.3 / 3 /***
Low MMSE (<26)	217(10.0)	158 (9.3)	6 (18.8)	39 (11.1)	14 (14.7)	6.5 / 3 / 0.09
CHANGES TO-T1; LIFE EVENTS						
Partner died	155(7.1)	97 (5.7)	1 (3.1)	43 (12.3)	14 (14.7)	28.0 / 3 /***
New ADL disability	128(5.9)	86 (5.1)	2 (6.3)	29 (8.3)	11 (11.6)	11.1 / 3 / *
New IADL disability	448(20.6)	308 (18.2)	10 (31.3)	98 (27.9)	32 (33.7)	29.8 / 3 /***
New chronic diseases	422(19.4)	300 (17.7)	8 (25.0)	82 (23.4)	32 (33.7)	19.7 / 3 /***

5.3.2 Temporal sequencing

Pure generalized anxiety disorder Table 2 shows that the 25 subjects with GAD had the highest remittance rate (48%). 3 subjects (12%) remained in the same category, but 6 (24%) subjects developed DEP. DEPGAD emerged in 4 persons (16%).

Pure depression Of the 199 subjects with DEP at baseline, 82 (41.2%) no longer had DEP or GAD at follow-up. 86 subjects (43.2%) remained in the same category at both assessments. Only 4 subjects (2%) of those with DEP at baseline developed GAD, whereas 27 (13.6%) developed DEPGAD.

Mixed anxiety depression Among the 34 subjects with DEPGAD at baseline, remission rates were low (27%). A relatively high proportion of subjects remained within the same diagnostic category (44%). DEP appeared in 27%. Only 1 person developed GAD (3%).

Cross tabulation of all course types proved statistically significant (Pearson Chi-Square test 28.14, df 6, p<0.001). Dichotomizing course types showed that there was no statistically significant difference in the probability of remission between DEP and GAD. Subjects with DEPGAD showed significantly lower remission rates than subjects with DEP or GAD (Pearson chi2 2.96, df 1, one sided p=0.043). Comparing baseline categories on the outcome of DEPGAD or 'not DEPGAD' did not show a statistically significant difference between GAD and DEP, but showed that subjects with baseline DEPGAD were more likely to keep the combined disorder than change into either of the pure forms (Pearson chi2 18.47, df 1, p<0.001).

TABLE 2: STABILITY OF DIAGNOSTIC CATEGORIES ACROSS ASSESSMENTS (all responders with baseline generalised anxiety disorder and/or depression, excluding baseline organic cases,N=258, % of responders per baseline category)

Diagnosis at baseline:		at follow-up: No DEP/ GAD	GAD	DEP	DEPGAD
Pure generalised anxiety	(25)	12 (48.0)	3 (12.0)	6 (24.0)	4 (16.0)
Pure depression	(199)	82 (41.2)	4 (2.0)	86 (43.2)	27 (13.6)
Depression with GAD	(34)	9 (26.5)	1 (2.9)	9 (26.5)	15 (44.1)

5.3.3 Associations of risk factors with course of illness

Stable vs. worsened Bivariate analyses showed that in subjects with either GAD or DEP, developing DEPGAD was associated with the occurrence of chronic diseases between assessments (RR 2.68, 95% c.i. 1.32-5.42, overall Chi2 test 8.16, df 1, p=0.0043) (data not shown). Severity of DEP and/or GAD was not associated with course type, nor was the presence of a personal history. In the multivariate model (backward stepwise logistic regression modelling) the association with new chronic illness remained (RR 2.90, 95% c.i. 1.43-5.89), and mixed anxiety depression was also inversely associated with an age above 74 years (RR 0.45, 95% c.i. 0.22-0.95, overall Chi2 test at last step 12.8, df 2, p=0.0017) (data not shown).

Stable vs. remitted. None of the risk factors showed significant differences between strata of subjects with a single disorder at baseline who had remitted at follow-up. In subjects with depression with co-existing generalized anxiety disorder at baseline, partial or complete remission was not associated with any of the risk factors either.

5.3.4 Predictors of incidence at follow-up

In the sample without depression, anxiety or dementia at baseline (n=1915), 24 subjects (1.3 %) had developed GAD at follow-up. 250 (13.1%) had DEP and in 49 persons (3.6%) DEPGAD had occurred.

[Table 3A] shows the multinominal logistic regression models for each diagnostic category. Only having a personal history of depression or anxiety was significantly associated with the onset of GAD. As the numbers were relatively small, these associations were also tested in bivariate analyses yielded no other statistically significant associations with GAD at follow-up. The occurrence of DEP was associated with having chronic diseases at baseline and baseline IADL disability, with loss of spouse and with a decrease in functional abilities (IADL) between assessments. DEPGAD was predicted by having a personal history, and by a decrease in IADL functioning.

There were three significant differences between pure depression and depression with co-existing GAD; the mixed category shows significantly higher odds ratios for age (65-74 vs. 75-84 years), a personal history of depression and/or anxiety disorder, and decreases in both ADL and IADL functioning.

The most parsimonious models (table 3B) showed similar results for GAD and DEP, with a personal history just failing to reach statistical significance in DEP. Having a personal history was more strongly associated with the occurrence of DEPGAD. DEPGAD was also predicted by baseline (ADL) and newly occurring functional disabilities (ADL and IADL) and loss of spouse. Risk ratios of baseline and newly occurring functional limitations were generally higher in DEPGAD. Loss of spouse showed similar associations with the occurrence of both categories.

TABLE 3A: ASSOCIATIONS OF RISK FACTORS WITH INCIDENCE OF GENERALISED ANXIETY, DEPRESSION AND DEPRESSION WITH COEXISTING GAD (N=1915, multinominal logistic regression model, Odds Ratios, italics: difference between strata according to the criterium of mutually exclusive c.i.)

Diagnosis at follow up:

Risk factors:	**GAD (24)**	**DEP (250)**	**DEPGAD (49)**
Age > 74	1.33 (0.53-3.32)	*1.27 (0.94-1.72)*	*0.61 (0.32-1.18)*
Female	2.62 (0.95-7.22)	1.03 (0.75-1.42)	1.32 (0.68-2.57)
Only basic education	1.16 (0.49-2.74)	0.96 (0.72-1.29)	1.27 (0.68-2.34)
Not / no longer married	0.56 (0.22-1.42)	1.19 (0.85-1.66)	0.78 (0.39-1.57)
Social support	0.53 (0.14-1.93)	0.83 (0.56-1.21)	0.58 (0.25-1.38)
Personal history depression/anxiety	2.79 (1.06-7.35)	*1.42 (0.96-2.09)*	*4.27 (2.25-8.13)*
Family history mental illnesses	0.96 (0.27-3.39)	1.39 (0.92-2.09)	0.89 (0.35-2.22)
Chronic ilnesses at baseline	1.37 (0.60-3.14)	1.47 (1.11-1.95)	1.06 (0.58-1.95)
ADL disability at baseline	0.78 (0.00-6.29)	1.25 (0.65-2.39)	2.62 (0.90-7.61)
IADL disability at baseline	1.31 (0.44-3.92)	1.80 (1.26-2.57)	1.50 (0.71-3.17)
MMSE < 26	2.02 (0.63-6.44)	0.67 (0.40-1.12)	1.45 (0.62-3.40)
Loss of spouse	-	3.36 (2.09-5.38)	2.54 (0.96-6.68)
New medical illness	1.71 (0.66-4.44)	1.31 (0.94-1.83)	1.74 (0.90-3.35)
Recent decrease ADL functioning	0.60 (0.00-4.79)	1.02 (0.57-1.81)	2.41 (0.99-5.86)
Recent decrease IADL functioning	1.56 (0.60-4.09)	*1.43 (1.02-1.99)*	*3.04 (1.58-5.86)*

Overall likelihood Chi-square test: 135.5, df: 45, p<0.001

TABLE 3B: Multivariate logistic regression (Odds Ratios in parsimonuous model with Pin<0.05, P out<0.10, backstep procedure).

GAD (34)	**DEP (250)**	**DEP GAD (49)**
Personal history 2.58 (1.01-6.58)	Personal history 1.44 (0.99-2.11) Chron dis (baseline) 1.45 (1.10-1.91) IADL disability (baseline) 1.78 (1.28-2.48) Loss of spouse 2.93 (1.93-4.47) Recent IADL decrease 1.53 (1.12-2.10)	Personal history 4.48 (2.38-8.38) ADL disability(baseline)2.84(1.04-7.77) Loss of spouse 2.90 (1.22-6.93) Recent ADL decrease 2.39 (1.01-5.65) Recent IADL decrease 2.91(1.56-5.44)

5.4 Discussion

The aim of the current study was to describe the natural course of pure depression, pure generalized anxiety disorder and depression with co-existing generalized anxiety disorder in a large and representative sample of community living elderly, and to investigate whether different risk profiles were associated with occurrence and prognosis of each of these types of psychopathology.

Main findings

Assessment of the natural course of three diagnostic categories showed that, first of all, the prognosis of either category in the elderly is poor, with remission rates under 50% after a three-year interval. When comparing categories, GAD was the least stable category with only 12% of anxious subjects remaining within that category at follow-up. A significantly larger number of subjects with baseline GAD developed either DEP or DEPGAD at follow-up. DEP and DEPGAD appeared to be much more stable diagnostic categories, and these subjects were highly unlikely to develop GAD at follow-up. Although, due to relatively small numbers, not al of these transitions could be statistically tested, these data clearly suggest a fixed pattern of temporal sequencing. GAD in elderly subjects either remits or progresses into depression or mixed anxiety depression, whereas subjects with DEP or DEPGAD are highly unlikely to develop GAD at follow-up. Although this is in line with findings in younger adults (de Graaf et al. 2003), such sequential patterns have not systematically been described in this age group before.

Studying the course of DEPGAD showed that, with only 27% remission at follow-up, the prognosis of this mixed category is significantly worse than that of either of the single conditions. This confirms findings of earlier, mostly cross-sectional research showing that also in the elderly, higher levels of comorbidity indicate more severe psychopathology (Lenze, Mulsant, Shear, Alexopoulos, Frank, & Reynolds, III 2001;Schoevers, Beekman, Deeg, Jonker, & Van Tilburg 2003). This may have important implications. Recent data suggest that DEPGAD can effectively be treated in the elderly (Lenze et al. 2003). Early intervention in depressed subjects with comorbid anxiety may significantly reduce chronicity and all of its negative consequences, both for the individual patient and for the use of health services (Katon et al. 2003).

Studying whether specific risk factors were associated with either persistence or remission of baseline psychopathology, or with the development of DEPGAD, yielded a limited number of statistically significant associations. The finding that the progression to mixed anxiety depression in subjects with GAD or DEP was predicted by comorbid medical illness, supports earlier research showing that medical comorbidity carries a higher risk for chronicity and worsening of affective disorder (Cole, Bellavance, & Mansour 1999). The finding that the progression from a single disorder to depression with co-existing generalized anxiety disorder was also associated with age below 74, fits the concept of a decrease of this type of vulnerability at a higher age, with the most vulnerable subjects selectively leaving the population at an earlier stage (Penninx et al. 1999;Schoevers et al. 2000b;van Ojen et al. 1995).
Apart from studying prognosis, we also attempted to study the risk profile for onset

of any of the three subtypes of psychopathology at follow-up in subjects without baseline psychopathology. GAD was only predicted by a personal history of depression and/or anxiety, but this may have been due to relatively low numbers. Onset of both DEP and DEPGAD was associated with functional limitations, chronic illnesses and loss events. This is in line with findings from earlier studies on depression incidence (Cole & Dendukuri 2003) that did not make a distinction between depression with or without coexisting anxiety. According to the criterion that the confidence limits should mutually exclude the point estimates of the relative risk in the opposite stratum, we found three risk factors that showed statistically significant differences between DEP and DEPGAD. Again, the younger old were more likely to have the mixed condition, in line with the idea of more severe pathology. Decreases in functional abilities also showed significantly stronger associations with DEPGAD than with GAD. The strongest predictor of DEPGAD was the presence of longstanding, and possibly genetically defined vulnerability, exemplified by a personal history of depression and/or anxiety.

Limitations

The current study is an improvement over existing studies on depression and generalized anxiety in the elderly in the sense that it uses a prospective design in a community sample using established measurement instruments and comprehensive set of risk factors associated with late-life psychiatric disorders.

The principal limitation is the fact that symptomatology has been assessed two times with a three-year interval. Subjects may have seen both relapse and remittance during the study interval and not all of this variation is accounted for in the data. Likewise, episodes of both depression and anxiety with a shorter duration are generally underrepresented in studies with a limited number of assessments. This would suggest that overall, the actual course of depression and generalized anxiety disorder in the population may be somewhat less gloomy than this study shows. Still, the level of chronicity is comparable to what is generally found in studies on late-life depression (Cole, Bellavance, & Mansour 1999), even when studies were able to use more frequent measurements (Beekman et al. 2002).

A second limitation is the fact that this study is a naturalistic follow-up in the community, not controlling for ongoing treatment that may have affected the results. Comparable samples of community living elderly have demonstrated that case finding is generally poor, with the majority of subjects with depression and/or anxiety not receiving any treatment at all for their complaints (Beekman, Copeland, & Prince 1999;German et al. 1987). Our study is no exception to this. It is however fair to conclude that, if treatment had actually affected prognosis in some subjects, this would have lead to an underestimation of the level of chronicity and other adverse consequences in our study.

Thirdly, although the total number of subjects included in this study was relatively large, and the prevalence of generalised anxiety (4.7%) was well within the range suggested by earlier findings (Beekman et al. 1998;Beekman, de Beurs, van Balkom, Deeg, Van Dyck, & Van Tilburg 2000;Flint 1994), stratification of the sample sometimes resulted in low numbers of subjects in the different cells. Especially when analysing pure generalised anxiety disorder, this may have limited the possibility to

find statistically significant differences with the risk profile of the other categories of psychopathology. A conclusion on specificity of risk factors for generalised anxiety disorder can therefore only be tentative. Still, both the temporal patterns and the differences between depression and depression with co-existing generalised anxiety disorder were rather pronounced and statistically significant, also in more detailed analyses. It should however be noted that reduction of the alpha level, e.g. by using Bonferroni correction because of multiple comparisons, was not performed in this study. This would be warranted if a conclusion were based on a single outcome within a larger set of calculations. However, when assessing multiple risk factors and searching for risk profiles with an a-priori hypothesis, this method may actually mask valid results, especially when numbers are limited.

A fourth limitation is that selective attrition to the follow-up assessment of the study has occurred among the very frail. Subjects with cognitive impairment and subjects with lower educational level were more likely to be nonresponders at follow-up. This a normal pattern in epidemiological studies. If this has affected the results, it again would lead to an underestimation of the actual situation in the community with regard to prevalence and prognosis of the disorders under study.

The current study provides arguments that may be relevant to the debate on a dimensional versus a categorical interpretation of GAD and DEP. The pattern of temporal sequencing, with GAD often progressing to DEP or DEPGAD, can be taken as an indication favoring a communal concept of anxiety and depression. Studying the specificity of risk factors for onset of either category, reflective of the "same genes, different environments" hypothesis put forward by Kendler et al (Kendler, Heath, Martin, & Eaves 1987;Kendler et al. 1992;Kendler 1996), however did not show that the risk profile for DEP differed from that for GAD. Although this may in part be explained by smaller numbers of GAD cases, our data do not provide support for the idea that anxiety and depression may be associated with different risk profiles. Further study is however needed to confirm this.

The finding that a longstanding, possibly genetic vulnerability is most strongly associated with DEPGAD does appear to be congruent with the findings of Kendler et al. (Kendler 1996) in twin studies. They suggested a strong and identical contribution to both GAD and DEP by genetic factors. As previous research showed that comorbidity indicates higher severity levels of both DEP and GAD, it is in line with this view that these associations were more prominent in subjects with the mixed condition.

Overall, our data show that in the elderly, both DEP and GAD often have a chronic course, in which GAD often progresses to DEP or DEPGAD. Comorbidity is associated with longstanding vulnerability, ill health and functional decline, and has a gloomy prognosis. These findings may be of considerable relevance for both our theoretical understanding of these commonly occurring disorders in later life, and for preventative purposes.

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6

Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in the Netherlands

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British Journal of Psychiatry (2000) 176: 568-575

Abstract

Background

Previous studies suggest that depression is associated with subsequent cognitive decline in elders with impaired cognition.

Aims To investigate whether depressed elders with normal cognition are at increased risk of cognitive decline and Alzheimer's disease (AD).

Methods

Two independent samples of older people with normal cognition were selected from the community-based Amsterdam Study of the Elderly (AMSTEL) and the Longitudinal Aging Study Amsterdam (LASA). In AMSTEL, depression was assessed with the Geriatric Mental State. Clinical diagnoses of incident AD were made using a two-step procedure. In LASA, depression was assessed with the CES-D. Cognitive decline was defined as a drop of 3 or more points on the MMSE at follow-up.

Results

Multiple logistic regression analyses showed that both in the AMSTEL and the LASA sample, depression was associated with an increased risk of AD and cognitive decline, respectively, but only among subjects with higher levels of education.

Conclusions

Although differential loss to follow-up may have influenced the results to some extent, the findings suggest that in a subgroup of more highly educated elderly people depression may be an early manifestation of AD before cognitive symptoms become apparent.

Declaration of interest

None.

6.1 Introduction

Recent studies (Bassuk et al, 1998; Chen *et al*, 1999; Yaffe *et al*, 1999) demonstrate the growing interest in the question whether depression in dementia may be a cause or a consequence of the dementia process. In 1996, Devanand et al reported that depressed mood increased the risk of Alzheimer's disease (AD). In this study, depressed mood was more common in subjects with greater baseline cognitive impairment, giving them a greater probability to develop AD. Other prospective studies were inconsistent. Dufouil *et al* (1996) and Henderson *et al* (1997) did not find a relation between depression and subsequent cognitive decline, while Bassuk *et al* (1998) and Chen et al (1999) did find such a relation, but only among subjects in whom cognitive impairment was already apparent. To further study the nature of the relationship between depression and cognitive decline/dementia, we investigated whether depressed elderly individuals with normal baseline cognition were at increased risk of cognitive decline and AD. We used data from two cohorts of elderly people living in the community.

6.2 Methods

6.2.1 Baseline samples

Data on incident AD were obtained from the Amsterdam Study of the Elderly (AMSTEL), whereas data on cognitive decline were obtained from the Longitudinal Aging Study Amsterdam (LASA). For both studies, Medical Ethics Committee approval was obtained. The sampling procedures of both studies have been described elsewhere (Launer et al, 1993; Deeg et al, 1993; Beekman et al, 1995). In brief, for the AMSTEL study 5,666 noninstitutionalized elderly people, aged 65 to 84 years, were selected from 30 general practices spread across the city of Amsterdam. Within each practice a fixed proportion of people was randomly selected from each of four 5-year age strata (65-69 years to 80-84 years) to obtain equal-sized strata. 4,051 (71.5%) people gave their written consent and participated in the study. The LASA cohort is based on random, sex and age stratified (six 5-year age strata from 55 to 84 years), samples drawn from 11 municipal population registries (both urban and rural) in three regions of the Netherlands. The baseline sample of the LASA cohort consists of 3,107 people.

6.2.2 Baseline measurements and study samples

AMSTEL

In 1990-1991 trained lay people interviewed all 4,051 participants at home. The interview comprised the Dutch version of the Geriatric Mental State Schedule (GMSS) (Copeland *et al*, 1976; Gurland *et al*, 1976; Hooijer *et al*, 1991), questions on sociodemographic characteristics, current health status, medical history, and four mental status tests, among which the Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975). Depression was measured using the GMSS, in conjunction with its computerized diagnostic system AGECAT (Dewey & Copeland, 1986). The GMSS is a structured interview to identify various psychiatric disorders, specifically designed for use with elderly individuals. AGECAT consists of the application of hierarchical rules to the items of the GMSS in order to reach a diagnosis for various psychiatric disorders (e.g., depression and dementia syndromes) with different levels of confidence. The presence and absence of depression was indicated by GMS-AGECAT depression syndrome levels 3-6 and 0-2, respectively.

To select a study sample with normal cognition, a cohort without dementia was firstly selected by excluding from the baseline sample all subjects (N=273) with a DSM-III-R dementia diagnosis (APA, 1987) (for a more detailed description see Jonker *et al*, 1998) or a GMS-AGECAT dementia diagnosis (i.e., organic illness syndrome levels of 3-5). Second, from this cohort without dementia all subjects with subthreshold levels of dementia were excluded, i.e., with GMS-AGECAT dementia levels of 1-2 or MMSE scores of 25 and less (N=631). In all, 904 subjects were excluded, resulting in a study sample of 3,147 nondemented subjects with normal cognition (i.e. MMSE scores of 26-30 and GMS-AGECAT organic illness score 0).

LASA

In 1992-1993, trained lay people interviewed all 3,107 participants at home. Cognitive functioning was measured with the MMSE. Depressive symptomatology was measured with the Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Beekman *et al*, 1997). This is a twenty item self-report scale developed to measure current depressive symptomatology in the community. The CES-D generates a total score which can range from 0 to 60. In order to identify respondents with clinically relevant levels of depression, the generally used cut-off score of ≥16 was also used. To minimize overlap between affective symptoms and symptoms possibly due to physical illness, analyses were also performed using a subscale constructed of seven items of the CES-D reflecting negative affect (bothered, blues, depressed, fearful, lonely, cried and sad) (Radloff & Teri 1986). The negative affect subscale ranged from 0 to 20 points with higher scores indicating greater severity.

For the present study, a sample with normal cognition was selected by excluding all subjects of the baseline sample with MMSE scores <26, resulting in a study sample of N=2,399 people.

6.2.3 Follow-up measurements

AMSTEL

At follow-up in 1994, all subjects who were available were interviewed again by trained lay people using the same interview procedure as in 1990/91. A subsample of subjects who were suspected of having developed dementia were invited for diagnostic evaluation. The screening procedure and diagnostic evaluation have been described elsewhere (Geerlings *et al*, 1999). In brief, all subjects with MMSE scores of 23 or less or with impairment in orientation in time, recent memory or learning were invited for diagnostic evaluation. During home visits, physicians specifically trained for this purpose administered the Cambridge examination for mental disorders in the elderly (including a structured psychiatric interview, the Cambridge Cognitive Examination, and a physical examination) (Roth *et al*, 1988). Clinical diagnoses of AD were made according to DSM-IV criteria (APA, 1994). Diagnoses were determined during weekly meetings with the senior neurologist (C.J.) and the neuropsychologist (M.I.G.).

LASA

At follow-up in 1995-1996, all respondents who were available were interviewed again during home visits using the same interview procedure as was used at baseline.

6.2.4 Statistical analyses

AMSTEL

Multiple logistic regression analyses were performed to assess the effect of depression on incident AD. Covariates used in the analyses were age, sex, level of education, memory complaints and psychiatric history. Level of education was expressed in full-time years of education needed to obtain the highest grade of education completed. In the analyses, it was used both as a continuous and as a dichotomous variable (dichotomized at the median of the study sample into £8 years versus >8 years of education; 8 years of education is comparable with two years of secondary education after having completed primary school). Memory complaints were assessed with the question: "Do you have complaints about your memory?" Answers were coded yes or no. Psychiatric history was assessed with the question: "Have you ever had emotional or nervous illness requiring treatment?". If answered positively, age of onset was assessed. Psychiatric history was categorized as no history or first onset at age 60 or above versus psychiatric history before age 60.

First, the analyses were performed with adjustments for the potential confounders. Second, since the strength of the association between depression and incident AD may be different for people with different demographic characteristics and for those with or without memory complaints or psychiatric history, we also tested possible interactions between depression and age, sex, education, memory complaints and psychiatric history, respectively.

LASA

Multiple logistic regression analyses were performed to assess the effect of depressive symptomatology on cognitive decline. Cognitive decline was defined as a drop of 3 or more points (>1 standard deviation) on the MMSE at follow-up. Depressive symptomatology was used in the analyses as a continuous variable (total CES-D score, and negative affect score), as a dichotomized variable (CES-D ≥16 versus <16), and as a categorical variable (the core depression item from the CES-D [during the past week I felt depressed] was used to examine the association between mild depressed mood (some of the time versus no) and incident cognitive decline and a severe depressed mood (often/always versus no) and incident cognitive decline, respectively. The same covariates as in the AMSTEL sample were used. However, in LASA data on psychiatric history were not collected and were therefore not used in the analyses of the LASA data. Interactions between the different depression definitions and the covariates were also tested. Finally, to correct for possible differences in baseline MMSE scores between the two education groups, we also performed the analyses with additional adjustments for baseline MMSE score (range 26-30).

6.3 Results

AMSTEL

Table 1 shows the baseline characteristics of the AMSTEL study sample (N=3,147), according to the presence or absence of depression.

Table 1. Baseline characteristics of the AMSTEL study sample (N=3,147), according to the presence or absence of depression

	Depression (N=329)	No depression (N=2,818)	
Mean age (SD)	73.6 (5.7)	73.7 (5.7)	p=0.82[1]
Sex			
Male	62 (18.8%)	1156 (41.0%)	
Female	267 (81.2%)	1662 (59.0%)	p=0.000[2]
Mean yrs of education (SD)	8.0 (2.3)	8.5 (2.6)	p=0.000[3]
Memory complaints			
No	263 (80.2%)	2563 (91.0%)	
Yes	65 (19.8%)	253 (9.0%)	p=0.000[2]
Psychiatric history			
No / late onset	261 (79.6%)	2527 (89.8%)	
Early onset	67 (20.4%)	286 (10.2%)	p=0.000[2]

Note: the numbers do not always add up to 3,147 persons because of missing values on some variables.
[1] t-test; [2] Chi-square test; [3] Mann-Whitney U test.

The follow-up duration was 3.2 years, on average. Figure 1 shows the number of people who were available for follow-up and who were lost to follow-up. At follow-up, 53 people received a diagnosis AD.

Figure 1: Sample discription AMSTEL

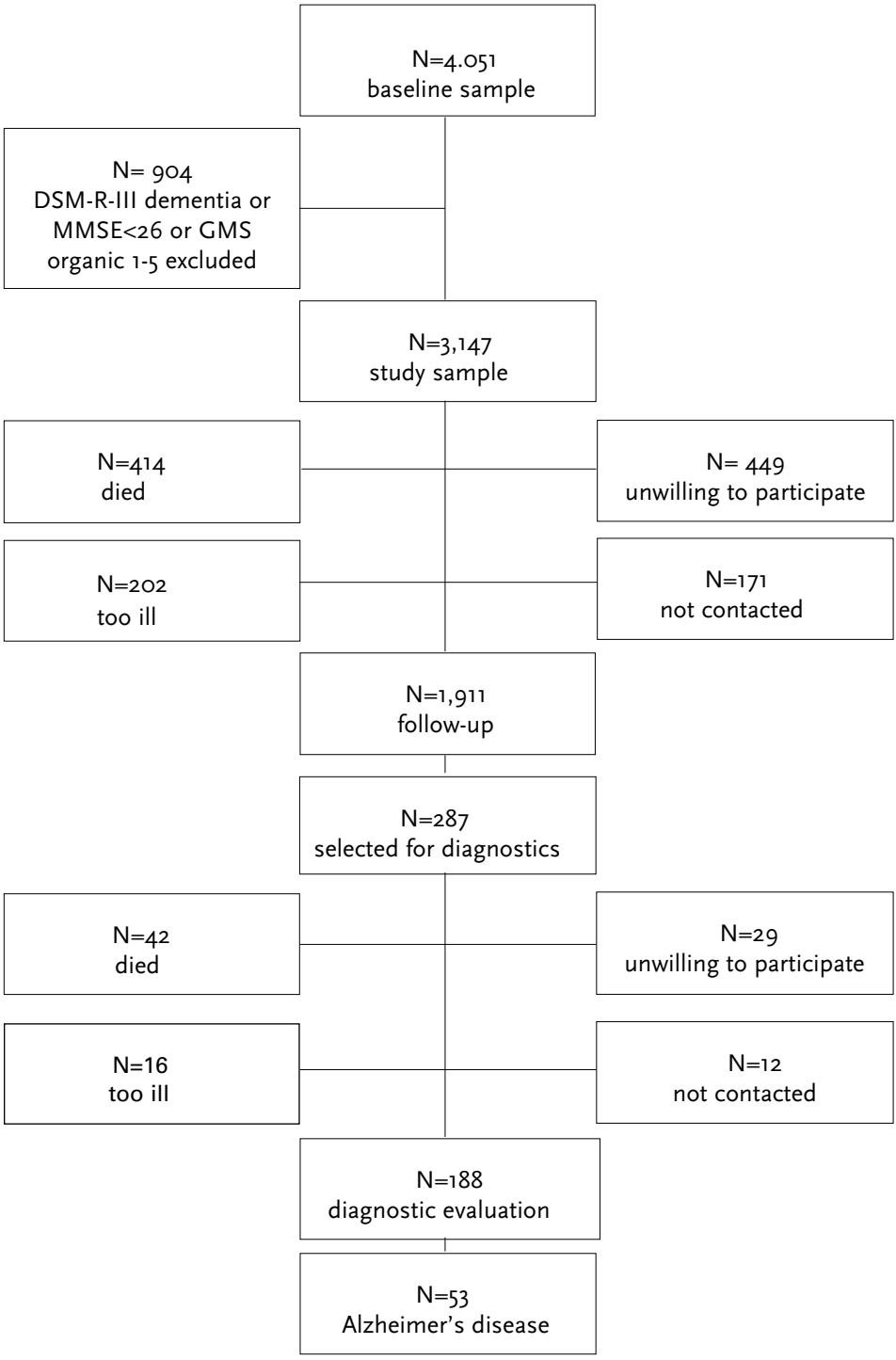

Table 2 shows the baseline characteristics for those who were and were not available for follow-up.

Table 2. Baseline characteristics of the AMSTEL study sample (N=3,147)for subjects who were and were not avaible for follow-up in 1994

	Interview (N=1,911)	Lost to follow-up (N=1,236)	
Mean age (SD)	73.1 (5.5)	74.6 (5.7)	p=0.000[1]
Sex			
Male	721 (37.7%)	497 (40.2%)	
Female	1190 (62.3%)	739 (59.8%)	p=0.16[2]
Mean yrs of education (SD)	8.6 (2.6)	8.2 (2.4)	p=0.000[3]
Memory complaints			
No	1699 (89.0%)	1127 (91.3%)	
Yes	210 (11.0%)	108 (8.7%)	p=0.04[2]
Psychiatric history			
No/Late onset	1692 (88.7%)	1069 (88.9%)	
Early onset	216 (11.3%)	137 (11.1%)	p=0.86[2]
Depression			
Absent	1725 (90.3%)	1093 (88.4%)	
Present	186 (9.7%)	143 (11.6%)	p=0.10[2]

Note: the numbers do not always add up to 3,147 persons because of missing values on some variables. [1] t-test; [2] Chi-square test; [3] Mann-Whitney U test

Table 3 shows the crude and adjusted odds ratios of incident AD associated with depression, age, sex, education, memory complaints and psychiatric history. Depression moderately increased the risk of AD. In the multivariate model, with adjustments for all other variables, the odds ratio of AD associated with depression decreased towards a statistically nonsignificant level.[Table 3]

Table 3. Crude and adjusted odds ratios with corresponding 95% confidence inter vals for the association between depression, age, sex, education, memory complaints, psychiatric history and incident Alzheimer disease (AMSTEL)

	Crude OR (95% CI)	Adjusted[1] OR (95% CI)
Depression (yes vs no)	2.21 (1.09-4.48)	1.67 (0.76-3.63)
Age (per year increase)	1.19 (1.12-1.26)	1.18 (1.11-1.25)
Sex (women vs men)	2.10 (1.10-4.03)	1.44 (0.73-2.84)
Education (per year increase)	0.81 (0.71-0.93)	0.86 (0.75-0.99)
Memory complaints (yes vs no)	2.79 (1.47-5.30)	2.79 (1.39-5.59)
Psychiatric history (no/late onset vs early onset)	0.31 (0.08-1.29)	0.30 (0.07-1.26)

[1] Adjusted for all other variables mentioned in the Table.

Interaction terms added to the model containing all covariates showed that the association between depression and AD was modified by education (centered variable) (likelihood ratio test, p=0.023). The interaction term was also statistically significant when education was used as a dichotomous variable (p=0.004). There were no statistically significant interactions between depression and memory complaints or between depression and psychiatric history, nor were there between depression and age or gender.

To interpret the modifying effect of education on the association between depression and incident AD, we performed logistic regression analyses within two education groups (dichotomized at the median value of the study sample). Depression highly increased the risk of AD among subjects with >8 years of education, but not among subjects with ≤8 years of education [Table 4].

Table 4. Odds ratios (95% confidence interval) adjusted for all other variables of the association between depression, age, sex, memory complaints and psychiatric history and incident Alzheimer's disease, for subjects ≤8 years of education and >8 years of education, respectively (AMSTEL)

	≤8 years of education N=871 OR (95% CI)[1]	>8 years of education N=1,036 OR (95% CI)[1]
Depression (yes vs no)	0.63 (0.18-2.19)	5.31 (1.88-15.00)
Age (per year increase)	1.17 (1.08-1.27)	1.19 (1.09-1.29)
Sex (women vs men)	2.52 (0.86-7.38)	0.96 (0.38-2.46)
Memory complaints (yes vs no)	2.15 (0.77-5.97)	3.27 (1.26-8.49)
Psychiatric history (no/late onset vs early onset)	(-) [2]	0.72 (0.15-3.46)

[1] Adjusted for all other variables mentioned in the Table.

[2] Not enough observations

LASA

Table 5 shows the baseline characteristics of the LASA study sample (N=2,399) according to the presence or absence of depression.
The duration of follow-up averaged 3.1 years. Figure 2 shows the number of people who were available for follow-up and who were lost to follow-up.

Table 5. Baseline characteristics of the LASA study sample (N=2,399), according to the presence or absence of depressive symptomatology

	CES-D 16+ (N=296)	CES-D <16 (N=2,092)	
Mean age (SD)	70.7 (8.7)	69.2 (8.5)	p=0.004[1]
Sex			
• Male	104 (35.1%)	1060 (50.7%)	
• Female	192 (64.9%)	1032 (49.3%)	p=0.000[2]
Education			
• ≤8 years	186 (63.1%)	1194 (57.3%)	
• >8 years	109 (36.9%)	891 (42.7%)	p=0.054[2]
Memory complaints			
• No	187 (63.2%)	1657 (79.2%)	
• Yes	109 (36.8%)	434 (20.8%)	p=0.000[2]

Note: the numbers do not always add up to 2,399 persons because of missing values on some variables

Figure 2: Sample description LASA

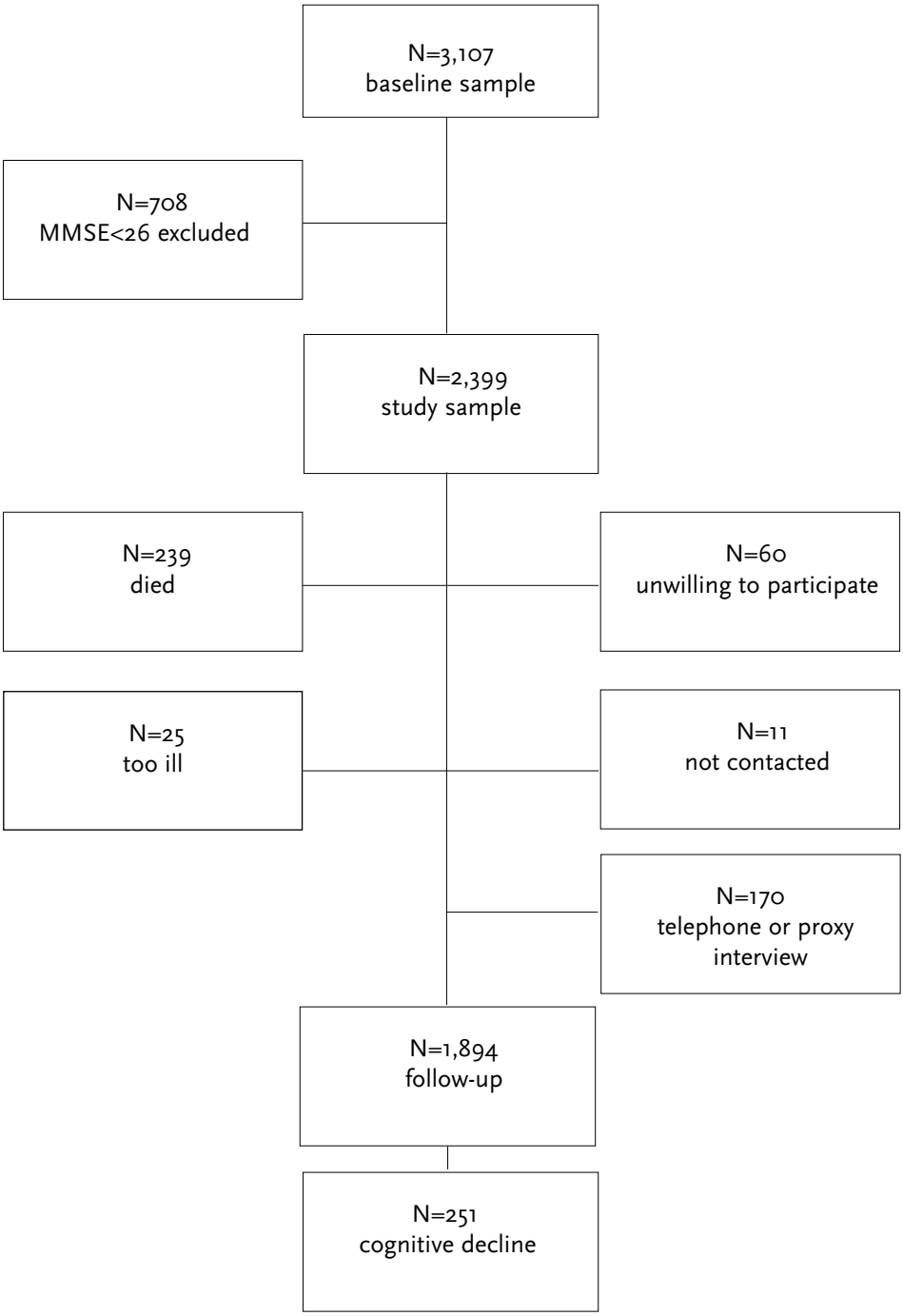

Table 6 shows the baseline characteristics for subjects who were and were not available for follow-up.
At follow-up, 251 people showed a drop of 3 or more points on the MMSE.

Table 6. Baseline characteristics of the LASA study sample (N=2,399) for subjects who were and were not available for follow-up

	Interview (N=1,894)	Lost to follow-up (N=505)	p-value
Mean CES-D score (SD)	7.1 (7.1)	8.2 (7.7)	p=0.0051
CES-D score			
< 16	1669 (88.4%)	423 (84.4%)	
16 and higher	218 (11.6%)	78 (15.6%)	p=0.015[2]
Mean negative affect (SD)	1.8 (2.7)	2.2 (3.1)	p=0.059[1]
Felt depressed			
Rarely or never	1571 (83.0%)	401 (79.9%)	
Some of the time	253 (13.4%)	65 (12.9%)	
Often/always	68 (3.6%)	36 (7.2%)	p=0.002[2]
Mean age (SD)	68.5 (8.3)	72.8 (8.4)	p=0.000[3]
Sex			
Male	892 (47.1%)	278 (55.0%)	
Female	1002 (52.9%)	227 (45.0%)	p=0.001[2]
Mean baseline MMSE (SD)	28.2 (1.3)	27.8 (1.3)	p=0.000[1]
Memory complaints			
No	1463 (77.3%)	387 (76.6%)	
Yes	430 (22.7%)	118 (23.4%)	p=0.757[2]
Education			
≤ 8 years	1054 (55.7%)	334 (66.3%)	
> 8 years	838 (44.3%)	170 (33.7%)	p=0.000[2]

Note: Not all numbers add up to 2,339 persons because of missing values on some variables.

[1] Mann-Whitney U test

[2] Chi-square test

[3] t-test

Multiple regression analyses adjusting for age, sex, education and memory complaints showed that neither higher scores on the continuous CES-D nor CES-D scores of 16+ were associated with subsequent cognitive decline (adjusted OR=1.01; 95% CI=0.99-1.03 and OR=1.07; 95% CI=0.70-1.62, respectively). However, negative affect increased the risk of cognitive decline (adjusted OR per point increase=1.05; 95% CI=1.00-1.09). A severe depressed mood was also associated with subsequent cognitive decline (adjusted OR=1.97; 95% CI=1.09-3.56), but a mild depressed mood was not (OR=1.05; 95% CI=0.71-1.57).

When the interaction between CES-D (centered variable) and education (dichotomous variable) was entered into the model containing CES-D (as a continuous variable), age, sex, education and memory complaints, the association between depressive symptoms and cognitive decline was modified by education (p=0.012). A similar result was found when the dichotomized variable was used in the interaction term (p=0.047) and when negative affect was used in the interaction term (p=0.017). Finally, the interaction between a severe depressed mood and education was borderline significant (p=0.076), but the interaction between mild depressed mood and education was not (p=0.74). No significant interactions between depressive symptomatology and one of the other covariates were found.

Logistic regression analyses stratified by level of education showed that depressive symptoms were associated with cognitive decline among subjects with more than 8 years of education, but not among those with ≤8 years of education (Table 7). Although the association between CES-D scores of 16+ and cognitive decline was attenuated after adjusting for the possible confounders, higher scores on the continuous CES-D, higher negative affect scores and a severe depressed mood remained predictive of subsequent cognitive decline (Table 7). Among less educated subjects, no association between depressive symptomatology and cognitive decline was found, regardless of the definition of depressive symptomatology. When the multivariate analyses were performed with additional adjustments for baseline MMSE score, the results were highly similar [Table 7].

Table 7. Associations (odds ratios with 95% confidence intervals) between four definitions of depressive symptomatology and subsequent cognitive decline, according to level of education (LASA)

	Education*	
	> 8 years (N=838)	≤ 8 years (N=1,054)
	OR (95% CI)	OR (95% CI)
CES-D score (per point increase)	1.05 (1.02-1.08)†	1.00 (0.98-1.02)†
	1.04 (1.01-1.08)‡	1.00 (0.98-1.02)‡
	1.05 (1.01-1.08)§	1.00 (0.98-1.02)§
CES-D score (16+ vs <16)	2.00 (1.05-3.81)†	0.83 (0.50-1.40)†
	1.79 (0.91-3.51)‡	0.83 (0.49-1.41)‡
	1.83 (0.93-3.60)§	0.84 (0.49-1.43)§
Negative affect score (per point increase)	1.14 (1.06-1.24)†	1.02 (0.96-1.07)†
	1.13 (1.04-1.22)‡	1.01 (0.96-1.07)‡
	1.13 (1.04-1.23)§	1.02 (0.96-1.08)§
Felt depressed (reference: rarely or never)		
Some of the time	1.15 (0.57-2.31)†	1.06 (0.67-1.69)†
	1.11 (0.54-2.29)‡	1.04 (0.65-1.68)‡
	1.15 (0.56-2.38)§	1.03 (0.64-1.67)§
Often/always	4.39 (1.75-10.99)†	1.55 (0.75-3.21)†
	3.92 (1.47-10.41)‡	1.44 (0.68-3.05)‡
	4.10 (1.54-10.90)§	1.49 (0.70-3.16)§

The numbers do not add up to 1,894 persons because of some missing values on the variable education.
† Crude associations
‡ adjusted for age, sex and memory complaints
§ adjusted for age, sex, memory complaints and baseline MMSE score.

6.4 Discussion

We investigated whether depression in older people with normal cognition was associated with subsequent cognitive decline and incident AD. Both the findings in AMSTEL and in LASA showed that depression increased the risk of AD and cognitive decline, respectively, but only among people with higher levels of education.

Depression as a psychological reaction

Most commonly, two explanations have been suggested for the frequent occurrence of depression in AD patients. First, depression may be a psychological reaction to perceived cognitive decline (Migliorelli et al, 1995) that may play a role particularly in mild stages of AD when patients may still be aware of their failing cognitive capacities (Ott et al, 1992). Although this explanation implies that depression is a consequence of the dementia process, depressive symptoms may become apparent before the diagnosis of AD is made. The development of AD is a gradual process that may start long before the diagnostic criteria are met. Patients may notice these changes in cognition at an early stage of the disease, and develop depressive symptoms as a reaction. However, although the prevalence of depression has been found to be inversely related to the severity of dementia (Fischer et al, 1990), others found no association between depression and insight into cognitive deficits (Verhey et al, 1993; Cummings et al, 1995), suggesting that the association is not purely a psychological one. Moreover, if a psychological explanation were true, the association between depression and incident AD would be modified by memory complaints, since these may reflect realistic self-observation of cognitive decline (Geerlings et al, 1999). Although memory complaints were more prevalent among depressed subjects than among nondepressed subjects, we did not find that the association between depression and incident AD was stronger among those with memory complaints. Finally, a psychological mechanism does not explain the observed interaction between depression and education.

Depression as an early symptom of AD

Our data may be more in concordance with the second explanation that hypothesizes that depression is an early symptom of the neuropathological process of AD. Studies on neurochemical and neuropathological changes in the brain of AD patients suggest that they may have lower thresholds for depressive disorders, or that the dementia process contributes to the development of depression (Zubenko & Moossy, 1988; Zweig et al, 1988; Förstl et al, 1992). It could be hypothesized that depression as an early symptom or a subclinical expression of AD may have become more overt in more highly educated subjects. More highly educated people may have greater 'reserve capacity'. This may be a 'brain reserve', reflected in a greater number of large neurons, greater brain weight or increased neocortical synaptic density (Katzman 1993), or a 'cognitive reserve', reflected in greater intellectual capacity or more adequate coping skills to deal with the dementia process (Stern et al, 1994). Several studies suggest the neuropathologic process of AD may be more advanced in elderly people with higher educational and occupational attainment (EOA) com-

pared with those with lower EOA (Stern et al, 1995a; 1995b) despite similar clinical severity. Thus, it is possible that in people with greater (cognitive) reserve the cognitive symptoms of AD may be delayed but not the depressive symptoms of the disease.

In the LASA sample, the association between depressive symptoms and cognitive decline became stronger when the analyses were restricted to affective symptoms and to a more severe form of these symptoms. The observation that a severe depressed mood was strongly associated with subsequent cognitive decline may also be supportive of the hypothesis that depression may be an early manifestation of a dementia process. A severe depressed mood is a more specific indicator of major depression (Meyers & Bruce, 1998) and this could be suggestive of some biological relationship rather than a purely psychological one (Migliorelli et al, 1995).

Psychiatric history

In the AMSTEL sample, no modifying effect of psychiatric history on the association between depression and AD was observed as might have been expected if late onset depression were associated with organic illness (Alexopoulos et al, 1988). However, there may not have been enough observations in the subgroups to find the interaction term to be statistically significant, since the majority (80%) of depressed people at baseline reported no psychiatric history or a late onset history. This finding in itself suggests that the depression that we observed in our study sample is indicative of a dementia process.

LASA and AMSTEL

The most notable strength of this study was that we were able to analyze data from two independent samples. Both the AMSTEL and the LASA study are prospective community-based studies in the Netherlands; both cohorts contain elderly people who were interviewed at home, and the follow-up interval between the first and the second assessment of both studies was highly similar. An important difference is that the samples were drawn independently of one another and for different purposes. Moreover, depression and cognitive decline or dementia were assessed using different instruments. In the AMSTEL study depression was assessed with the GMSS, which is an instrument based on the British tradition, while the CES-D, used in the LASA study, is more widely used in the United States. Furthermore, although both instruments measure a broad spectrum of depressive symptoms, the CES-D contains fewer items than the GMSS and does not rely on clinical judgement of the interviewer. With respect to the outcome variable, the differences between a clinical diagnosis of AD and cognitive decline based on a subtraction score on the MMSE may be even greater. In view of these differences in both determinant and outcome, it is striking that the results of both the LASA and the AMSTEL study demonstrated that depression increased the risk of cognitive decline and AD, only among subjects with higher levels of education.

Loss to follow-up

We have to consider that our findings may be biased due to differential loss to follow-up. Particularly in the AMSTEL sample, the proportion of subjects lost to follow-up was considerable. Although depressed people were not more likely to be lost to follow-up in this sample, in the LASA sample depressed subjects did become lost more often. However, we consider it unlikely that in the LASA sample the great difference in odds ratios between the two education groups for those with a severe depressed mood is explained by differential loss to follow-up alone.

Summary

We observed in two independent community-based samples that depressed elderly people with normal cognition and higher levels of education were at increased risk of incident cognitive decline and AD. The data do not support the hypothesis that depression is primarily a psychological reaction to deteriorating cognitive capacities. Instead, they are supportive of the hypothesis that depression is a subclinical expression or an early symptom of an underlying dementia process, which may become apparent in a subgroup of more highly educated older people in whom commonly used mental status tests do not yet detect a decline from a previous level of cognitive functioning. The data do not provide proof of possible pathogenetic mechanisms, however, and it remains to be determined whether treatment of depression would result in a delay of the clinical expression of cognitive decline and dementia.

6.5.1 Clinical implications

1 Depression, and in particular a severe depressed mood, may be an early or suclinical manifestation of cognitive decline and AD in elderly people with higher levels of education.
2 In these people, commonly used mental status tests, such as the MMSE, are inadequate to detect subtle cognitive decline.
3 The subclinical expression of cognitive decline or dementia may be different for different subgroups of elderly people, according to their educational level.

6.5.2 Limitations

1 Although our data confirm the clinical impression that late-onset depression is associated with organic illness, it is uncertain whether the question about psychiatric history in the AMSTEL study indeed assessed a history of *depression*.
2 The nature of this study does not allow any inferences on possible pathogenetic mechanisms that may underlie the observed association between depression and incident AD.
3 Based on the findings of this study no suggestions can be made as to whether treatment of depression would result in a delay of the clinical expression of cognitive decline and dementia.

6.6 Acknowledgements

The Amsterdam Study of the Elderly (AMSTEL) was supported by grants of The Netherlands Health Research Promotion Programme (SGO) and the Netherlands Foundation of Mental Health (NFGV). The AGECAT computer program was installed with the kind cooperation and final authorization of Michael E. Dewey, Department of Psychiatry, University of Liverpool.
The Longitudinal Aging Study Amsterdam is financed primarily by the Ministry of Welfare, Health and Sports of the Netherlands.

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7

The association of depression and gender with mortality in old age

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British Journal of Psychiatry (2000) 177: 336-342

Abstract

Background

The association between depression and increased mortality risk in older persons may depend on severity of depressive disorder and gender.
Aims:
To investigate the association between major and 'mild' depressive syndromes and excess mortality in community-living elderly men and women.

Method

Depression (GMS-AGECAT) was assessed in 4051 older persons, with a six-year follow-up of community death registers. The mortality risk of neurotic and psychotic depression was calculated after adjustment for demographic variables, physical illness, cognitive decline and functional disabilities.

Results

75% of men and 41% of women with psychotic depression had died at follow-up. Psychotic depression was associated with significant excess mortality in both sexes. Neurotic depression was associated with a 1.67-fold higher mortality risk in men only.

Conclusions

In the elderly, major depressive syndromes increase the risk of death in both sexes, mild depression only in men.

Declaration of interest

Grants detailed in Acknowledgements. No conflict of interest.

7.1 Introduction

The association between depression and an increased risk of death has been established for major depressive disorder (Tsuang & Woolson, 1977), but remains inconclusive for more prevalent minor, or 'mild' depressive syndromes. Earlier studies in the elderly differed in their assessment of depression, in controlling for physical health, functional impairments and organic disorder, and in follow-up time (Davidson et al, 1988, Fredman et al, 1989, Thomas et al, 1992, Sharma et al, 1998, Pulska et al, 1998). Although the association between depression and mortality may be gender-related (Zheng et al, 1997), this possible effect modifier has rarely been examined. In order to establish the relationship between depression and mortality in the elderly, studies are needed that include a range of potential risk factors, with a sufficient sample size and follow-up time, and specific attention to gender differences and to different depression severity levels. The current study has these characteristics.

7.2 Methods

7.2.1 Sample

The study is part of the Amsterdam Study of the Elderly (AMSTEL), a longitudinal study designed to screen a large and representative sample of non-institutionalised community living older persons on mental health problems, medical diagnoses and demographic characteristics. The sampling and data collection procedures and non-response have been described in depth elsewhere (Launer et al, 1993, 1994). In short, a random sample was drawn from the registers of 30 general practices in the city Amsterdam. These registers include almost all of the non-institutionalised population, who have to consult their general practitioner to gain access to the health care system. The mean proportion of elderly individuals (15%), and the profile of the over-65 general practice-population in terms of age and gender, corresponded to the non-institutionalised Amsterdam population. An age-stratified sample was drawn in the 65 to 84 age bracket, and all those who responded and gave their informed consent were interviewed (71.5%). In total, 4051 subjects were enrolled for the baseline interviews, which were conducted between May 1990 and November 1991.

7.2.2 Baseline measures

A one-hour interview was developed to gather information on psychiatric symptoms, demographic and medical status, previous history and family history. The interview consisted of the Dutch translation of the Mini-Mental State Examination (Folstein et al, 1975), all Geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland et al, 1986), the Activities of Daily Living (ADL) scale (Katz et al, 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton and Brody, 1969), and the CAMDEX-interview (Roth et al, 1986). The inter-

view was administered during home visits by lay interviewers who were specially trained using video sessions and were regularly supervised.

Depression and dementia. Diagnoses of dementia and depression were made according to the GMS-AGECAT system (Copeland et al, 1986, 1988). The Dutch language version has proven reliability for epidemiological work in replication studies (Hooijer et al, 1991). Depression caseness was defined as a GMS-AGECAT level 3 or higher. A distinction is made between neurotic and psychotic depression, indicating increasing severity levels of depression.

Sociodemographic factors. Potentially confounding covariates were age, sex and level of education. Educational status was dichotomised into lower (primary school or less) and higher (more than primary school) education.

Environmental vulnerability factors. Marital status was assessed based on the questions in GMS-AGECAT.

Physical health. The presence of chronic diseases was assessed with the pertinent Camdex questions on cardiovascular diseases, cancer, lung disease, diabetes, Parkinson's disease, arthritis and epilepsy. Cognitive status was assessed by MMSE-score. Subjects were considered to have functional disability if their ADL or IADL scores were two or more points below the maximum score on the respective scales.

7.2.3 Mortality

The follow-up for recording deaths extended from the date of the clinical examination until the first of July 1996. The dates of death were ascertained through the registers of the municipality of Amsterdam, or the municipalities where subjects had moved to during the study period. The follow-up period was 6 years, with an average of 55.5 months (sd 16.7) ranging from 1 to 73 months. Data were missing on 6 subjects (0.1%).

7.2.4 Data analysis

Baseline sample characteristics were compared between men and women, using chi-square statistics. Mortality rates per 1000 person-years were calculated according to depressed mood status. Bivariate associations of mortality at follow-up (deceased or alive on 01-07-1996) with independent variables at baseline were assessed by calculating relative risks. When the 95% confidence interval of the latter did not include one, the association was regarded to be statistically significant.
Kaplan-Meyer curves and Cox proportional hazard regression models were used to further examine the association between depression and time to mortality in men and women separately. The mortality risk was expressed as the mortality rate ratio (R.R.). In multivariate analysis, the effect of depression on mortality was studied for the two levels of depression (neurotic/psychotic), with successive adjustment for potential confounding factors: sociodemographic factors, environmental factors, cardiovascular and other chronic diseases, cognitive decline and functional disability. As disability may be a consequence of depression (Penninx et al, 1998) and therefore may cause overcorrection for the effect of depression on mortality, this variable was entered as a last, separate step. The difference between two mortality rate ratios was

considered to be statistically significant if the confidence intervals of either variable did not overlap with the value of the opposing variable.

7.3 Results

7.3.1 Sample characteristics

Depression prevalence at baseline was 12.9% overall (neurotic 10.9 %, psychotic 2.0 %), with 6.9 % depression in men and 16.5 % in women. The demographic and functional profiles of the study sample are presented in [Table 1]. In bivariate analysis men and women differed on most disease variables: men had more myocardial infarction and lung disease, women had more arthritis and diabetes. Functional disabilities were more common in women. The majority of men (72.6 %) were married, whereas women were more often not or no longer married (65.8 %).

TABLE 1: BASELINE SAMPLE CHARACTERISTICS FOR MEN AND WOMEN
(*= p<0.05, **= p<0.01, ***= p<0.001, ns= not significant; p>0.05)

VARIABLES	MEN(%)	WOMEN(%)	STATISTICS Chisq/df/p
N	1523	2528	
Depression			82.1/1/***
None	1418 (93.1)	2110 (83.5)	
Neurotic	81 (5.3)	360 (14.2)	
Psychotic	24 (1.6)	58 (2.3)	
Age			23.3/3/***
65-69	350 (23.0)	486 (19.2)	
70-74	396 (26.0)	578 (22.9)	
75-79	389 (25.5)	661 (26.1)	
80-86	388 (25.5)	803 (31.8)	
Education			79.9/1/***
More than Primary School	1014 (66.6)	1321 (52.3)	
Primary School or less	509 (33.4)	1207 (47.7)	
Myocard.infarction:			
No/never	1298 (85.2)	2337 (92.4)	53.7/1/***
Yes	225 (14.8)	191 (7.6)	
Stroke:			
No/never	1428 (93.8)	2392 (94.7)	Ns
Yes	95 (6.2)	135 (5.3)	
Cancer:			
No/never	1369 (89.9)	2233 (89.9)	Ns
Yes	154 (10.1)	295 (11.7)	
Lung disease:			26.5/1/***
No/never	1215 (79.8)	2173 (86.0)	
Yes	308 (20.2)	355 (14.0)	

VARIABLES	MEN(%)	WOMEN(%)	STATISTICS Chisq/df/p
Arthritis: No	1378 (90.5)	1979 (78.3)	99.6/1/***
Yes	145 (9.5)	549 (21.7)	
Diabetes: No	1405 (92.3)	2286 (90.4)	3.9/1/*
Yes	118 (7.7)	242 (9.6)	
Epilepsy: No/never	1497 (98.3)	2484 (98.3)	Ns
Yes	26 (1.7)	44 (1.7)	
Parkinson's: No	1493 (98.0)	2499 (98.9)	4.5/1/*
Yes	30 (2.0)	29 (1.1)	
MMSE			12.06/2/**
26-30	1274 (83.7)	2007 (79.4)	
22-25	163 (10.7)	359 (14.2)	
0-21	86 (5.6)	162 (6.4)	
ADL disability			10.5/1/**
None	1425 (93.8)	2293 (90.9)	
Yes	95 (6.3)	230 (9.1)	
IADL disability			33.1/1/***
None	1205 (79.4)	1796 (71.2)	
Yes	313 (20.6)	726 (28.8)	
Marital status			560/1/***
Married	1105 (72.6)	865 (34.2)	
Unmarried	417 (27.4)	1661 (65.8)	
Social support			58.3/1/***
None	1302 (85.5)	1907 (75.4)	
Yes	221 (14.5)	621 (24.6)	

7.3.2 Associations of risk factors with mortality

The total follow-up time of the sample was 18726 person years. 1035 (25.6 %) subjects had died during the study period. The crude mortality rate was 55.3 deaths per 1000 person-years. Bivariate analysis of baseline characteristics with mortality showed that all risk factors, except arthritis, were associated with mortality in both men and women [Table 2]. 75% of men with psychotic depression had died at follow-up, whereas in women this was 'only' 41.4%. The presence of neurotic depression doubled the mortality in men, from 30.3% (without depression) to 59.3%. In women the presence of neurotic depression only slightly raised the mortality from 20.5% to 23.1% (mortality risk not statistically significant).
In Kaplan-Meyer analysis, depression was found to have a significant negative effect on survival. This effect was more pronounced in men than in women. In men, both neurotic and psychotic depression were associated with higher mortality, in women this was only the case for psychotic depression [Figures 1 and 2].
Stepwise hierarchical regression using the Cox proportional hazards model, with successive adjustment for potential confounding and explanatory variables, also showed different results for men and women [Table 3]. In women, the mortality risk for 'all depression' was significantly lower than in men, and was reduced to a statistically non-significant level when adjusting for other variables. The unadjusted mortality risk for neurotic depression was not statistically significant in women (R.R. 1.14, 95% C.I. 0.90-1.45), and less than half of the associated mortality risk in men (R.R. 2.67, 95% C.I. 1.98-3.60), yielding a statistically significant difference between the sexes. In men, the higher initial mortality risks for both all depression and for neurotic depression still showed a statistically significant impact of depression after adjustment for all other possible explanatory factors.
Although the initial mortality rate ratio for psychotic depression was considerably higher in men (R.R. 3.77 vs. 2.43 in women), the difference was not statistically significant. Successive adjustment for other variables then reduced the mortality rate ratio for psychotic depression in both men and women to a statistically non-significant level. However, if the last step, adjustment for functional disabilities, was not taken into account, the mortality rate ratio for psychotic depression in women remained statistically significant (R.R. 1.66, C.I. 1.08-2.55), whereas in men it only just failed to reach statistic significance (R.R. 1.64, C.I. 0.96-2.78). It should be noted that, especially in men, the numbers of psychotically depressed patients were rather small to perform statistical testing with a relatively large number of control variables (24 psychotically depressed men, 58 psychotically depressed women). Finally, there were no substantial interactions between depression (all, neurotic, psychotic) and somatic or organic disorders in both men and women.

TABLE 2: BIVARIATE ASSOCIATIONS OF RISK FACTORS WITH MORTALITY IN MEN AND WOMEN (Deceased or alive on 01-07-1996, % deceased of baseline category, mortality rate ratio with 95% confidence interval, * reference category)

MORTALITY	MEN% (n)	Mortality risk (95% c.i.)	WOMEN) % (n	Mortality risk (95% c.i.)
TOTAL	**32.6 (496)**		**21.4 (539)**	
Depression:				
None *	30.3		20.5	
Neurotic	59.3	1.95 (1.60-2.38)	23.1	1.13 (0.92-1.39)
Psychotic	75.0	2.47 (1.94-3.15)	41.4	2.02 (1.47-2.77)
Age:				
65-69 *	15.4		8.7	
70-74	21.2	1.37 (1.01-1.88)	14.6	1.68 (1.19-2.39)
75-79	37.8	2.45 (1.86-3.23)	22.0	2.54 (1.84-3.50)
80-86	54.5	3.53 (2.72-4.59)	33.4	3.86 (2.84-5.24)
Education:				
More than P.S.	29.3		18.6	
Primary School or less	39.1	1.33 (1.15-1.54)	24.4	1.31 (1.13-1.53)
Myocard.inf.:				
No/never	31.0		20.2	
Yes	41.8	1.35 (1.13-1.61)	35.6	1.76 (1.43-2.17)
Stroke: No/never	31.7		20.7	
Yes	45.3	1.42 (1.13-1.80)	33.3	1.61 (1.25-2.07)
Cancer: No/never	31.1		20.6	
Yes	46.1	1.48 (1.23-1.79)	27.2	1.32 (1.07-1.62)
Lung disease: No	28.9		20.5	
Yes	47.2	1.63 (1.41-1.89)	26.8	1.31 (1.08-1.59)

TABLE 2: BIVARIATE ASSOCIATIONS OF RISK FACTORS WITH MORTALITY IN MEN AND WOMEN (Deceased or alive on 01-07-1996, % deceased of baseline category, mortality rate ratio with 95% confidence interval, * reference category)

MORTALITY	MEN% (n)	Mortality risk (95% c.i.)	WOMEN % (n)	Mortality risk (95% c.i.)
TOTAL	**32.6 (496)**		**21.4 (539)**	
Arthritis: No	32.2		21.3	
Yes	36.1	1.12 (0.89-1.41)	21.6	1.01 (0.85-1.21)
Diabetes: No	31.3		20.0	
Yes	47.5	1.51 (1.23-1.86)	34.3	1.72 (1.41-2.08)
Epilepsy: No/never	32.2		21.1	
yes	53.8	1.67 (1.16-2.40)	38.6	1.83 (1.25-2.68)
Parkinson's: No	32.1		21.2	
Yes	58.6	1.83 (1.33-2.50)	37.9	1.79 (1.12-2.87)
MMSE:				
26-30 *	27.3		17.5	
22-25	56.8	2.08 (1.77-2.44)	28.5	1.63 (1.34-1.97)
0-21	65.1	2.38 (1.99-2.85)	53.1	3.03 (2.55-3.60)
ADL disability				
None	29.5		19.3	
Yes	78.9	2.68 (2.35-3.05)	40.9	2.12 (1.77-2.52)
IADL disability				
None	25.7		14.3	
Yes	58.5	2.27 (1.99-2.60)	38.3	2.67 (2.31-3.09)
Marital status				
Married	30.6		17.4	
Unmarried	37.7	1.23 (1.06-1.44)	23.5	1.35 (1.14-1.60)
Social support				
None	29.6		18.4	
Yes	50.5	1.71 (1.46-1.99)	30.4	1.65 (1.42-1.93)

Figure 1: Kaplan-Meyer survival curve for women

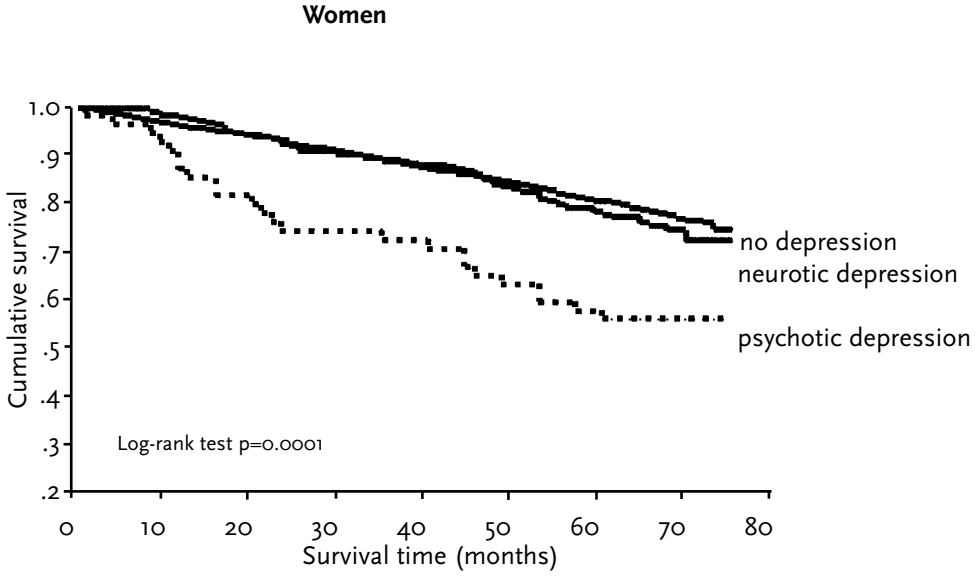

Figure 2: Kaplan-Meyer survival curve for men

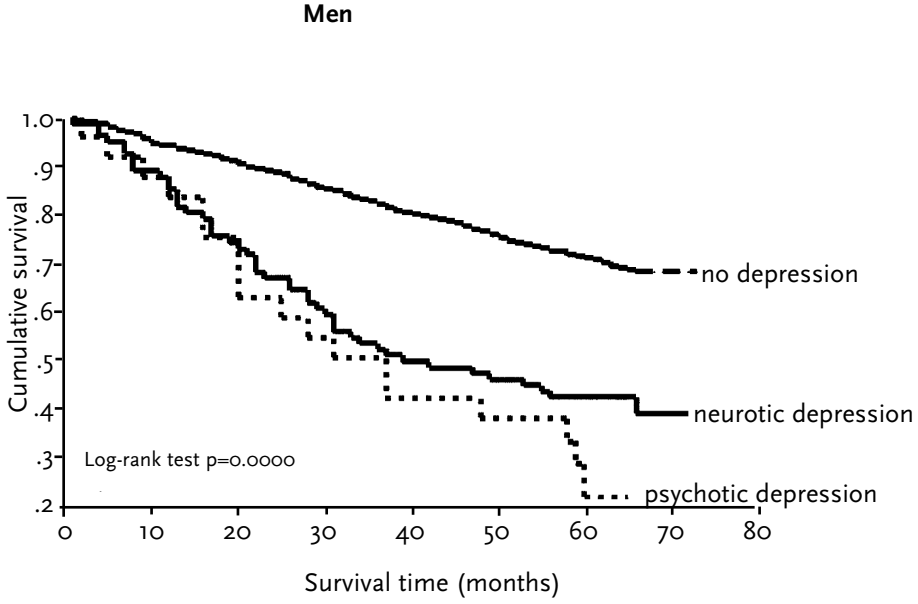

TABLE 3: MORTALITY RATE RATIOS FOR DEPRESSION IN MEN AND WOMEN WITH SUCCESSIVE ADJUSTMENT FOR POTENTIAL CONFOUNDERS AND EXPLANATORY VARIABLES (Cox proportional hazards model, 95% C.I.)

	WOMEN		
MORTALITY RATE RATIO FOR DEPRESSION	**All depression (418) Vs none N=2528**	**Neurotic (360) Vs none N=2470**	**Psychotic (58) Vs none N=2168**
UNADJUSTED RATIO	1.30 (1.05-1.60)	1.14 (0.90-1.45)	2.43 (1.61-3.67)
ADJUSTMENT FOR*:			
+ age, education	1.28 (1.04-1.59)	1.13 (0.90-1.43)	2.43 (1.61-3.67)
+ marital status	1.28 (1.04-1.59)	1.13 (0.89-1.43)	2.43 (1.61-3.67)
+ myocard. infarction, stroke	1.26 (1.02-1.56)	1.13 (0.89-1.43)	2.26 (1.49-3.43)
+ other diseases	1.18 (0.95-1.47)	1.05 (0.83-1.34)	2.05 (1.35-3.14)
+ MMSE	1.11 (0.89-1.38)	1.02 (0.80-1.30)	1.66 (1.08-2.55)
+ ADL, IADL disability	0.99 (0.79-1.23)	0.93 (0.73-1.18)	1.37 (0.88-2.10)

(* stepwise analysis, subsequently adding independent variables to the model)

MEN

All depression (105) Vs none N=1523	Neurotic (81) Vs none N=1499	Psychotic (24) Vs none N=1442
2.90 (2.23-3.76)	2.67 (1.98-3.60)	3.77 (2.35-6.05)
2.65 (2.04-3.44)	2.47 (1.83-3.34)	3.25 (2.02-5.22)
2.68 (2.06-3.49)	2.49 (1.85-3.37)	3.27 (2.02-5.30)
2.49 (1.90-3.25)	2.35 (1.74-3.19)	2.78 (1.70-4.54)
2.05 (1.54-2.71)	1.90 (1.39-2.60)	2.26 (1.34-3.82)
1.88 (1.42-2.49)	1.90 (1.39-2.59)	1.64 (0.96-2.78)
1.60 (1.20-2.15)	1.67 (1.22-2.30)	1.26 (0.73-2.18)

7.4 Discussion

This study sought to identify if depression may influence survival in community-living elderly. Due to the large sample size, the relatively long follow-up time and the incorporation of a wide range of other risk factors of mortality, the design of the study was suitable to perform this task. Specific attention was paid to gender differences, and to differences in depression severity level, based on the hypothesis that these two aspects may be important in understanding some of the contradictory findings of earlier studies.

Main findings

The overall prevalence of depression (12.9%) was well within the range of what has been found in other studies of depression in community-living elderly (Beekman et al, 1999). The unadjusted mortality risks showed depression to be associated with mortality, with a considerably stronger impact on survival of the more severe, psychotic depression. This trend is consistent with earlier findings (Penninx et al, 1999), and confirms that the more severe the depression is, the higher the associated mortality.

These effects, however, were modified by gender. Although, consistent with the literature (Wolk & Weisman 1995), the total prevalence of depression was found to be 2.4 times higher in women than in men, its negative effect on survival in women was less pronounced. A very large proportion of psychotically depressed men (75%) had died after a follow-up of six years, whereas in women this was clearly lower, although still considerable (41.4%). Likewise, neurotic depression in men showed a much higher mortality risk than in women.

After controlling for other explanatory variables, this overall impression did not change. The mortality risk of psychotic depression remained statistically significant in women, and very nearly significant in men, when the last step in subsequent adjustment was not taken into account. As functional disability has been found to be a consequence of depression, and the numbers of psychotically depressed men were rather small, it appears to be a reasonable conclusion that psychotic depression is associated with a higher mortality risk in both men and women. The gender differences were however most striking when investigating the more prevalent neurotic depression. Even unadjusted, neurotic depression in women was not found to be significantly associated with mortality. The mortality risk in men however remained statistically significant after controlling for all competing factors that may have affected survival.

Methodological considerations

A first methodological explanation for the gender differences observed may be that there has been report bias, differentially affecting prevalence rates of depression in men and women. One possible explanation is that women are culturally more prone to report depressive complaints, and therefore have higher depression scores. A de-facto broader definition of depression in women would thus conceal the real effect

that more severe, clinically relevant levels of depression may have on mortality. There are some data that support this proposition (Angst et al, 1984), but most studies failed to confirm it (Wolk & Weissman 1995). Symptom-patterns in men and women are very much alike and studies in different adult age groups consistently show a female preponderance in depression (Sonnenberg et al, 2000). If the current study would only take into account psychotic depression, the gender distribution of this condition would be found to be less skewed (women have 1.4 times more psychotic depression than men, instead of 2.7 times that of men in neurotic depression). Still, the mortality rate ratio for psychotic depression was almost two times higher in men, demonstrating a robust difference between the effects of depression in men and women.

A second methodological explanation for the observed gender difference may be that depressed subjects are more inclined to report negatively about their own health (Raphael & Cloitre, 1994). In studies such as ours, in which every effort was made to control for confounding, report bias may lead to overcorrection in multivariate analysis. Due to the higher prevalence of depression, this effect may be stronger in women. However, the unadjusted mortality rate ratios for depression are already much lower or statistically insignificant in women, suggesting that a possible control-bias does not account for the difference. Report bias thus appears to be an improbable explanation for the observed gender-differences.

A third source of bias may be selective non-response. A previous study in this sample by Launer et al (1994) revealed that nonresponders to the baseline assessment more often reported a heart attack, stroke, and diabetes, and were more likely to be unmarried, to have a lower education, to do poorly on cognitive tests and to have a history of psychiatric illness. There were no differences in response rate between men and women (OR 1.0, C.I. 0,6-1,5). We therefore conclude that only the very ill and cognitively impaired may have been underrepresented in the current study. This appears similar to the nonresponse pattern found in other community studies. Risk factors for mortality were however well represented in men and women throughout the age strata of the study population. Due to the efficient functioning of Dutch community registers, measurement of the outcome variable of this study was 99.9% complete. Thus, the results do not appear to be fundamentally affected by this nonresponse pattern.

The conclusion is therefore justified that depression is associated with a higher mortality in older men than in older women. This is especially true for depression syndromes generally considered 'milder', which do not meet criteria for major depressive disorder. Our findings offer an explanation for some of the contradictory findings of earlier studies on pervasive or minor depression and mortality, most of which did not specifically address gender as an effect modifier.

Implications

Both the theoretical and clinical implications of this finding are considerable. Earlier research has shown that depressive symptoms are of major importance to physical, social and role functioning (Beekman et al, 1997). Our data show that depression also exerts an influence on mortality in men, after controlling for the effects of a variety of serious somatic conditions. Even though there is growing consensus on the

fact that mild or 'subthreshold' depressive syndromes (not meeting full diagnostic criteria for DSM-IV or ICD-10) identified by screening methods such as GMS-AGE-CAT deserve clinical attention (Pincus et al, 1999), recognition is poor (German et al, 1987). The majority of depressed patients living in the community do not receive any specific treatment for their depressive complaints. Treatment studies however confirm the gender-specific pattern, and suggest that the potential effect of depression on mortality can be affected by treatment. Avery and Winokur (1976) showed that treatment of clinically admitted patients with major depression significantly reduced the number of deaths through myocardial infarctions. They found the impact of adequate treatment of depression to be especially influential on the survival of older men. A study by Craig et al (1981), comparing pre-drug era and post-drug era patient samples, revealed that the decline in mortality associated with the introduction of psychiatric drug treatment was also especially marked in elderly men.

Possible explanations for the observed gender-differences

Although it has since long been pointed out that untreated depressed subjects tend to be in worse health due to continuous agitation, malnourishment, intercurrent infections and cardiovascular problems (Malzberg, 1937), and are also more likely to die from accidents or suicide (Tsuang et al, 1978), a clear explanation for the sex specific pattern has not been provided.

A first explanation may be that men have more cardiovascular pathology, the course of which is affected more strongly by comorbid depression. A number of studies have shown depression to be related to a less favourable course of cardiovascular disease (Avery and Winokur 1976, Frasure-Smith 1995). These studies however investigated the impact of major depression, and not of less severe depressive syndromes.

A tentative psychological explanation for the excess mortality in men, may be that men are less equipped to deal with feelings of hopelessness and depression than women. Women are more inclined to discuss such feelings with others (Briscoe et al, 1982), are more open to accept support from others when experiencing them (Longino and Lipman, 1981), and therefore are more able to sustain and overcome feelings of depression (Grootheest et al, 1999). The male coping style is more externalising, and feelings of depression will only be experienced by men when other, more typical forms of coping have not been successful. A depressive syndrome in men thus signifies a more invalidating and threatening condition than such a syndrome in women, which is reflected in the robust differences in mortality.
A third, possibly related mechanism explaining the gender differences we found, may be that depressed elderly men are more inclined to commit suicide than depressed women (Conwell et al, 1996).

As the current data do not include the causes of death, the question on the exact mechanism can not directly be addressed. The finding of a relation between 'milder' depression and mortality, especially in elderly men, is however robust in this study. If the clinician were to focus solely on patients with DSM IV major depressive disorder (A.P.A., 1994), a diagnostic convention imposed on a continuum of depressive symptoms of varying severity and duration, this appears once more to be an under-

estimation of the actual level of morbidity. Although the majority of the community-dwelling elderly with depressive syndromes that were investigated in this study had not been treated for depression, earlier data suggest that they might have derived important benefits from it. With an average total prevalence of 13.5% (Beekman et al, 1999), late-life depressive syndromes are likely to be found in all medical settings, and may affect the course of a variety of conditions. This study lends a strong basis to the notion that, together with patients suffering from more severe levels of depression, especially elderly men with neurotic or 'minor' depression deserve to be recognised and treated more vigorously than is currently practised.

7.5.1 Clinical implications

1 Late-life depression is associated with excess mortality, with a higher impact of more severe levels of depression.
2 Major depressive syndromes are associated with excess mortality in both sexes. Mild or minor depressive syndromes are related to a higher mortality risk in older men, but not in older women.
3 Late-life depression often remains unrecognised and untreated by the health services. Research however suggests that, together with other vital aspects of life, survival may be positively affected by adequate treatment of depression.

7.5.2 Limitations

1 The current data do not include the causes of death, the question on the exact mechanism linking depression and mortality can therefore not be directly addressed.
2 Selective attrition to the baseline assessment of the study has probably occurred among the very frail.
3 The study is a naturalistic follow-up in the community, not controlling for (low levels of) ongoing treatment.

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8

Depression and excess mortality; a bio-psycho-social relationship?

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Nederlands Tijdschrift voor Geneeskunde (2004) 148 : 1133-1137

Abstract

Depression is a highly prevalent disorder at all levels of health care delivery. Depression is associated with an untoward course of medical illnesses, and with excess mortality. Several mechanisms may contribute to these associations. First of all, depression affects behaviour. Depressed patients have more unhealthy living habits, are less compliant with medical treatment, and show a higher number of accidents and suicides. Secondly, biological aspects of depression are important in the context of an association with excess mortality. Dysregulation of the neuro-immune system, hyperactivity of the HPA-axis, and autonomic dysregulation may all have a negative effect on both the prognosis of somatic illnesses and longevity. A third aspect of interest is depression treatment. Although the beneficial effects of pharmacotherapy for depression are uncontested, this also has side effects. It remains unclear whether treatment may affect survival. Further research is needed to disentangle the mutual influences of depression and somatic illnesses, to search for possible pathogenetic mechanisms that may underlie both depression and medical disorders, and to assess the effects of depression treatment on biological dysregulations and survival.

8.1 Introduction

Depression is a highly prevalent psychiatric disorder in adult populations (Kessler et al. 1994). The negative influence of depression on physical and social functioning, subjective health, pain and the use of health care facilities is comparable with, or even greater than that of chronic physical illnesses (Hays et al. 1995;Ormel et al. 1998;Wells et al. 1989).

Depression also affects longevity. In large community studies among both younger adults (Zheng et al. 1997) and older persons (Penninx et al. 1999), an association has been found between depression and excess mortality(Schoevers et al. 2000). The same association was found in medical patients.

Excess mortality associated with depression has been described in patients with myocardial infarction(Frasure-Smith, Lesperance, & Talajic 1995), diabetes (Black & Markides 1999;Honig 2000), kidney disease (Peterson et al. 1991), cancer (Pirl & Roth 1999;Spiegel & Giese-Davis 2003), and numerous other illnesses (Herrmann-Lingen, Klemme, & Meyer 2001;Katon 2003). In these studies, depression was associated with an excess mortality risk of 1,5 to 5 times that of patients without comorbid depression (Cole & Bellavance 1997;Wulsin, Vaillant, & Wells 1999). The association of depression with excess mortality appears to be independent of the mortality risk that can be attributed to physical illnesses (Cuijpers & Smit 2002;Katon 2003;Penninx et al. 2001).

Findings such as the above have been described not only for major depression, the most severe form of depression (American Psychiatric Association, American Psychiatric Association, & Task Force on DSM-IV 1994), but also for less severe or minor depression (Enzell 1984;Ganguli, Dodge, & Mulsant 2002;Penninx, Geerlings, Deeg, van Eijk, Van Tilburg, & Beekman 1999). Minor or 'subthreshold' depression is a term to define clinically relevant forms of depression associated with significant social and functional impairment, although they remain below the diagnostic threshold for major depression (Pincus, Davis, & McQueen 1999). In this paper, 'depression' includes also minor or subthreshold depression. In community studies, the prevalence ranges from 9 to 20% (Beekman, Copeland, & Prince 1999). In medical patients the prevalence of depression is around 25%, and even higher in patients with more severe medical conditions (Katon & Sullivan 1990;Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen, & Kendler 1994). Inversely, depressed patients also have higher levels of physical illnesses (Wells et al. 1991), including a higher incidence of cardiovascular pathology and myocardial infarctions (Ford et al. 1998;Wulsin & Singal 2003).

These data underline the importance of depression for both the prognosis of the individual patient in primary and secondary care, and for public health. Still, there is limited consensus on the mechanisms that may explain the association between depression and excess mortality. The current paper presents a brief overview of the mechanisms that have been put forward in the literature (Medline search with title words: 'depression and mortality', from 1977-2002). Explanations for the depression-mortality association can be divided into two domains. The first domain concerns the behaviour of depressed patients and the implications this may have for

onset and course of medical illnesses. The second domain is that of the biological, possibly pathogenic, mechanisms that may be associated with depression, physical illnesses and different forms of treatment.

8.2 Depression and illness behaviour

Depression is associated with unhealthy nutritional habits and life styles (Krauchi, Reich, & Wirz-Justice 1997;Wallin & Rissanen 1994), a decrease in physical activities (Stephens 1988), smoking and excessive alcohol use (Aneshensel & Huba 1983;van Gool et al. 2003). Through these mechanisms, depression most probably affects both physical health (Wells, Golding, & Burnam 1988), and mortality risk (Katon 2003).

In medical patients, treatment adherence is negatively affected by comorbid depression (Blumenthal et al. 1982;Carney et al. 1995a;Cooper-Patrick et al. 1999;Ziegelstein et al. 2000). A recent meta-analysis covering the last 30 years, clearly showed that the presence of depression triples the chance of non-compliance with medical treatment in a large number of somatic illnesses (DiMatteo, Lepper, & Croghan 2000). A separate meta-analysis on non-compliance in diabetes patients demonstrated a significant association between hyperglycaemia and comorbid depression, in both early and late onset diabetes patients (Lustman et al. 2000). Also by affecting treatment adherence, depression may be associated with an untoward prognosis of medical illnesses.

Another form of behaviour associated with depression is suicidality. Studies on the prognosis of patients with psychiatric disorders consequently show higher mortality levels through suicide. Still, other forms of unnatural causes of death, such as accidents, are also found in excess in depressed patients (Black, Warrack, & Winokur 1985), especially when patients also have somatic illnesses (Brodaty et al. 1997;Hoyer, Mortensen, & Olesen 2000;Tsuang & Woolson 1978). Although it may not be easy to determine whether death has occurred through suicide or parasuicidal behaviour, especially in the presence of comorbid physical illnesses requiring medical treatment, it has become clear that not all of the excess mortality associated with depression can be attributed to suicide (Lindesay 1989;Maris 2002;Murphy et al. 1988;Murphy et al. 1987;Penninx, Beekman, Honig, Deeg, Schoevers, van Eijk, & Van Tilburg 2001).

8.3 Depression and biological dysregulation

Research in depressed patients has demonstrated dysregulations of a number of neuro-endocrinal circuits. Examples of this are hyperactivity of the HPA (Hypothalamic-Pituitary-Adrenocortical) axis, activation of the autonomic nervous system, and activation of pro-inflammatory cytokines. Such dysregulations frequently occur in combination, and may constitute a possible pathogenic basis for the association between depression and the occurrence or untoward cause of physical illnesses.

8.3.1 Pathogenic mechanisms

The association of depression with hyperactivity of the HPA-axis has often been replicated, and is usually demonstrated by either the dexametason suppression test or the dexametason-CRH (Corticotrofine Releasing Hormone) test. These tests show abnormal values in 25 to 80% of depressed patients (Holsboer 2000;Pariante 2003;Raison & Miller 2003). An excess production of CRH in the hypothalamus leads to higher release of adrenocorticotrophic hormone (ACTH) in the pituitary gland, resulting in hypercortisolemia and hypertrofia of the adrenal cortex (Musselman & Nemeroff 1996). Dysregulation of the HPA axis may be due to a disturbed negative feedback of the glucocorticoid receptors in the hippocampus and the paraventricular nucleus of the hypothalamus (Holsboer 2000). Through a similar mechanism, chronic stress may also cause depression. Hypercortisolemia not only causes depressive symptoms, but also has physical consequences such as insulin resistance and accumulation of visceral fat (Bjorntorp & Rosmond 1999). The combination of 'upper-body obesity', glucose intolerance, hypertension and hypertriglyceridemia (the "deadly quartet") is associated with an elevated cardiovascular risk (Kaplan 1989). Through alterations in both behaviour (decreased physical activities) and neuroendocrine systems (hypercortisolemia) depression also leads to a decrease in bone density and a higher risk of fractures; women with a personal history of depression had lower bone density than matched controls, in combination with higher levels of urinary cortisol (Michelson et al. 1996).

Genetically determined disturbances in cerebral glucocorticoid receptor functioning appear to play an important role in the pathogenesis of affective disorders (Muller, Holsboer, & Keck 2002). Hyperactivity of the HPA axis is found significantly more often in first grade family members of patients with affective disorder (Krieg et al. 2001). It is therefore not unlikely that genetic disturbances in the functioning of the HPA-axis are associated with a higher prevalence of both depression and somatic illnesses.

A second important pathophysiological mechanism is the association between depression and neuro-immune dysregulation. Depression is associated with higher levels of pro-inflammatory cytokines, such as interleukine-1 en interleukine-6 (Maes et al. 1995;Penninx et al. 2003). An acute phase response, with elevated levels of C-reactive protein (CRP) and alpha-1 anti chymotrypsin (alpha-1-ACT), activation of interleukin-1 receptors in the paraventricular nuclei of the hypothalamus, and higher release of CRH leads to higher adrenocortical production of cortisol (Maes, Meltzer, Bosmans, Bergmans, Vandoolaeghe, Ranjan, & Desnyder 1995;Sapolsky et al. 1987). Excess concentrations of interleukin-6 and CRP are associated with a higher risk of myocardial infarction and stroke (Ridker et al. 1998;Ridker et al. 2000;Ridker, Glynn, & Hennekens 1998). In line with this, an infiltration of inflammatory cells is found in all stages of atherosclerotic plaque formation (Shah 2000). The neuro-immune dysregulation associated with depression may thus be related to both onset and untoward course of cardiovascular pathology (Musselman, Evans, & Nemeroff 1998). Still, it remains unclear whether depression precedes neuro-immune dysregulation or whether it is a consequence. The latter possibility is illustrated by the finding that low doses of endotoxines may cause symptoms of depression, anxiety and memory

complaints in healthy volunteers (Reichenberg et al. 2001).

Thirdly, depression is also associated with sympathoadrenergic dysregulation, with elevated levels of norepinephrine and its metabolites (Esler et al. 1982;Roy et al. 1988). Autonomic hyperactivity is associated with a decrease in heart rate variability, which in itself is a strong predictor of ventricular arrhythmias and acute heart failure (Carney et al. 1995b;Rechlin et al. 1994;Yeragani et al. 2002). The association between depression and decreased heart rate variability has however not been confirmed in all studies, and may be found in subgroups of depression only (Volkers et al. 2003). Autonomic dysregulation also leads to an up regulation of platelet serotonin receptors and an increased intracellular calcium mobilization, yielding stronger platelet activation and aggregation, and a higher risk of trombotic events (Musselman, Evans, & Nemeroff 1998;Schins et al. 2003). Thus, autonomic dysregulation may also play a role in the excess mortality associated with depression, although the scale of its contribution still has to be determined.

In conclusion, the above pathogenic mechanisms may be associated with both onset and course of depression and physical illnesses. Still, the temporal and causal associations between these disorders need further study.

In elderly persons, the association between depression and excess mortality may be based on different mechanisms than in younger adults. 'Vascular depression', a syndrome specific for later life, is characterised by psychomotor retardation, loss of interest, functional disabilities (IADL) and autonomic symptoms. This disorder is primarily determined by cerebral (fronto-striatal) white matter hyperintensities, probably as a result of (micro)vascular lesions that may be negatively associated with survival (Alexopoulos et al. 2002;Steffens et al. 2002).

8.3.2 Treatment

An entirely different explanation for the excess mortality associated with depression could be found in the toxic effects of antidepressant medication. Tricyclic antidepressants are considered less safe due to possible abnormalities of cardiac conduction, arrhythmias and postural hypotension, especially in people with medical illnesses and higher age (Glassman, Roose, & Bigger, Jr. 1993;Muskin & Glassman 1983;Roose & Dalack 1992;Warrington, Padgham, & Lader 1989). However, limitedly available evidence suggests that adequate biological treatment of depression, either by pharmacotherapy or Electro Convulsive Therapy (ECT) may positively affect the survival of depressed patients (Avery & Winokur 1976;Craig & Lin 1981;Muller-Oerlinghausen et al. 1992). It has been suggested that selective serotonin reuptake inhibitors (SSRI) may lead to a normalization of serotonin-mediated platelet activation in depressed patients (Musselman et al. 2000), and a protective effect against recurrence of myocardial infarction (Sauer, Berlin, & Kimmel 2001). An intriguing placebo-controlled randomised trial showed that treatment with antidepressants for 12 weeks during the first 6 months after stroke, significantly increased the 9-year survival of both depressed and non-depressed patients (Jorge et al. 2003).
These findings suggest that antidepressants may influence the above pathophysiological mechanisms. Currently, it is unclear whether this is a direct consequence of medication, or whether it can be attributed to the remission of depression. A meta-

analysis showed that psychosocial interventions also have a statistically significant positive influence on prognosis and survival in patients with coronary heart disease (Linden, Stossel, & Maurice 1996). Recently, two placebo-controlled studies investigated the influence of different treatment modalities for depression on the prognosis of patients after myocardial infarction. Six months of cognitive therapy, if necessary combined with an SSRI, did not reduce mortality or increase invent-free interval after 29 months follow-up (Berkman et al. 2003). In the second study, sertraline was shown to be a safe and effective treatment for recurrent depression in patients with recent MI or unstable angina, but it was not associated with a more beneficial course of cardiological parameters in comparison with placebo (Glassman et al. 2002;van den Brink et al. 2002). It is clear that more research is necessary to determine the associations between treatment of depression, the prognosis of comorbid medical illnesses and longevity.

8.4 Discussion

From this review of mechanisms that could explain the association between depression and excess mortality, it can be concluded that these are complex interactions in which depression and medical illnesses may have multiplicative negative effects on survival. Underlying pathogenetic mechanisms as well as psychological factors may be responsible for the impressive comorbidity of somatic illnesses and depression.

Suggestions for further research

The available literature on the association between depression and mortality is mainly composed of studies on associations between these phenomena that do not make causal inferences. Prospective studies with an extensive follow-up time, and the full spectrum of explicatory and potentially confounding variables are needed to address onset and reciprocal influences of depression and medical illnesses, and their association with survival. It is also of interest to determine whether the association between depression and mortality can be attributed to specific biological symptoms of depression, or to psychological phenomena such as depressive thoughts and suicidal ideation. Research on the genetics of depression, such as dysfunctions in the HPA-axis, may provide more clarity on possible underlying pathogenetic mechanisms. RCT's with sufficient follow-up time are needed to address the potential effects on survival of psychotherapeutic and pharmacological treatments of depression. Such studies may also lead to a better understanding of the pathofysiological mechanisms underlying the association between depression, somatic illnesses and excess mortality.

Clinical relevance

Depression is a serious psychiatric condition that causes substantial individual suffering. It is also associated with a higher incidence and an untoward course of a large number of medical conditions, with significantly higher levels of health care use (Katon et al. 2003). Although a direct effect of depression treatment on survival has not been demonstrated, it is clear that both psychosocial interventions (Linden, Stossel, & Maurice 1996) and pharmacotherapy (Gill & Hatcher 1999;Gill & Hatcher

2000) for depression are effective in medically ill patients. Still, the recognition of depression in both primary (German et al. 1987) and secondary care (Hansen et al. 2001) is far from adequate. Considering the above, the clinical implications of this cannot easily be underestimated.

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9

Do severity, length of exposure and symptom profile of depression predict 10-year mortality in community living elderly?

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Abstract

Context

Depression is associated with an increased mortality risk. It is not known to what extent depression characteristics such as severity, duration or specific symptoms contribute to the association with excess mortality.

Objectives

To investigate the association between severity, duration and symptom profiles of depression with mortality in community-living elderly.

Design

Ten-year prospective epidemiological study. Assessment of depression at baseline and at three-year follow-up (GMS-AGECAT). Cox proportional hazards analyses of depression according to severity and length of exposure, adjusted for demographic variables, physical illnesses, cognitive decline and functional disabilities. Associations between specific baseline symptoms and symptom profiles and 10-year mortality were studied in the full cohort, and in subjects with clinical depression

Setting and participants

Randomly selected cohort of 3746 non-demented older community-living persons in the city of Amsterdam.

Main outcome measures

Mortality at 10 years from baseline for the full cohort, and mortality 6 years from the follow-up assessments for non-demented subjects participating in both assessments (N=1989).

Results

Both moderate (MRR 1.29, 95% C.I. 1.03-1.61) and severe depression (MRR 1.34, 95% C.I. 1.07-1.68) predicted 10-year mortality after multivariate adjustment. Chronic depression was associated with a 41% higher mortality risk in 6-year follow-up compared to subjects without depression. Somatic depression items were predictive of excess mortality in the full cohort. In subjects with depression, only depressive thoughts, suicidal ideation and guilt, were specifically associated with excess mortality.

Conclusions

Severity, chronicity and specific symptom profiles of depression are associated with a higher mortality risk. This may have important implications for both preventive and treatment strategies of late-life depression.

Declaration of interest

Grants detailed in Acknowledgements. No conflict of interest.

9.1 Introduction

Unipolar major depression is expected to become the second leading cause of disability world-wide in 2020, with only ischemic heart disease causing higher disease burden and economic impact (Murray & Lopez 1997). Depression is also associated with excess mortality(Wulsin, Vaillant, & Wells 1999), both in the community (Cuijpers & Smit 2002), in medical patients (Katon 2003) and in studies that specifically focussed on the elderly(Ganguli, Dodge, & Mulsant 2002;Penninx et al. 1999).

Still, relatively little attention has been paid to discriminating subtypes of depression with a particularly disadvantageous prognosis. This may be of considerable interest for the clinician, as it may guide both preventive and treatment strategies. On a theoretical level, it may further our understanding of the processes underlying the association between depression and excess mortality.

The most obvious line of investigation would be to determine whether the association between depression and mortality depends on depression severity. Although the detrimental effects of depression with regard to physical health and various aspects of functioning are directly related to the number of depression symptoms (Hays et al. 1995;Ormel et al. 1998), few studies have made comparisons of mortality risk according to depression severity measures. Dichotomizing severity levels as major and minor depression (Penninx, Geerlings, Deeg, van Eijk, Van Tilburg, & Beekman 1999), or psychotic and neurotic depression (Schoevers et al. 2000) did not show a statistically significant association of severity with excess mortality after adjustment for other explanatory variables. Using more continuous measures of severity however yielded an association with mortality in two studies (Geerlings et al. 2002;Schulz et al. 2000).

The association of depression with mortality may also be affected by length of exposure to depression. In depressions with a longer duration, the negative effects of depression on both biological and psychosocial functioning have had more time to accumulate. Although this seems plausible, again very few studies have examined this parameter (Geerlings, Beekman, Deeg, Twisk, & Van Tilburg 2002).

A third approach disentangling the depression concept is to study specific symptoms of depression in relation to excess mortality. Data on specific symptoms of depression and mortality are scarce. Feelings of hopelessness and pessimism have been found to be predictive of eventual suicide (Beck et al. 1985) or death from violence or injury (Everson et al. 1996). Motivational depletion was important in explaining the depression-mortality effect in one large study of community living elderly (Schulz, Beach, Ives, Martire, Ariyo, & Kop 2000). A 'vital exhaustion syndrome' consisting of excessive fatigue, irritability and demoralization was associated with onset and untoward course of ischemic heart disease (Kop et al. 1994;Prescott et al. 2003). The 'vascular depression' concept has received considerable attention as a depression subtype specific for the elderly population, characterized by psychomotor retardation, reduced interest in activities, impaired instrumental activities of daily living and limited vegetative symptoms (Alexopoulos et al. 2002). The frontostriatal dysfunction in vascular depression is associated with cerebrovascular pathology that may also affect mortality. Very few symptoms of depression are pathognomonic, and

other conditions may also lead to such 'isolated symptoms'. Studies that are currently available have often examined isolated symptoms of depression regardless of the presence of a depression according to diagnostic criteria. It is therefore of considerable interest to examine whether associations of specific depression symptoms with mortality differ in subjects with and without a depression diagnosis.

In order to establish associations between specific depression characteristics and survival, prospective community based studies are needed that include a comprehensive set of confounders, large sample sizes and a relatively long follow-up time. The AMSTEL study is community based and started in 1990, with a follow-up three years later, and collection of mortality data until 10 years after baseline. The research questions for this study were first to describe the impact of depression on mortality according to depression severity and length of exposure to depression, and second to investigate whether specific depression symptoms or symptom profiles show stronger associations with excess mortality.

9.2 Methods

9.2.1 Sample

The Amsterdam Study of the Elderly (AMSTEL) is a longitudinal study in a large and representative sample of non-institutionalized community living older persons on mental health problems, medical diagnoses and demographic characteristics. Informed consent was asked and obtained from each participant before starting the study. The study was approved by the Medical Ethical Committee of the Vrije Universiteit Amsterdam.

Sampling, data collection procedures and response have been described in depth elsewhere (Launer et al. 1993;Launer, Wind, & Deeg 1994). In short, a random and representative sample was drawn from the non-institutionalized Amsterdam population over 65 to 84 years old. An age-stratified cohort of 4051 subjects was enrolled for the baseline interview, which was conducted between May 1990 and November 1991. GMS-AGECAT dementia was present in 261 subjects (6.4%).

The study sample for this study consisted of all 3746 subjects participating in the baseline assessment who did not have GMS-AGECAT dementia, of whom vital status could be ascertained. At three year follow-up (median 38 months), data were available in 2144 (57.2 %) subjects. At follow-up, 553 (14.8%) persons were deceased, 604 (16.1%) persons refused further participation, 254 (6.8%) were too ill or cognitively impaired to respond, and 191 (5.1%) were not available for interview due to other reasons. Of the responders, 155 subjects (7.2 %) had developed dementia between the two assessments. These subjects were excluded from the survival analyses after 1994. The study group for the assessment of the effect of length of exposure to depression thus consisted of 1989 subjects without GMS-AGECAT dementia.

9.2.2 Baseline measures

A one-hour interview was developed to gather information on psychiatric symptoms, demographic information and medical status. The interview consisted of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), all Geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland, Dewey, & Griffiths-Jones 1986), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969), and the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and regularly supervised. The same GMS-AGECAT package with an identical algorithm was used in the second wave of the study. When re-interviewing, raters were unaware of previous data and diagnoses.

Depression and dementia Depression and dementia were diagnosed using GMS-AGECAT (Copeland et al. 1988;Copeland, Dewey, & Griffiths-Jones 1986), an established and widely used instrument that diagnoses cases of late-life depression requiring clinical attention in the community (Copeland et al. 1992;Copeland, Dewey, & Griffith-Jones 1990) and in hospital patients (Ames & Tuckwell 1994). GMS-AGECAT has proven reliability for epidemiological work in replication studies (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988;Hooijer, Jonker, & Dewey 1991).

Depression severity In order to study the association of different severity levels of depression with mortality, a sum score was composed out of the total number of 31 items for depression in GMS-AGECAT (see Table 1 for items and item scores). According to the scores of subjects with depression at baseline, a severity variable was calculated that classified the lower tertile of the scale as 'mild depression' (2-12 points), the middle tertile as 'moderate depression' (13-19 points), and the upper tertile as 'severe depression' (20-48 points). In a second approach, a continuously scaled variable of the total depression item score (0-48) to was used to indicate severity.

Length of exposure Longitudinal patterns of the exposure to depression were assessed in the subjects that participated in both waves of the study (n=1989). To investigate whether a longer period of exposure to depression would show a higher mortality risk, two measurements of depression allowed four different categories. Subjects were classified as 'no depression', 'remitted depression' (depressed at baseline and no longer depressed at follow-up), 'incident depression' (newly depressed at follow-up) and 'chronic depression' (depressed at both assessments).

Symptom profiles In order to study the impact of specific symptom profiles on mortality, several approaches were used. First, the full range of geriatric depression symptoms identified in GMS-AGECAT were investigated. Second, the nine DSM-IV depression criteria were derived from these items and assessed separately. Depression items were also clustered into 4 symptom dimensions: affective symptoms, somatic symptoms, cognitive symptoms and depressive thoughts (see Table 1 for DSM symptoms and item clustering). For each symptom dimension a continuous variable was calculated by adding the sum of the constituent item scores. In

order to verify whether the symptom clusters that were constructed on theoretical grounds were also statistically related, a factor analysis was performed on the 31 baseline depression items. All associations with a component loading above 0.40 were considered when comparing this statistically driven model with the symptom clusters that were chosen on a priori notions. This procedure showed considerable agreement. The domains of depression chosen on a priori notions remained almost completely intact, although fewer items qualified to be included in each specific factor [Table 1] shows the results of factor analysis].

Covariates Potentially confounding covariates included age, sex and level of education. Educational status was assessed as the number of years of education (5-18 years). Marital status was assessed based on the questions in GMS-AGECAT. The presence of chronic diseases was assessed with the pertinent Camdex questions on cardiovascular diseases, cancer, lung disease, diabetes, Parkinson's disease and epilepsy. Cognitive status was assessed by MMSE-score. Subjects were considered to have functional disability if their ADL scores were two or more points below the maximum score on the scale. This indicates that subjects were 'in need of help' to perform at least two of the tasks mentioned, or were unable to perform at least one task.

TABLE 1: GMS DEPRESSION ITEMS AMSTEL STUDY WITH COMPILATION OF SYMPTOM CLUSTERS AND DSM SYMPTOMS

Item	Question	Answer
D1	Have you been sad / depressed recently?	Yes sometimes
		Often / severely
D2	How often have you cried last month?	Yes
		Often (severely) / almost every day or more
D3	Felt like crying but no tears came?	Yes
		Often (severely) / almost every day
D4	Do you worry, and if so,	
	do your worries trouble you?	Yes, unable to stop, keep crossing my mind
D5	Obs: appears sad / depressed	Definite, some of the time
		Definite (excessive) & most of the time
D6	Obs: eyes moist / tearful / crying	Definite, some of the time
		Definite (excessive) & most of the time
D7	How is your interest in things?	Less interest
D8	How is your appetite?	Diminished desire for food
		Strongly diminished desire for food
D9	Have you lost weight last 3 months?	Lost weight, amount unclear
		9 pounds or more
D10	Do you have trouble falling asleep?	Yes
D11	Do you wake up early?	Two hours earlier than usual, > 2 times a week
D12	Difficulty in relaxing?	Difficulty in relaxing
		Much difficulty in relaxing
D13	Obs: appears tense / worried	Definite, some of the time
		Definite (excessive) & most of the time
D14	Do you have the feeling that you started to	Subjective slowing
	think slower lately?	Severe subjective slowing
D15	Obs: slowness	Slow in movements
		Very slow in all movements
D16	Not enough energy (to do what you want)?	Loss of energy / fatigue
D17	Do you tend to feel guilty? Is that reasonable?	Excessive guilt, not in proportion to subject
D18	Can you concentrate (radio / TV)? Untill the end?	Difficulty concentrating
		Much difficulty concentrating
D19	Can you concentrate (reading)?	Difficulty concentrating
		Much difficulty concentrating
D20	Do you find it hard to make up mind / decisions?	Feels indecisive
		Feels very indecisive
D21	Obs: difficulty concentrating on interview?	Obvious difficulty concentrating on interview
		Cannot concentrate on interview
D22	Obs: indeciveness	Appears indecisive
D23	Have you felt life was not worth	Yes, sometimes
	living last 3 months?	Yes, clearly / severely
D24	Have you wished you were dead	
	(because life is a burden)?	Yes
D25	Have you thought of killing yourself / quitting?	Yes, felt suicidal
D26	Have you actually tried to kill yourself?	Has actually done or planned something
D27	What time of day do you feel worst?	In the mornings
D28	Loss of energy; worst at what time of the day?	Mornings
D29	Have you been irritated / easily annoyed lately?	Yes, a little
		Yes, very much
D30	How do you see / what expectations do you	Pessimism justified by circumstances
	have for your future?	Pessimistic/future looks bleak/unbearable /
		general feeling of hopelessness
D31	Do you get annoyed with yourself as well?	Yes, a little
		Yes, very much

Item	Item score	DSM IV Symptom	Symptom cluster	Factor Analysis
D1	1			
	2	I Depressed mood	Affective	1
D2	1			
	2	I	Affective	
D3	1		Affective	
	2			
D4	2		Thoughts	3
D5	1			
	2	I	Affective	1
D6	1			
	2	I	Affective	1
D7	2	II Anhedonia/Loss interest	Affective	
D8	1			
	2	III Anorexia	Somatic	
D9	1			
	2	III	Somatic	
D10	2	IV Sleep disturbance	Somatic	
D11	2	IV	Somatic	3
D12	1			
	2	V Psychomotor agit/retard	Affective	
D13	1			
	2	V	Affective	1
D14	1			
	2	V	Cognitive	4
D15	1			
	2	V	Somatic	
D16	2	VI loss of energy / fatigue	Somatic	3
D17	2	VII Guilt / worthlessness	Thoughts	
D18	1			
	2	VIII Concentrat / Indecis.	Cognitive	4
D19	1			
	2	VIII	Cognitive	4
D20	1			
	2	VIII	Cognitive	
D21	1			
	2	VIII	Cognitive	4
D22	2	VIII	Cognitive	
D23	1			
	2	IX Suicidal	Thoughts	2
D24	2	IX	Thoughts	2
D25	2	IX	Thoughts	2
D26	2	IX	Thoughts	2
D27	2		Somatic	3
D28	2		Somatic	3
D29	1			
	2		Affective	
D30	1		Thoughts	
	2			
D31	1			
	2		Affective	

9.2.3 Mortality

The follow-up for recording deaths extended from the date of the baseline examination until the 31st of December 2000. Dates of death were ascertained through the registers of the municipality of Amsterdam, or the municipalities where subjects had moved to during the study period. Data on vital status were missing in 47 subjects (98.8 % complete).

9.2.4 Data analysis

Baseline sample characteristics and participation in the follow-up study were analyzed using Chi^2 statistics. Cox proportional hazards regression models were used to examine the association between depression and time to deaths. The mortality risk was expressed as the mortality rate ratio (M.R.R.). When the 95% confidence interval of the latter did not include one, the association was regarded to be statistically significant.

In multivariate analysis, ten-year mortality from 1990 to 2000 according to depression severity (mild, moderate or severe depression, each compared with 'no depression', and a separate analysis using the continuous depression severity score) was studied in a kaplan-meyer curve and Cox proportional kazard regression model, with stepwise adjustment for potential confounding factors. In the first step, sociodemographic factors (age, gender, years of education, marital status) were entered. The second step adjusted for cardiovascular diseases, the third step for all other diseases and in the fourth step the MMSE score was entered. As functional limitations are strongly associated with depression (Penninx et al. 1998), and overcorrection for the effect of depression may result when entering this factor in a multivariate logistic regression model, this factor was adjusted for in the last step. Results are presented for each step in the multivariate model. Differences between strata were considered statistically significant when the confidence intervals mutually excluded the opposite MRR value.

Mortality according to length of exposure to depression (remitted depression, incident depression and chronic depression vs. no depression, and remitted depression vs. chronic depression) was studied in a similar Cox regression model, with survival time counted from date of 1994 interview until 2000.

To determine possible associations between specific depression symptoms and mortality, all of the 31 depression items were entered in a Cox regression model together with the other explanatory or confounding variables, including also ADL functional status and depression diagnosis. Backward stepwise analysis was used to reach the most parsimonious model predicting 10-year mortality. A similar approach was used for the nine DSM-IV symptoms, and subsequently for the four symptom clusters. In order to determine whether specific depression items would be predictive of excess mortality within the subsample with clinical depression, this procedure was repeated in the depressed subjects. As the association between specific depression items and mortality may be confounded by depression severity, these analyses were also performed controlling for severity. Risk ratios are also presented for the

other remaining predictors of mortality in the most parsimonuous models.

9.3 Results

9.3.1 Sample characteristics

Baseline characteristics are shown in [Table 2]. At baseline, depression was present in 455 subjects (12.1 %). 165 subjects had mild depression, 146 had depression of moderate severity, and 144 severe depression. The total follow-up time of the sample was 28156.5 person years. 1844 (49.2 %) subjects had died during the study period. The crude mortality rate was 65.5 deaths per 1000 person-years. The average follow-up period from the baseline assessment of subjects who were still alive at 1/1/2001 was 117.8 months, ranging from 109.2 to 127.2 months. The average follow-up period of subjects participating in the 1994 assessment who were still alive at 1/1/2001 79.6 months, ranging from 72.3 to 95.9 months.

Univariate comparison of baseline characteristics with mortality showed that all characteristics, except arthritis and epilepsy, were associated with 10-year mortality [Table 2].

TABLE 2: BASELINE SAMPLE AND 10 YEAR MORTALITY
(deceased at 01-01-2001, *= p<0.05, **= p<0.01, ***= p<0.001, ns= not significant with p>0.05)

VARIABLES	BASELINE	DECEASED(%)	STATISTICSChisq/df/p
N	3746	1844 (49.2)	
Age			
65-69	803	219 (27.3)	453.3/3/***
70-74	929	338 (36.4)	
75-79	974	533 (54.7)	
80-86	1040	754 (72.5)	
Gender			
Men	1425	831 (58.3)	76.0/1/***
Women	2321	1013 (43.6)	
Education			
More than			
Primary School	2231	1017 (45.6)	29.3/1/***
Primary School or less	1515	827 (54.6)	
Marital status			
Married	1853	859 (46.4)	12.0/1/**
Not / no longer			
married	1890	983 (52.0)	
Myocard.infarction:			
No/never	3346	1586 (47.1)	57.1/1/***
Yes	382	258 (67.5)	
Stroke: No/never	3545	1709(48.2)	27.3/1/***
Yes	201	135 (67.2)	
Cancer: No/never	3332	1609 (48.3)	10.6/1/**
Yes	414	235 (56.8)	
Lung disease: No	3136	1480 (47.2)	31.8/1/***
Yes	610	364 (59.7)	
Diabetes: No	3417	1624 (47.5)	44.9/1/***
Yes	329	220 (66.9)	
Epilepsy: No/never	3691	1810 (49.0)	3.5/1/ns
Yes	55	34 (61.8)	
Parkinson's: No	3692	1798 (48.7)	28.2/1/***
Yes	54	46 (85.2)	
Arthritis: No	3107	1517 (48.8)	0.28/1/n.s.
Yes	639	327 (51.2)	
MMSE			
26-30	3195	1476 (46.2)	89.9/2/***
22-25	465	297 (63.9)	
0-21	86	71 (82.6)	
ADL disability: No	3492	1656 (47.4)	70.0/1/***
Yes	254	188 (74.0)	
Depression			
No	3291	1586 (48.2)	11.6/1/**
Yes	455	258 (56.7)	
Depression severity score			
No depression	3291	1586 (48.2)	13.8/3/**
Mild (2-12)	165	86 (52.1)	
Moderate (13-19)	146	88 (60.3)	
Severe (20-48)	144	84 (58.3)	

9.3.2 Severity

Subjects with a depression of moderate or high severity showed an excess mortality risk of 46% and 35% respectively, when compared to subjects without depression. [figure 1] After multivariate adjustment, both moderate (MRR 1.29, 95% C.I. 1.03-1.61) and severe depression (MRR 1.34, 95% C.I. 1.07-1.68) still showed a statistically significant association with excess mortality. At the last step, entering functional impairment, these risk ratios just failed to reach statistical significance, most likely due to overcorrection of the effect of depression [Table 3]. The differences between each of the mild, moderate and severe strata were not statistically significant, as the 95% confidence intervals were not mutually exclusive. A severity effect was confirmed in a similar analysis with the continuously scaled total depression item score with an MRR of 1.02 (95% CI 1.01-1.02) per scalepoint increment after multivariate adjustment.

TABLE 3: DEPRESSION SEVERITY AND 10 YEAR MORTALITY
Deceased by 01-01-2001, Mortality Rate Ratio with 95% C.I. after correction for other explanatory variables, comparing 'mild' / 'moderate' / 'severe' depression with 'no depression', N=3746

MRR	Mild vs no depression	Moderate vs no depression	Severe vs no depression
Unadjusted ratio	1.13 (0.91-1.40)	1.46 (1.18-1.81)	1.35 (1.08-1.68)
Adjusted for:			
Demographics	1.24 (1.00-1.55)	1.52 (1.22-1.89)	1.65 (1.32-2.06)
Cardiovascular disease	1.23 (0.98-1.53)	1.48 (1.19-1.84)	1.60 (1.28-2.00)
Other diseases	1.15 (0.92-1.43)	1.36 (1.09-1.69)	1.41 (1.12-1.77)
MMSE	1.13 (0.90-1.40)	1.29 (1.03-1.61)	1.34 (1.07-1.68)
Functional (ADL) impairment	1.09 (0.88-1.37)	1.24 (0.99-1.55)	1.24 (0.98-1.56)

Figure 1 Survival and depression severity

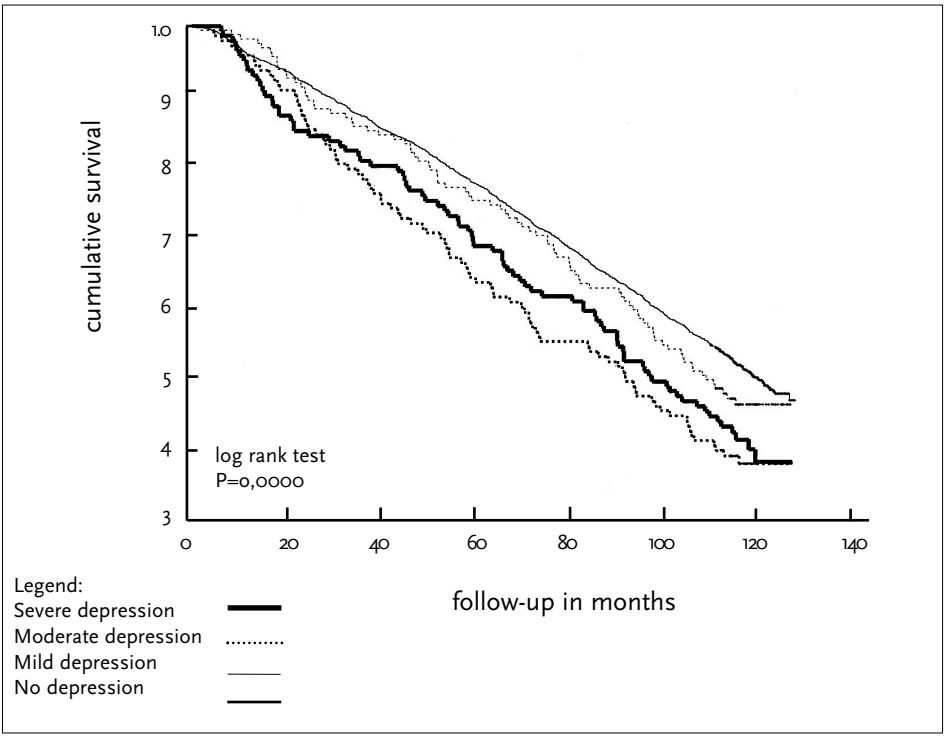
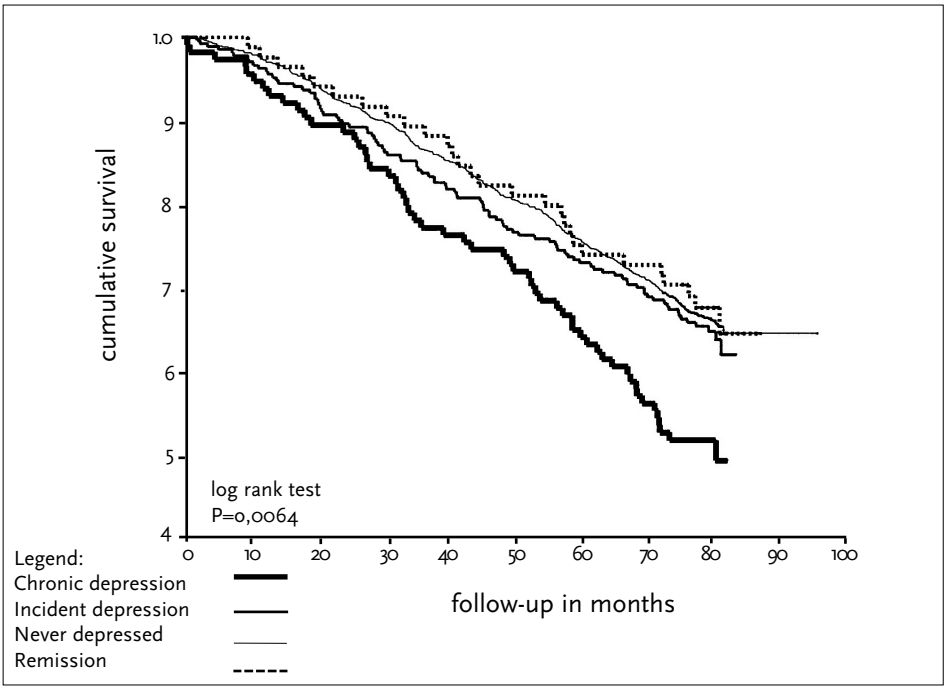


Figure 2 Survival and length of exposure



9.3.3 Length of exposure

Of the 229 subjects with baseline depression who participated at follow-up, 95 (41.5 %) had remitted, and 134 (58.5 %) were still depressed at follow-up. Incident depression was present in 302 subjects (14.4% of subjects that participated in both waves of the study).

Figure 2 shows the kaplan-meyer curve. The unadjusted mortality risks of remitted and incident depression were not statistically significant. Only chronic depression showed a significant association with excess mortality (MRR 1.65, 95% C.I. 1.25-2.17) (Table 4). This association remained statistically significant in stepwise multivariate analysis (MRR 1.41, 95% C.I. 1.05-1.89), also at the last step, entering functional limitations (MRR 1.38, 95% C.I. 1.03-1.85).

TABLE 4: LENGTH OF EXPOSURE FROM T0-T1 WITH MORTALITY 1994-2000
Deceased between follow-up 1994 and 01-01-2001, Mortality Rate Ratio with stepwise adjustment for other variables, organic cases at follow-up excluded, N=1989

MRR	Remitted vs no depression	Incident vs no depression	Chronic vs no depression
Unadjusted ratio	0.97 (0.66-1.42)	1.07(0.86-1.34)	1.65 (1.25-2.17)
Adjusted for:			
Demographics	1.14 (0.77-1.67)	1.11 (0.89-1.38)	1.81 (1.36-2.39)
Cardiovascular disease	1.12 (0.76-1.64)	1.06 (0.85-1.32)	1.76 (1.33-2.33)
Other diseases	1.06 (0.72-1.56)	1.05 (0.84-1.31)	1.54 (1.15-2.07)
MMSE	1.05 (0.71-1.54)	1.04 (0.83-1.30)	1.41 (1.05-1.89)
Functional (ADL) impairment	0.98 (0.66-1.45)	1.03 (0.83-1.28)	1.38 (1.03-1.85)

9.3.4 Specific symptoms and symptom profiles

GMS-AGECAT items: Controlling for all the other symptoms, predictors of excess mortality in the whole cohort were (in decreasing order of effect size) (Table 5); slowness (MRR 1.70, 95% C.I.1.30-2.20), loss of appetite (MRR 1.24, 95% C.I. 1.11-1.39) and loss of energy (MRR 1.15, 95% C.I. 1.09-1.21). Indecisiveness / loss of concentration showed a protective effect relative to the other items (MRR 0.87, 95% C.I. 0.77-0.98), and inappropriate feelings of guilt just failed to reach statistical significance in the same direction. Repeating these analyses within the depressed subjects yielded one new item, death wishes (MRR 1.14, 95% C.I. 1.00-1.29) (data not shown). Adding a continuous depression severity variable to the model did not change the results in either the full sample or the depressed sample, showing that the association with mortality of specific depression items is not confounded by depression severity (data not shown).

DSM-IV items: In the full cohort, loss of energy (MRR 1.35, 95% C.I. 1.22-1.50), psychomotor agitation / retardation (MRR 1.22, 95% C.I. 1.02-1.45), and suicidal ideation (MRR 1.21, 95% C.I. 1.04-1.40) were associated with excess mortality. Indecisiveness / loss of concentration showed a statistically significant association in the opposite direction (MRR 0.81, 95% C.I. 0.72-0.91) [Table 5]. In the subjects with depression, the association of suicidal ideation with excess mortality was even more pronounced than in the full sample (MRR, 1.35, 95% C.I. 1.05-1.73). Interestingly, inappropriate feelings of guilt again showed an association in the opposite direction (MRR 0.54, 95% C.I. 0.35-0.83). Controlling for depression severity did not significantly affect these results (data not shown).

Symptom clusters: In the full cohort, only somatic depression symptoms were associated with mortality (MRR 1.11, 95% C.I. 1.06-1.16) (Table 5). Repeating these analyses in subjects with depression showed that none of the four symptom clusters retained statistical significance with regard to excess mortality. Controlling for depression severity in the full sample, somatic symptoms were no longer associated with mortality.

TABLE 5: PARSIMONIOUS MODELS FOR 10 YEAR MORTALITY
Cox regression analyses, Backstep modelling with P in at 0.05 and P out at 0.05

FULL COHORT (N=3746)

GMS items	MRR	DSM items
D15 slowness obs.	1.70 (1.30-2.20)	VI loss of energy
D8 loss of appetite	1.24 (1.11-1.39)	V psychomotor agit/retard
D16 loss of energy	1.15 (1.09-1.21)	IX suicidal
D20 indecis /concentr	0.87 (0.77-0.98)	VIII indecisive / concentr
D17 guilt	0.88 (0.76-1.01)	
Age	1.10 (1.09-1.11)	Age
Gender	0.52 (0.48-0.58)	Gender
Myocardial infarction	1.47 (1.29-1.69)	Myocardial infarction
Stroke	1.30 (1.09-1.55)	Stroke
Cancer	1.34 (1.16-1.54)	Cancer
OPD	1.30 (1.16-1.46)	OPD
Diabetes	1.56 (1.35-1.80)	Diabetes
MMSE	0.94(0.92-0.96)	MMSE
ADL disablity	1.46 (1.24-1.71)	ADL disability

DEPRESSED SUBJECTS (N=455)

GMS items	MRR	DSM items
D15 slowness obs.	1.50 (1.02-2.19)	IX suicidal
D24 death wish	1.14 (1.00-1.29)	VIII guilt
D17 guilt	0.88 (0.76-1.01)	
Age	1.08 (1.05-1.10)	Age
Gender	0.33 (0.25-0.44)	Gender
Stroke	1.65 (1.08-2.51)	Stroke
Cancer	1.55 (1.12-2.14)	Cancer
OPD	1.43 (1.07-1.90)	OPD
MMSE	0.92(0.89-0.96)	MMSE

	Symptom clusters	
1.35 (1.22-1.50)	Somatic	1.11 (1.06-1.16)
1.22 (1.02-1.45)		
1.21 (1.04-1.40)		
0.81 (0.72-0.91)		
1.10 (1.09-1.11)	Age	1.10 (1.09-1.11)
0.52 (0.47-0.57)	Gender	0.51 (0.46-0.56)
1.45 (1.27-1.66)	Myocardial infarction	1.46 (1.27-1.66)
1.34 (1.12-1.60)	Stroke	1.35 (1.13-1.62)
1.32 (1.15-1.51)	Cancer	1.32 (1.15-1.51)
1.30 (1.15-1.46)	OPD	1.30 (1.17-1.47)
1.57 (1.36-1.81)	Diabetes	1.56 (1.35-1.80)
0.94 (0.92-0.95)	MMSE	0.94 (0.92-0.96)
1.51 (1.28-1.78)	ADL disability	1.48 (1.26-1.74)
	Parkinson's	1.36 (1.01-1.84)
	Epilepsy	1.41 (1.00-1.99)

	Symptom clusters	
1.35 (1.05-1.73)		
0.54 (0.35-0.83)		
1.08 (1.06-1.11)	Age	1.08 (1.06-1.11)
0.32 (0.24-0.42)	Gender	0.33 (0.25-0.44)
1.67 (1.10-2.53)	Stroke	1.74 (1.15-2.63)
1.49 (1.08-2.06)	Cancer	1.47 (1.07-2.03)
1.39 (1.05-1.84)	OPD	1.48 (1.12-1.96)
0.91 (0.88-0.95)	MMSE	0.91 (0.88-0.95)

9.4 Comment

This study systematically examined whether severity, duration of exposure and specific symptom profiles of depression are associated with a higher mortality risk. The findings may have important implications for both prevention and intervention in late life depression, and provide cues for further research on the mechanisms linking depression and excess mortality.

Studying survival according to different levels of depression severity is based on the hypothesis that a higher 'dosage' of depression would result in a higher mortality risk for the individual patient. This would be in line with cross-sectional studies that have demonstrated the detrimental effects of depression with regard to physical health and various aspects of functioning to be directly related to the number of depressive symptoms (Hays, Wells, Sherbourne, Rogers, & Spritzer 1995;Ormel, Kempen, Deeg, Brilman, van Sonderen, & Relyveld 1998). The current study confirms this hypothesis, as moderate to severe levels of depression were associated with a higher mortality risk.

Similarly, the dosage of depression can be quantified as the length of exposure to depression. Subjects with chronic depression had a 41% higher mortality risk in 6-year follow-up than subjects who were not depressed at either assessment. Subjects with either incident or remitted depression did not have a higher mortality risk. Length of exposure thus plays a vital role with respect to longevity. This once more underlines the detrimental effects of chronic depression, that has already been shown to have a profound negative influence for late-life physical and social adjustment (Vaillant et al. 1996), health service use (Beekman et al. 1997;Unutzer et al. 1997) and well-being (Hays, Wells, Sherbourne, Rogers, & Spritzer 1995;Ormel, Kempen, Deeg, Brilman, van Sonderen, & Relyveld 1998). With chronicity ranging around 50% (Cole, Bellavance, & Mansour 1999), and even higher at more severe levels of depression (Beekman et al. 2002), the clinical importance of these findings is considerable.

Studying the association between depressive symptoms and mortality on a population level showed that somatic symptoms such as slowness, loss of energy and loss of appetite predicted subsequent mortality. The majority of subjects with these symptoms did not have a depressive disorder. Although chronic diseases were carefully adjusted for in this study, these somatic symptoms may be related to conditions that were subclinical at the time of interview, but nevertheless affected 10-year survival. Somatic symptoms may also be an indicator of the severity of physical illnesses and likewise be associated with an untoward course. Classifying these symptoms as originating from either depression or medical illness is further complicated by the fact that depression is associated with biological dysregulations such as dysfunctions in the hypothalamic-pituitary-adrenocortical (HPA) system (Holsboer 2000;Musselman & Nemeroff 1996), autonomic dysregulation (Yeragani et al. 2002) and inflammatory processes (Penninx et al. 2003). All of these processes may also be associated with higher levels of comorbidity and excess mortality.

When the analyses were confined to subjects with clinical depression, the specific influence of somatic items almost disappeared. In depressed subjects, psychological

symptoms such as suicidal ideation appear to be much more prominently associated with mortality than somatic symptoms. Although it is obvious that suicidal ideation may affect survival, previous work suggests that suicide alone can not account for the excess mortality of depression (Lindesay 1989;Maris 2002;Murphy et al. 1988;Murphy et al. 1987;Penninx et al. 2001). Negative thoughts may also be related to a wider array of counterproductive and noncompliant behavior associated with ill health and mortality. Depression is associated with unhealthy life styles such as smoking, alcohol use (Aneshensel & Huba 1983;Goodwin & Jamison 1990) and physical inactivity (Stephens 1988), noncompliance with medical treatment (DiMatteo, Lepper, & Croghan 2000) and death from accidents (Brodaty et al. 1997;Hoyer, Mortensen, & Olesen 2000;Lindesay 1989;Murphy, Smith, Lindesay, & Slattery 1988;Murphy, Monson, Olivier, Sobol, & Leighton 1987;Wulsin, Vaillant, & Wells 1999). Although the current study was not able to determine whether these mechanisms have actually played a role in the mortality association, this is a plausible explanation. It also stresses the clinical relevance of assessing death wishes and suicidal ideation, not only for the prevention of actual suicide.

The finding that guilt had a protective effect compared with other depression symptoms came as a surprise. One may assume inappropriate guilt to be associated with various forms of destructive and self-punishing, possibly (para)suicidal behavior. As both guilt and suicidal ideation are depressive thoughts, this finding may be due to confounding and their association was tested. Subjects with inappropriate guilt were more likely to have death wishes (37.2%) than subjects without guilt (9.9%; chi^2 107.7, p= 0.000) in the full sample. A similar pattern of co-occurrence was found among the depressed. However, there was no interaction of guilt and death wishes on the outcome measure, suggesting that these are in fact distinct and separate associations.

In the third set of analyses, clustered somatic items were important in relation to survival in the full sample, whereas none of the symptom clusters was predictive of excess mortality in the depressed subsample. As Table 1 shows, the symptom cluster 'depressive thoughts' included both suicidal ideation, feelings of guilt and worrying. The opposing association of guilt on the outcome measure may have neutralized associations that were evident on a more detailed symptom level.

Literature on mortality and specific symptom profiles of depression is both scarce and contradictory, and often focused on suicide as cause of death (Baumeister 1990;Schneider, Philipp, & Muller 2001;Seidlitz et al. 2001). Our study is the first to examine these issues in a broader context of all cause mortality in a community sample. The distinction made in this study between isolated symptoms and symptoms as part of clinically relevant depression offers a possible explanation for contradictory findings of earlier studies that mainly assessed isolated symptoms. The finding that depressive thoughts are most influential with regard to mortality suggests that a behavioral component plays an important role in the interface between clinically relevant depression and excess mortality. However, further research is needed to determine whether this hypothesis is correct.

The current study is a naturalistic study in the community with a 10-year follow-up of mortality data. One limitation is, that a number of possible influences and changes

affecting the prognosis of the almost 4000 subjects that participated in the study were not accounted for in these analyses. Depression is a disorder with a variety of course types. Subjects that were depressed at baseline may have recovered, remitted, and/or subsequently relapsed, or may have become chronically depressed. Likewise, subjects without depression at baseline may have experienced depressive episodes during the study period, which may also have influenced their survival. Still, studies with a limited number of assessments tend to overrepresent chronic depression. When comparing course types, misclassification may therefore, if anything, have led to an underestimation of the strength of the association between length of exposure and mortality.

A second limitation is that subjects may have had treatment for their depression, which may have affected prognosis. Unfortunately the impact of treatment is probably very limited. Studies in comparable samples of community living elderly across different countries have consistently shown that case-finding is poor, and adequate treatment of depression even more so (German et al. 1987;Sonnenberg et al. 2003). Our study is no exception to this. Although the effects of treatment were probably very limited, this may again have lead to an underestimation of the strength of the association between depression and mortality.

A strength of the current study is that it was able to examine both severity, duration and specific symptoms with regard to their implications for survival, using a design that allowed to control for a large number of possibly confounding variables. It was possible to investigate both the DSM core symptoms of depression, and the more elaborate symptom array for elderly populations available through GMS-AGECAT.

In conclusion, the current study shows that several characteristics of depression are of importance when assessing the risk of mortality. Severity and chronicity of depression are directly related to an increased mortality risk. Furthermore, somatic depression symptoms, potentially related to both concurrent physical illnesses and to biological aspects of depression are important with regard to survival on a population level. More interestingly, specific depressive cognitions are important with regard to the survival of depressed subjects. Apart from indicating possible behavioral pathways explaining the depression-mortality association that has frequently been established in other studies, more active casefinding and treatment of persons at risk may yield important benefits from a clinical perspective.

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10

Prevention of late life depression in primary care; do we know where to begin?

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Submitted

Abstract

Context

Depression is a highly prevalent disorder causing a large amount of non-fatal disease burden. Even optimal treatment would reduce this burden by only 1/3. In older persons, depression has a predominantly chronic course. It is of great interest to investigate possible strategies to prevent the onset of late-life depression in primary care.

Objective

To compare two models for selective (persons at elevated risk) and indicated prevention (persons with subsyndromal symptoms of depression), and determine which is the optimal strategy for prevention of late-life depression.
Design, setting and participants:
Depression onset was assessed at three-year follow-up using GMS-AGECAT in a randomly selected cohort of 1,940 non-depressed and non-demented older community-living persons in the city of Amsterdam. A comprehensive set of risk factors that can easily be identified in primary care was available.
Main outcome measures:
The association of risk factors with depression incidence was expressed in terms of Absolute and Relative Risk estimates, Numbers-Needed-to-be-Treated, and Population Attributable Fraction. Prevention models are identified using Classification And Regression Tree (CART) analyses.

Results

In the indicated prevention model, subsyndromal symptoms of depression were associated with a risk of almost 40% of developing depression, an NNT of 5.8, and accounted for 24.6% of new cases. Adding more risk factors raised the AR up to 49.3%, with a lower NNT (3.2), but also lower AF values. In the selective prevention model, loss of spouse showed the highest risk (AR 37%, NNT 5.3, AF 8.2%), a risk that became even higher if subjects also had a chronic illness. Overall, the AF values in the indicated model were higher, identifying more persons at risk.

Conclusions

Considering the costs and benefits of both models in the context of the availability of evidence-based preventative interventions, indicated prevention aimed at elderly persons with depressive symptoms is the preferred option. The exclusive focus on treatment of depressive disorder should be readdressed. A new approach in public mental health is needed, with a stronger emphasis on preventive psychiatry.

Declaration of interest

Grants detailed in Acknowledgements. No conflict of interest.

10.1 Introduction

The adverse consequences of depression are well established. Currently, of all illnesses, depressive disorder is causing the largest amount of non-fatal burden, accounting for almost 12% of all years lived with disability worldwide (Ustun et al. 2004). Depression is also associated with excess mortality (Cuijpers & Schoevers 2004), higher demands on caregivers and higher service utilization, and has substantial economical implications (Charney et al. 2003). In community dwelling elderly, the prevalence of depression requiring clinical attention is 13.5 % (Beekman, Copeland, & Prince 1999), and more than 50% have a chronic course (Beekman et al. 2002;Cole, Bellavance, & Mansour 1999). Although effective treatment is available, case finding and adequate treatment in primary care are generally poor (Sonnenberg et al. 2003;Tiemens, Ormel, & Simon 1996). Still, even if all patients with depression were optimally treated with evidence-based interventions, only 34% of the disease burden in terms of Years Lived with Disability (YLD) could be averted (Andrews et al. 2004). From the public health perspective, it is therefore of great interest to consider the possibility of depression prevention (Smit et al. 2004b;Smit et al. 2004a). However, evidence-based preventive strategies aimed at reducing the incidence of late life depression in community living elderly are sparse.

In prevention, different strategies can be chosen according to the stages or transitions in the development of a disorder (Haggerty & Mrazek 1994) (Figure 1). Universal prevention aims to influence the behaviour of the whole population in order to prevent the onset of disease. Examples of universal prevention are programs informing the population about the risk of alcohol intake or the benefits of physical exercise. Selective prevention is aimed at persons who are at risk because they have been exposed to certain risk factors. In the case of depression, risk indicators are for example loss of spouse and physical illness (Schoevers et al. 2000). The third form, indicated prevention, targets persons who already have early or subsyndromal symptoms, in whom an intervention may reduce the likelihood of becoming a full-blown 'case' (Haggerty & Mrazek 1994;Munoz, Mrazek, & Haggerty 1996). An example of indicated prevention is cognitive therapy for the prevention of psychosis in people at ultra-high risk (McGorry et al. 2002;McGorry & Killackey 2002), or pharmacotherapy for people with Mild Cognitive Impairment (MCI) to delay the onset of Alzheimer's disease (Jelic & Winblad 2003).

The choice for a specific type of prevention depends on the 'untreated' prognosis of the disorder, in combination with the costs, benefits and possible adverse consequences of different types of intervention. An ethical dilemma is that, by identifying a healthy person as a possible future case and starting some kind of intervention, this in itself carries certain negative consequences and should only be applied if the alternative has a significantly higher probability of adverse consequences. In the case of depression, evidence-based universal prevention of depression is currently non-existent. Selective prevention may focus on persons with certain risk indicators such as exposure to loss events. Indicated prevention would be directed at persons with depressive symptoms below the diagnostic threshold for 'clinically relevant depression' (Cuijpers & Smit 2004;Pincus, Davis, & McQueen 1999). For both ethical rea-

sons and reasons of cost-effectiveness, preventative measures aimed at reducing incidence should target subjects with high a priori risk through exposure to multiple risk factors (Cuijpers 2003). Furthermore, for practical reasons, persons at risk should be easily identifiable in primary care, and risk profiles have to be simple and unambiguous. From a public health perspective, prevention should be cost-effective and lead to a substantial reduction of total disease burden. This implies that the selected risk indicators should be indicative of a substantial proportion of new cases.

The current study explores selective and indicated prevention models to identify high-risk groups among older GP patients, bearing in mind the above qualifications. It seeks to identify those combinations of exposures that predict the largest health gains in the most cost-effective way when prevention is successful in blocking the adverse effects of these risk factors. These risk factors could then be used in primary care as an easy to use checklist or screener to identify patients at elevated risk of becoming a future case of depressive disorder. For indicated prevention, the use of a screening instrument to detect subsyndromal depression would be required. As this is more time-consuming than recognising subjects on the basis of more straightforward risk factors needed for selective prevention, the benefits of both approaches are compared. The study is based on data from the Amsterdam Study of the Elderly (AMSTEL study), a large and prospective cohort study of depression in community living elderly incorporating a comprehensive set of risk factors associated with late-life depression (Schoevers, Beekman, Deeg, Geerlings, Jonker, & Van Tilburg 2000).

10.2. Methods

10.2.1 Sampling and non-response

The AMSTEL study is a prospective cohort study on the incidence of depression in a large and representative sample of non-institutionalised older persons (65+). Informed consent was asked and obtained from each participant before starting the study. The study was approved by the Medical Ethics Committee of the Vrije Universiteit Amsterdam. The population base for AMSTEL included all non-institutionalised individuals in the 65-84 age bracket who lived in the city of Amsterdam and were registered with a general practitioner at baseline. The study was actively supported by the general practitioners, whose lists were used as the sampling frame. In the Netherlands, general practitioners are the gatekeepers to the health care system and almost every citizen is on the list of a general practitioner. In this role, general practitioners in the Netherlands generally provide social support and have a long-standing personal relationship with their patients. Thus, the source population consisted of almost all of the non-institutionalised population. The sample was drawn from a list of 30 general practices spread throughout the city; practices were selected from all practices registered within the city of Amsterdam, 22 randomly and 8 by convenience from a network of general practitioners participating in medical research. The profile of the over-65 general practice-population in terms of age and gender, correspond to the non-institutionalised population in Amsterdam (Launer et al. 1993;Launer, Wind, & Deeg 1994). Within each practice, respondents were randomly selected from four age strata spanning five years each (65-69 to 80-84). In order to obtain equally sized age-strata at follow-up, the older old were over sampled. Out of a sampled total of 5,666, 4,051 (71.5%) responded and formed the baseline sample. Interviews with these subjects were conducted between May 1990 and November 1991. The profile of the over-65 general practice-population in terms of age and gender corresponds to the non-institutionalised Amsterdam population.

At follow-up three years later (median 38 months), 2,244 (55.4%) were reinterviewed, 656 (16. 2%) people were deceased, 662 persons (16.3%) refused further cooperation, 282 (7.0%) were too ill or cognitively impaired to respond, and 207 (5.1%) were not available for interview due to a variety of other reasons. For this study, subjects with depression (523; 12.9%) or dementia (261; 6.4%) at baseline were excluded. The study cohort consisted of all respondents at follow-up who were neither depressed nor demented at baseline, for whom complete data were available at follow-up (N=1,940).

10.2.2 Measures

A one-hour interview was developed to gather information on psychiatric symptoms, demographic and medical status, personal history of depression and family history. The interview consisted of the Dutch translation of the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), all Geriatric Mental State Examination-items related to organic, affective and anxiety syndromes (Copeland et

al. 1988;Copeland, Dewey, & Griffiths-Jones 1986), the Instrumental Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale(Lawton & Brody 1969), and part of the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were trained using video sessions and regularly supervised. The same GMS-AGECAT package with an identical algorithm was used in the second wave of the study. When re-interviewing, raters were unaware of previous data and diagnoses.

Psychiatric diagnoses Diagnoses of dementia, depression and generalised anxiety disorder were made according to the GMS-AGECAT system. Diagnostic levels 3-5 correspond reliably to cases of depression requiring clinical attention in both the community (Copeland, Dewey, & Griffith-Jones 1990) and in elderly hospital patients (Ames & Tuckwell 1994). GMS-AGECAT has a proven reliability in epidemiological studies, as became evident through replication studies (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988). GMS-AGECAT generates both a non-hierarchical syndrome level and a more narrowly defined diagnostic level. The diagnostic case level is calculated from the syndrome level using a hierarchy from organic to depression to anxiety disorder. In order to be able to also assess overlapping comorbidity influences, syndrome levels were used in the analyses as otherwise the diagnostic hierarchy would bias the results. Depression caseness at baseline and follow-up was defined as a GMS-AGECAT level 3 or higher (Copeland, Dewey, Henderson, Kay, Neal, Harrison, McWilliam, Forshaw, & Shiwach 1988). Subjects not depressed at baseline who had become depressed at follow-up were considered to be incident cases. Subjects with depression case levels 1 or 2 at baseline were classified as having 'subsyndromal depression'.

Risk indicators Socio-demographic variables included age, gender and educational level, the latter of which was dichotomised into lower (primary school or less) and higher (more than primary school) education. Living situation was assessed with the associated questions in GMS-AGECAT. A personal history of depression was ascertained by the relevant CAMDEX-question. The question was considered affirmative if treatment had previously been requested. The presence of chronic diseases was assessed with the pertinent Camdex questions on myocardial infarction, stroke, cancer, lung disease, diabetes, Parkinson's disease, arthritis and epilepsy. Cognitive status was assessed by MMSE-score. Cognitive impairment was defined as an MMSE score below 24. Sleeping disorder was determined by two questions from the GMS on "trouble falling asleep (yes, or 'I would have problems if I didn't use sleeping medication) and 'early wakening' (at least two times per week at least two hours earlier than usual). Disability was measured using a combined scale consisting of all ADL and IADL items (Kempen, Myers, & Powell 1995;Kempen & Suurmeijer 1990). Subjects were considered disabled if the total score was two or more points below the maximum. This indicates that subjects were 'in need of help' to perform at least two of the tasks mentioned, or were 'unable to perform' at least one task.

10.2.3 Data analysis

The analyses were conducted in several steps. First, standard epidemiological techniques were used to analyse the risk of becoming a case in subjects with or without being exposed to a certain risk indicator. These risks are denoted P1 and P0 for the exposed and unexposed group respectively. The absolute risk, AR, and relative risk, RR, were obtained by,

$$AR = P_1,$$
$$RR = P_1 / P0 ,$$

with the RR denoting the excess risk of becoming depressed in the exposed group relative to the unexposed group. The RR can be interpreted as a measure of the strength of association between exposure and disease onset. In this way, both the relative and the absolute risk (conditional on exposure status) of depression incidence are presented.

In a second step, the importance of risk indicators for onset of disorder at population level can be quantified. It is necessary to know how many persons are exposed to a certain risk factor, in order to determine the scale of both the problem and of possible interventions. This can be done by taking into account the level of exposure to a risk factor in the population, also called exposure rate (E). By combining the relative risk (RR) with the exposure to a risk factor (E) in the population, the population attributable fraction (AF) can be computed, as,

$$AF = E(RR-1) / (1+E(RR-1)).$$

The AF indicates by how many percentage points the incidence rate of depression in the population will be lowered when the adverse effect of the risk factor (or combination of risk factors) can be completely blocked. Therefore, the AF can be interpreted as the upper limit of the potential health gain in the population.

Similarly, a measure of the efficiency of a preventive intervention can be calculated: the Number-Needed-to-be-Treated (NNT) (Cook & Sackett 1995). In the context of an epidemiological study, the NNT can be interpreted as a measure of efficiency, showing how many people must be protected from the adverse influence of a risk factor in order to avoid one new case of depression. The NNT was obtained by,

$$NNT = 1/| P_1 - P0|.$$

It should be borne in mind that the NNT values presented here, are based on the assumption that an intervention is able to completely block the adverse influence of a risk factor on the onset of depression. Depending on the actual efficacy of each preventative intervention, the NNT should therefore be adapted. If an intervention has a 50% efficacy in containing the effect of a risk factor, the actual NNT should be multiplied by 2. Using Stata (Stata Corporation 2001) statistics like RR, AF and NNT can be obtained in a multivariate context controlling for competing risks (Smit, Beekman, Cuijpers, de Graaf, & Vollebergh 2004a).

In the third step, the RR, AF, NNT and E statistics were used to find the best values for efficiency (i.e., low NNT values), and the best values for health gains (i.e., highest AF values) for combinations of exposures. The idea is that people may be exposed to more risk factors simultaneously, and that joint exposures entail higher RRs, lower NNTs and perhaps higher (or lower) AF values. In other words, targeting preventative interventions on groups that have been exposed to specific combinations of risk factors may yield, by implication, higher health gains (RR, AF), against less effort (NNT).

To trace the effect of multiple exposures in all their combinations we used a method known as classification and regression tree (CART) analysis (Everitt B.S. 2003;Lemon et al. 2003), and adapted it for our purposes. CART analysis can graphically be represented as tree-like figures (see Figure 1, later). First, a parent node is selected that optimises the NNT, RR and AF values in preferably the smallest (E) groups. This parent node branches off in two directions, creating child nodes in which people are not only exposed to the risk factor in the parent node, but also to an additional risk factor in the child node. Therefore, the first generation of child nodes captures the effect of double exposures, the second generation of child nodes represents the effect of triple exposures, and so on. At each node, both branches (for subjects with and subjects without that specific risk indicator) are followed up to determine NNT, RR and AF values of combined exposures. Thus, the sample is split into smaller subgroups at each step.

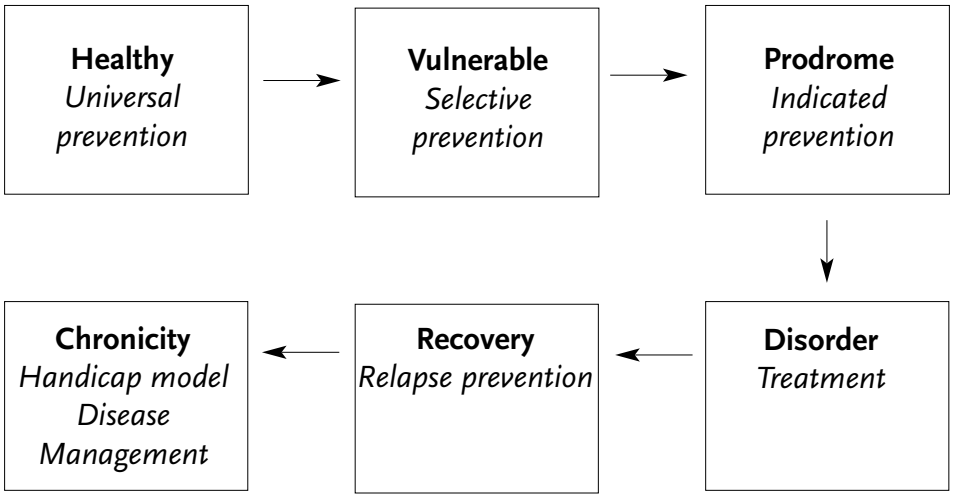
In CART analysis one has to make use of explicit decision rules for selecting child nodes and terminating branches. For identifying the best child node, the following hierarchy of decision rules was used:

1 Chose child node with the lowest NNT (i.e. greatest efficiency)
2 Chose child node with the highest AF (i.e. greatest health gain).
3 When ties occurred, the child node was selected with the smallest exposure (E) rate, because it was reasoned that targeting smaller groups is logistically and economically less demanding and more feasible given equal NNT and AF values.

The following rules were employed for the termination of branches:

1 R < 1.00 or RR not significant (i.e. no risk involved)
2 AF < 5% or AF not significant (i.e. no health gain)
3 NNT > 50 or NNT not significant (i.e. not efficient).

Figure 1: Types of prevention and treatment according to transitions in disease development



(adapted from A.T.F. Beekman, 2004)

10.3 Results

10.3.1 Sample characteristics and response pattern

The baseline sample characteristics are shown in Table 1 and have been described in more detail elsewhere (Schoevers, Beekman, Deeg, Geerlings, Jonker, & Van Tilburg 2000). In multivariate logistic regression analysis, non-response at follow-up was predicted by higher age, male gender, lower education, living alone, chronic disease(s), disability, organic caseness and depression (dichotomised as depression case level vs. no depression case level). After subjects who died between measurements were excluded from the sample, only lower education, living alone and baseline organic syndrome predicted non-response. At follow-up 309 subjects (15.9% of the study sample) had become depressed. The following analyses investigate the associations of risk factors with incident depression.

10.3.2 Predictors of late-life depression

Table 2 shows the predictor model and the associations with the onset of depression. Statistically significant associations between risk indicators and depression incidence were found for the following risk factors: medical illness, disability, a personal history of depression, recent loss of spouse, sleep disturbance, generalised anxiety disorder and subsyndromal depression. From these, the absolute risk of developing depression when exposed to a risk factor was calculated. The NNT values for the risk factors in the model range from 242 (living alone) to 4.1 for subjects with GAD. For each risk factor the associated AF was also calculated, ranging from 24.6 (subsyndromal depression) to 1.1 (living alone).

TABLE 1: SAMPLE CHARACTERISTICS AND ASSOCIATIONS WITH FOLLOW-UP (*= p<0,05, **= p<0,01, ***= p<0,001)

VARIABLES (Value at TO)		To (%)	T1 (% To)	Resp vs Nonresp Chi-2/df/p	Resp vs Non R. excl. deceased Chi-2/df/p
N		4051	2244 (55,4)		
AGE	65-69	836 (20,6)	544 (65,1)	89,2/3/***	17,2/3/***
	70-74	974 (24,0)	581 (59,7)		
	75-79	1050 (25,9)	581 (55,3)		
	80-86	1191 (29,4)	538 (45,2)		
SEX	Male	1523 (37,6)	817 (53,6)	3,02/1/ns	6,8/1/**
	Female	2528 (62,4)	1427 (56,4)		
EDUCATION				41,4/1/***	29,2/1/***
Higher than PS		2335 (57,6)	1394 (59,7)		
Primary school or less		1716 (42,4)	850 (49,5)		
SOCIO-ECON STATUS				21,1/2/***	11,9/2/**
High		182 (4,5)	121 (66,5)		
Middle		1803 (44,7)	1045 (58,0)		
Low		2050 (50,8)	1075 (52,4)		
LIVING SITUATION				1,03/1/ns	1,22/1/ns
With other(s)		2197 (54,2)	1201 (54,6)		
Alone		1854 (45,8)	1043 (56,3)		
SOCIAL SUPPORT				24,4/1/***	4,4/1/*
No/little social support		3209 (79,2)	1841 (57,4)		
Help from others		842 (20,8)	403 (47.9)		
CHRONIC DISEASES				24,9/1/***	0,4/1/ns
None		1894 (46,8)	1128 (59,6)		
One or more		2157 (53,2)	1116 (51,7)		
PSYCHIATRIC HISTORY				0,02/1/ns	1,6/2/ns
None		3449 (85,1)	1909 (55,3)		
Yes		602 (14,9)	335 (55,6)		
DISABILITY				91,6/1/***	10,5/1/**
Able		2931 (72,4)	1759 (60,0)		
Disabled		1120 (27,6)	485 (43,3)		
MMSE SCORE				161,3/2/***	84.8/2/***
26-30		3281 (81,0)	1969 (60,0)		
22-25		522 (12,9)	209 (40,0)		
0-21		248 (6,1)	66 (26,6)		
ORGANIC syndrome level				89.7/1/***	35,5/2/***
None		3790 (93,6)	2173 (57,3)		
Case		261 (6,4)	71 (27,2)		
SLEEP DISTURBANCE				1.49/1/ns	2,48/1/ns
None		2615 (64,6)	1467 (56,1)		
Yes		1436 (35,4)	777 (54,1)		
GENERALISED ANXIETY				1,56/1/ns	4,1/1/*
None		3923 (96,8)	2180 (55,6)		
Case		128 (3,2)	64 (50,0)		
DEPRESSION				19,4/2/***	10.48/2/**
None		2667 (65,8)	1534 (57,5)		
Subsyndromal		861 (21,3)	462 (53,6)		
Case level		523 (12,9)	248 (47,4)		

TABLE 2: PREDICTION MODEL; BIVARIATE ASSOCIATIONS WITH DEPRESSION ONSET

(Subjects without depression and/or dementia at baseline, N= 1940, analyses holding constant for other variables, E= Exposure Rate, RR= Relative Risk, AR= absolute risk of developing depression, NNT= numbers needed to be treated, AF= population attributable fraction)

RISK FACTORS	E (%)	RR (95% c.i.)	AR (%)	NNT	AF (%)
Female sex	60.5	1.20 (0.97-1.49)	Ns	35.2	10.8
Education (primary school or less)	35.6	1.12 (0.91-1.39)	Ns	54.9	4.1
Living alone	44.0	1.03 (0.84-1.26)	Ns	242	1.1
Medical illness	47.8	1.46 (1.19-1.80)	23.2	16.6	18.1
Disability	17.7	1.74 (1.39-2.17)	27.7	9.6	11.5
Mmse < 24	2.6	1.13 (0.62-2.07)	Ns	47.0	3.4
Personal history dep./anx.	13.0	1.61 (1.25-2.06)	25.6	11.2	7.3
Loss of spouse	6.9	2.29 (1.77-2.99)	36.4	5.3	8.2
Trouble sleeping	30.4	1.73 (1.41-2.12)	27.5	10.5	18.2
Generalised Anxiety Disorder	1.3	2.56 (1.57-4.19)	40.7	4.1	2.0
Subsyndromal depression	22.7	2.43 (1.99-2.97)	38.6	5.8	24.6

10.3.3 Indicated prevention model (CART analysis)

Following the algorithm described in paragraph 2.3, subsyndromal depression clearly was the preferred primary node (figure 2). Although the NNT of 5.8 was higher than that of GAD (4.1, see table 2), the associated AF of depression was far greater (24.6%), and that of GAD (2.0%) was below the threshold of 5% for the termination of branches. The prevention model was then continued for each branch, starting with subjects who had, and those who did not have subsyndromal depressive symptoms. In subjects with subsyndromal depression, the next branching candidate was having a disability. This step reduced the NNT to 3.9, but also limited the AF to 9.7%. The model was then further subdivided with living alone and female sex as following risk indicators. As the AF was below 5% at the next step (all →...subsyndromal symptoms → disability → living alone → female sex →..) the branch was terminated here. In subjects with subsyndromal depression who were not disabled, having a chronic illness (AR 34.2%, NNT 6.0) and living alone (AR 35.0%, NNT 5.6, AF 4.9%) were chosen as subsequent child nodes. In subjects who did not have depressive symptoms, loss of spouse was the strongest predictor, with an AR of 33.1% of developing depression, an NNT of 6.1 and AF 5.4%. Further branching was not performed as the AF became too small (<5%).

The way in which NNT, AF and E are interrelated is graphically illustrated in figure 3. It shows how adding more risk factors to the model results in a higher AR, a lower NNT, but also in a lower AF.

Figure 2: Indicated prevention model

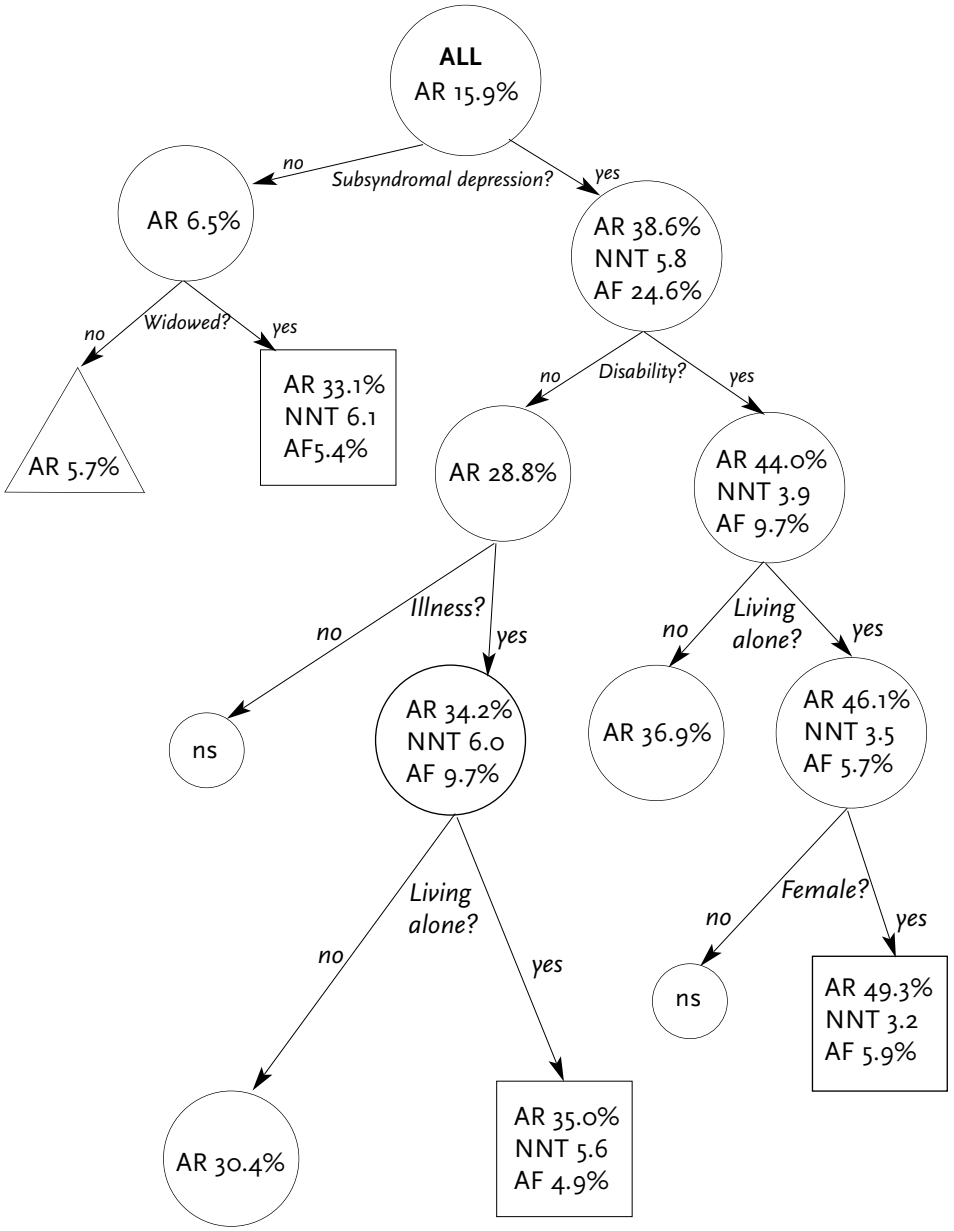
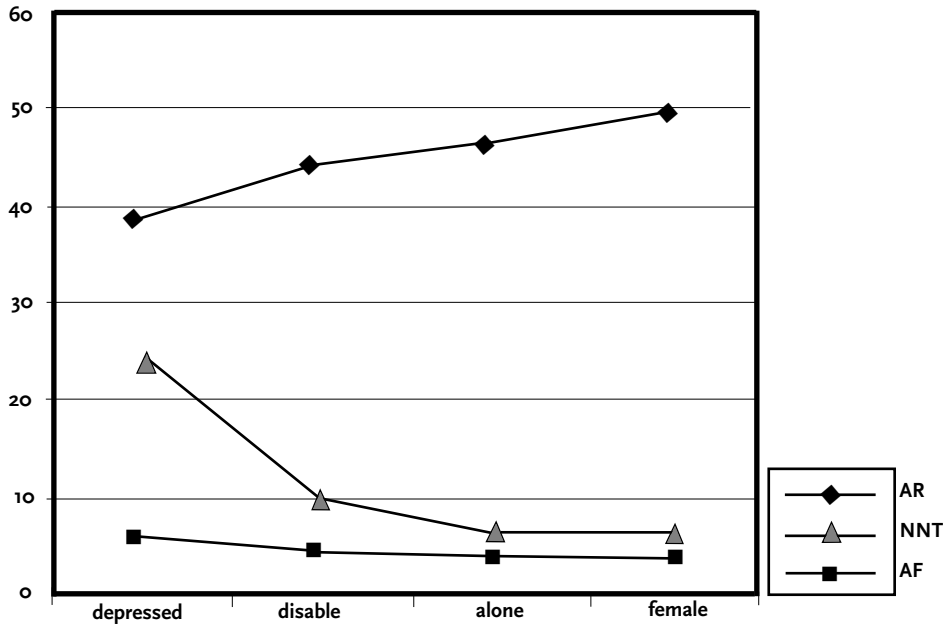


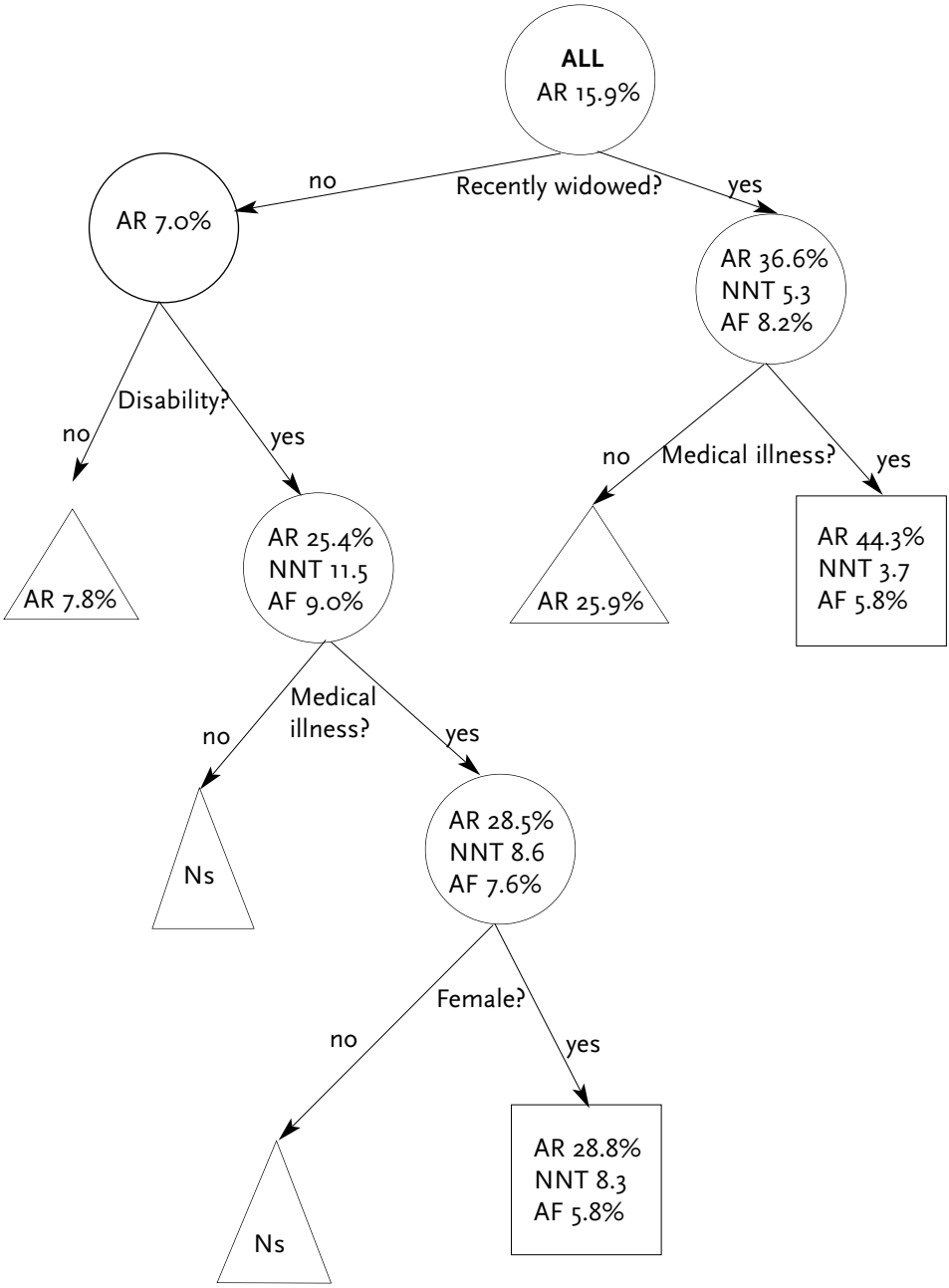
Figure 3: Consequences of adding risk factors to the prediction model in terms of Absolute Risk (AF, in %), Numbers Needed to be treated (NNT, in %), and Attributable Fraction (AF, in %).



10.3.4 Selective prevention model (CART analysis)

Figure 4 shows the model without subsyndromal symptoms of depression. Now the focus is on selective prevention and easy case-recognition by GPs. Following the algorithm described above, the first branching candidate on the basis of NNT and AF scores is loss of spouse, with NNT 5.3 and AF 8.2%. This was chosen as the primary (or parent) node. The selective prevention model then yielded medical illness as the next branching candidate in subjects who lost their spouse. This step reduced the NNT to 3.7, but also limited the AF to 5.8%. Because of this, further branching was not performed. In subjects who did not recently lose their partner, being disabled was the most important risk indicator, with NNT 11.5 and AF 9.0%. Further risk indicators were the presence of a chronic medical illness, and female gender. The latter step reduced the AF, but only slightly affected the NNT (from 8.6 to 8.3).

Figure 4: Selective prevention model



10.4. Discussion

In this study, high-risk groups for incident depression were identified in a large cohort of elderly GP patients. As case finding is generally poor, and both prevalence and persistence of late-life depression are of major concern, the goal was to identify groups in primary care with a high vulnerability for depression according to easily identifiable criteria. Prevention is of interest, bearing in mind that even optimal care can only reduce the burden of depression by 34% (Andrews, Issakidis, Sanderson, Corry, & Lapsley 2004). Since the detection of subsyndromal depressive symptoms requires more effort than recognising other, more easily identifiable risk indicators in primary care, two models were compared that either incorporated or excluded subsyndromal depression as a predictor of the future onset of a full-blown depressive disorder. Thus, the potential health benefits of preventative measures aimed at reducing the incidence of late-life depression could be determined, taking into account the time that should be invested in adequate case-finding in primary care. Although this approach, combining clinical, epidemiological and public health perspectives, has been strongly advocated (Munoz, Mrazek, & Haggerty 1996), it is relatively new to the field of common mental disorders.

Our findings suggest that indicated prevention — which involves identifying subsyndromal depressive symptoms as the most important risk indicator — is the preferred option for identifying groups at high risk of developing depression. Subjects with depressive symptoms had a risk of almost 40%, and accounted for 24.6% of new cases at follow-up. With an NNT of 5.8 — which carries the promise of efficient interventions in this group — these subjects are of major interest for preventative interventions. Further subdivision of the sample according to combinations of risk factors yielded groups with an even higher risk of developing depression and lower NNT values, but these more narrowly focussed approaches have a smaller impact on the incidence rate of depression in the population. For example, disabled women with subsyndromal symptoms who live alone had a 50% risk of becoming depressed, an NNT of only 3.2, but a relatively low AF (5.9%) indicating that the incidence rate would only fall by 5.9% at best.

In a recent meta-analysis on short-term psychotherapeutic interventions aimed at persons with subsyndromal depressive symptoms, these were found to reduce the incidence of depression by 30% (Cuijpers, van Straten, & Smit 2005). If this were applied to a sample such as ours, the NNT of intervention would be 19.3 (5.8 / 0.3) for persons with subsyndromal depression. For a relatively intensive form of treatment, this may be considered to be too great an effort, and it could be argued that one should start with those subjects who have the highest vulnerability. Further subdivision in the CART analysis then leads to smaller subgroups that were exposed to more risk factors. In women with disability who live alone, the adjusted NNT would be 10.7 (3.2 / 0.3). As an alternative to cognitive behavioural therapy, less costly forms of indicated prevention should also be taken into consideration. Both bibliotherapy (Cuijpers 1997) and the Coping With Depression course, a manualised form of self-help with instructions on mood management, were found to be effective therapies for unipolar depression, with effect sizes that are comparable to those of other

treatment modalities for depression (Cuijpers 1998). Very recently, minimal contact psychotherapy along these lines has been proven effective in reducing the onset of depression in primary care patients with subthreshold depression (Willemse et al. 2004). Also in low-cost computerised form, such interventions have proved effective (Christensen, Griffiths, & Jorm 2004;McCrone et al. 2004).

If one considers selective prevention of late-life depression, our analyses show that, in line with earlier findings (Cole & Dendukuri 2003), elderly persons who recently lost their spouses are at great risk of developing depression, and even more if they also have a chronic medical condition (AR 44%, NNT 3.7). Overall, the AF values in this model were somewhat smaller, which means that fewer cases can be prevented. Examples of preventative programs directed at persons who lost their spouse include self-help groups of fellow-sufferers that convene for emotional exchange and support, specific courses on competences needed to cope with single life, and 'widow-to-widow' programs in which women who had lost their husband earlier visit recently widowed persons for emotional and practical support. Although these programs have shown promising results in terms of post bereavement adaptation (Vachon et al. 1980) and social functioning (Van Lammeren & Geelen 1995), the evidence of efficacy in reducing depression onset is limited. In a meta-analysis of eight types of such interventions, Cuijpers et al. found an effect size of 0.34 in comparison with controls, but the number of published studies is still limited and this difference was not statistically significant (Cuijpers, Van Gageldonk, & Overtoom 2000). Considering the fact that these are low-cost community based interventions, randomised controlled trials are urgently needed.

Indicated prevention thus has the best chances of detecting large groups of subjects at high risk of developing depression, with NNT values that could make preventative actions cost-effective, using available evidence-based interventions. Still, in comparison with selective prevention, indicated prevention requires the extra effort of screening subjects for subsyndromal depression. A number of screening instruments have been validated for case finding in community living elderly. These include the CES-D, a 30-item questionnaire on depressive symptoms (Beekman, Copeland, & Prince 1999;Prince et al. 1999;Radloff 1977), but more recently also the 15-item version of the Geriatric Depression Scale has demonstrated its effectiveness for detecting elderly subjects with depressive symptoms in the community (Almeida & Almeida 1999;de Craen, Heeren, & Gussekloo 2003;Osborn et al. 2002;Sheikh & Yesavage 1986). Screening of large numbers of patients in primary care has been shown to be both feasible and effective (Bijl et al. 2003;Bijl et al. 2004). Primary care facilities therefore appear to be well equipped to find elderly persons with subsyndromal symptoms.

Strengths and limitations

The AMSTEL study is a large prospective cohort study with long follow-up times, and it incorporated a wide range of risk factors for late life depression measured independently of depression onset. The findings are representative for urban populations of community dwelling older persons, and are highly relevant for primary care.

Nonetheless, a number of limitations deserve mentioning. First of all, studies with a limited number of measurements tend to overrepresent chronic forms of dis-

order. Between assessments, subjects may have had both onset and remission of shorter episodes of depression. At the same time it may be concluded that, even with a three-year interval, the set of risk factors employed in this study can identify a large number of future cases of depression. Secondly, although the risk factors cover many domains relevant to depression, biological (genetic) risk indicators are less well represented in the dataset. Thirdly, it should be concluded that this study does not prove that preventative interventions are successful in community-living elderly. Available studies on indicated prevention were mostly performed in younger adults. However, as other forms of treatment of depression are also effective in the elderly, there would be no reason to doubt the efficacy of preventative interventions in elderly subjects. Considering the potential benefits of prevention there is an urgent need for randomised controlled trials to address this matter.

Conclusions

The results of this study stress the importance of preventative action for depression as the primary common mental disorder. And to answer the question put forward in the title of this paper: "Yes, we do know where to begin". Indicated prevention of depression is the preferred strategy. Still, as this involves screening patients for subclinical depression, selective prevention of depression may prove to be a good alternative. It will only require the use of a simple checklist of the relevant risk factors, and the expected health gains can also be substantial. Either way, primary care facilities are equipped to perform adequate case-finding. Nonetheless, even though minimal contact, low-cost, evidence-based interventions for persons with subsyndromal symptoms are available, their cost-effectiveness has to be established in proper randomised trials. Recent data however indicate that this may be the case (Smit, Ederveen, Cuijpers, Deeg, & Beekman 2004b;Willemse, Smit, Cuijpers, & Tiemens 2004). It is therefore time to reconsider whether the exclusive focus on treatment of common mental disorders should be adapted, and whether an allocation of personnel and resources for prevention may be more effective in reducing both individual suffering and the overall costs of health care.

Acknowledgements

The Amsterdam Study of the Elderly (AMSTEL) was supported by grants from the Netherlands Health Research Programme (SGO) and the Netherlands Foundation of Mental Health (NFGV). The NFGV also awarded Filip Smit a grant for participating in this study. The AGECAT computer program was installed with the kind co-operation and final authorisation of Michael E. Dewey, Department of Psychiatry, University of Liverpool.

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11

General discussion

11 General Discussion

In this chapter, the major findings of this thesis will be presented following the research questions formulated in chapter 1. In addition, the most important limitations and strengths of the design and implementation of the study will be discussed. The last paragraph describes the relevance of these findings from a theoretical, clinical and public health standpoint, leading to the formulation of recommendations for future research.

11.1 Brief summary of findings

1. *Can different etiologic pathways for the onset of late-life depression (through genetic/familial vulnerability, organic vulnerability or environmental vulnerability) be demonstrated in a longitudinal study of community-living elderly?*

[Chapter 2] This study sought to determine whether, in line with the vulnerability-stress model (Brown & Harris 1978), depression is the result of 'social stress' factors such as partner loss, relocation and (the occurrence of) chronic diseases or disability, and whether the influence of these is modified by the vulnerability or protective factors distinguished in this study. Higher age, personal history of depression, death of spouse, health related factors and comorbid organic or anxiety syndrome showed significant associations with depression incidence in bivariate analyses. It was shown that genetic/familial vulnerability, defined as having a personal or family history of psychiatric illness, and organic vulnerability did not modify the association between the investigated stress factors and incident depression. Subjects with these types of vulnerability were not more likely than others to develop depression in response to loss, to a decrease in physical wellbeing, or in response to deteriorating functional abilities. Having a personal history of depression was in itself a relatively strong predictor of depression onset. Although this may be suggestive of a 'kindling' effect, whereby the onset of a new episode of depression is more easily elicited by either external or internal stressors in subjects who have become sensitised through earlier episodes, interactions between a personal history and stress factors on the outcome measure could not be demonstrated. The third type of vulnerability, by environmental factors, did act as effect modifier; having a marital partner, and if unmarried having social support, significantly reduced the association between functional disability and the incidence of depression. This can be taken as modest support for the vulnerability-stress hypothesis to model the incidence of depression.

2. *Are risk factors related to incidence of late-life depression also related to prognosis? Can a vulnerability-stress model also be established for prognosis of late-life depression?*

[Chapter 3] In subjects with a depression at baseline, having a personal history of depression, having baseline functional limitations and emerging comorbid anxiety symptoms were associated with chronicity of depression. These risk factors also predicted depression incidence in the earlier study. Although other risk factors associated with incidence, such as recent life-events and changes in physical, functional or cognitive status, were not associated with the development of chronicity overall, the impact of these risk factors on the course of depression was predictive of chronicity after stratification of the sample. Effect modification by longstanding vulnerability characteristics was demonstrated, and the analyses were repeated in subjects with, or without a personal history. In subjects without a previous history of depression, functional disabilities, receiving instrumental support and also male gender were predictive of a chronic course. In subjects with a personal history of depression however, course type was not associated with other factors. Similarly, but for theoretical reasons, the sample was stratified according to gender. It was shown that in women the development of chronicity was more strongly associated with longstanding, possibly genetic vulnerability than in men. In men, recent psychosocial and health related characteristics showed stronger associations with course type than in women. It was concluded that more recent life stresses are related to prognosis in depressed subjects without a personal history, and in depressed men. The risk profile for depression onset differs from that associated with the development of chronicity, in the sense that chronicity is more strongly associated with both longstanding vulnerability and gender.

3. *Depression and generalised anxiety disorder; dimensions of a single disorder, or different and distinct disease entities?*

[Chapter 4] In this cross-sectional study, it was shown that comorbidity of depression and generalised anxiety disorder increases with higher severity levels of either category. This is suggestive of a dimensional rather than a distinctly different interpretation of these phenomena. A related issue is whether pure depression, pure generalised anxiety disorder or mixed anxiety-depression may show different associations with risk factors for these disorders. This proved not to be the case for concurrent risk factors, but longstanding vulnerability showed significantly stronger associations with mixed anxiety-depression than with pure anxiety and pure depression. Comorbidity was also twice as likely in women than in men. It was concluded that in the elderly, a dimensional classification is more appropriate than a categorical classification of depression and generalised anxiety. It was also concluded that mixed anxiety-depression is a more severe form of psychopathology that is almost specific to women in this age group.

4. *Pure depression, pure generalised anxiety disorder and mixed anxiety-depression; different course types and/or fixed patterns of temporal sequencing? Can different risk profiles be distinguished for onset in a prospective design?*

[Chapter 5] In a study of course types, remission rates at follow up were significantly higher for subjects with pure depression or pure generalised anxiety than in subjects with mixed anxiety-depression, of whom only 27% had remitted at three year follow-up. A pattern of temporal sequencing was established, with anxiety often progressing to depression or mixed anxiety-depression. A prospective study of risk factors and onset of either category showed that pure depression and mixed anxiety-depression were predicted by loss events, ill health and functional disability. Onset of pure generalised anxiety, and more strongly that of mixed anxiety-depression, was associated with longstanding, possibly genetic vulnerability. It was concluded that, in comparison with either pure depression or pure anxiety, mixed anxiety-depression represents more severe and more chronic psychopathology, associated with longstanding vulnerability. These longitudinal findings were also interpreted as favouring a dimensional versus a categorical classification of generalised anxiety disorder and depression.

5. *Is depression indicative of subsequent cognitive decline and Alzheimer's disease (AD) in elderly persons with normal cognition?*

[Chapter 6] In this study on the nature of the relationship between depression and cognitive decline/dementia, the research question was investigated in two independent samples of older people with normal cognition. Similar analyses were performed in samples without cognitive impairment from both the Amsterdam Study of the Elderly (AMSTEL) and the Longitudinal Aging Study Amsterdam (LASA). Although both studies used different methodology and research instruments, it was concluded that in both studies depression was associated with an increased risk of subsequent AD and cognitive decline respectively, but only among subjects with higher levels of education. It was suggested that in a subgroup of more highly educated elderly people, depression may be an early manifestation of AD before cognitive symptoms become apparent, rather than a psychological reaction to subjective and subclinical memory cognitive complaints.

6. *Is there an association between depression in community living older persons and an increased mortality risk? And if so, does this association depend on severity of depressive disorder and/or gender?*

[Chapter 7] Earlier community-based studies had found opposing results as to whether depression (according to a variety of different definitions, research instruments and severity levels) was associated with excess mortality. As both gender and severity of depression may theoretically have acted as confounders, the study of mortality was performed with a special interest in these associations. Using a six-year follow-up of community death registers, the mortality risk of neurotic (mild) and psychotic (severe) depression was calculated after adjustment for demographic vari-

ables, physical illness, cognitive decline and functional disabilities. Psychotic depression was associated with significant excess mortality in both sexes. Neurotic depression was associated with a higher mortality risk in men only. It was concluded that in the elderly, major depressive syndromes increase the risk of death in both sexes, whereas mild depressive syndromes only show this association in men.

7. *What mechanisms can be responsible for the excess mortality associated with depression?*

[Chapter 8] In a review article on this issue, it was shown that a number of different processes may play a role in this association. First of all, depression affects behaviour. Depressed patients show more unhealthy living habits, less compliance with medical treatment, and a higher number of accidents and suicides. Secondly, biological correlates of depression such as dysregulation of the neuro-immune system; hyperactivity of the HPA-axis, and autonomic dysregulation may all have a negative effect on both the prognosis of somatic illnesses and longevity. Although the literature suggests that treatment of depression positively affects some biological parameters, it remains unclear whether successful treatment of depression may lead to better survival.

8. *Do depression characteristics such as severity, duration or specific symptoms contribute to the association with excess mortality?*

[Chapter 9] A second study of mortality data was performed at ten-year follow-up. It was concluded that both moderate and severe depression, now defined by the number of GMS depression symptoms at baseline, predicted 10-year mortality after multivariate adjustment. Also chronic depression, defined as having a depression at baseline and at three-year follow-up, was associated with a significantly higher mortality risk compared to non-depressed subjects. Somatic depression items were predictive of excess mortality in the full cohort, regardless of the presence of clinical depression. In subjects with depression, only depressive thoughts, suicidal ideation and guilt, were specifically associated with excess mortality, albeit in opposing directions. Subjects with suicidal ideation were at higher risk to die, whereas guilt showed a protective effect relative to the other depression symptoms. This was taken to indicate that both severity, chronicity and specific symptom profiles of depression are indicative of a higher mortality risk, with a differential pattern in symptoms associated with mortality depending on depression severity.

9. *Is community-based prevention of late-life depression feasible?*

[Chapter 10] As case finding in late-life depression is generally poor, and optimal treatment would only partially reduce the disease burden of depression, two models for prevention of late life depression in community living elderly were presented. For reasons of cost-effectiveness an for ethical reasons, preventative measures should be targeted at subjects with a high risk of developing depression through exposure to multiple risk factors. A distinction was made between indicated prevention, in

subjects with early or subsyndromal symptoms, and selective prevention in persons who are at risk because they have been exposed to certain risk factors. Prediction models for the onset of depression were calculated in terms of Absolute and Relative Risk estimates, Numbers-Needed-to-be-Treated, and Population Attributable Fraction. It was found that subsyndromal symptoms of depression were associated with a risk of almost 40% to develop depression, an NNT of 5.8, and accounted for 24.6% of new cases. Adding more risk factors yielded higher AR, lower NNT, but also lower AF values. In the selective prevention model, persons who recently lost their spouse were at highest risk (AR 37%, NNT 5.3, AF 8.2%), a risk that became even higher if they also had a chronic medical illness. Considering costs and benefits of both models in the context of the availability of evidence-based preventative interventions, indicated prevention aimed at elderly persons with depressive symptoms is the preferred option. It was concluded that the exclusive focus on treatment of depressive disorder should be readdressed, and more attention should be given to the possibilities of prevention in psychiatry.

11.2 Methodological considerations

11.2.1 Sampling and non-response

The AMSTEL study is a prospective cohort study with an age-stratified, random sampling procedure enabling good representativeness of the community living population and its prevailing psychopathology. The sampling procedure was independent of the referral filters of health care (Goldberg & Huxley 1980) that introduce major biases in the clinician's impression of prevalence, clinical picture and course of major mental disorders such as depression (Cohen & Cohen 1984). Still, a number of potential sources of bias deserve a more careful description (Bouter & Van Dongen 2000;Sackett 1979).

First of all, selection bias may have affected the external validity of the study population. The sample was drawn from an elderly population living in the city of Amsterdam, excluding elderly persons living in institutions. Although their numbers are rather small compared to the whole population, generalisations towards hospital and institutionalised populations are of limited legitimacy. This can also be said for persons who were not sufficiently fluent in Dutch to understand the questions comprising the GMS-AGECAT interview. Ethnic minority groups and (immigrant) populations of non-Dutch origin are probably underrepresented in this study. Although the total number of older persons originating from these groups was rather limited at the time this study was started (Van Zee, Brinkman, & Vermeulen Windsant 1990), there has been a considerable increase over the last years, and recent data suggest that prevalence levels of depression may be substantially higher among these groups (van der Wurff et al. 2004). Generalisation is also hampered towards rural populations, who generally have lower levels of psychopathology than people living in large cities (Peen & Dekker 2003;Peen & Dekker 2004). As the subjects in this study were in the 65-84 age bracket, these results also have limited value for younger adults, and for the growing group of very old elderly (above 84 years).

Non-response patterns in the baseline sample revealed that non-response was associated with cognitive impairment and health problems in the younger old (<75), whereas in the older old (75-84 years) no correlates of non-response were found (Launer, Wind, & Deeg 1994). This indicates that the very frail were underrepresented in this study. The presence of clinically relevant depression, the core variable in this study, was however not associated with attrition to the baseline cohort.

Overall, these patterns are similar to what is found in other community studies, and, with the above limitations in mind, the sampling procedure resulted in a representative sample of community-living elderly that is among the largest cohorts of elderly individuals internationally.

11.2.2 Loss to follow-up

As was described in chapter 2.3, the total loss to follow-up was relatively large in this study. This was partly due to oversampling of the older old in order to obtain equally sized strata at follow-up. Not surprisingly, attrition was associated with higher age, male sex, lower education, chronic disease(s), disability and organic syndrome. As can be expected from these characteristics, a relatively large number of people had died during the first phase of the study period. Two studies in this thesis specifically investigated the associations between risk factors and excess mortality at 6 and 10 years follow-up, and found that depression carried an excess mortality risk. As data on vital status were almost complete, the mortality studies were not affected by any form of attrition bias. Apart from non-response because of death, 16.3% of the baseline sample refused further participation at 3-year follow-up. This is comparable to later studies such as the LASA study (Deeg et al. 2002). Multivariate analyses of non-response, excluding the deceased, revealed that only lower education, being unmarried and having an organic syndrome remained as predictors of all other types of attrition. Importantly, depression and generalised anxiety did not significantly affect response-rate at follow-up in multivariate analyses.

It can thus be concluded that people in less favourable socio-economic and social circumstances, people with chronic diseases, functional disabilities and cognitive decline, and men were relatively underrepresented at three year follow-up. This is a common finding in community based studies such as the AMSTEL study. Although the primary disorders under study and the whole array of potential risk factors were well represented in the study cohort, it cannot be ruled out that, especially in the very frail, associations between risk factors might have been somewhat different from the overall findings. A similar remark can be made about the studies on course types (Chapters 3 and 5) in which selective attrition of depressed subjects to the follow-up assessment of the study also occurred among the very frail. Depressed subjects with functional disabilities or cognitive impairment were more likely to be too ill to respond at follow-up. Most probably, the prognosis of depression in these subjects was even worse than in those who were still included the study at three-year follow-up.

In the studies on cognitive decline described in chapter 6, differential loss to follow-up may have somewhat affected the results. In the AMSTEL study, the overall proportion of subjects lost to follow-up was considerable, although not associated with baseline depression. In the LASA sample the overall loss to follow-up was smaller, but depressed subjects did have higher attrition rates than subjects without depression. As the main results were similar in both studies, it is unlikely that loss to follow-up could have accounted for the highly statistically significant results.

11.2.3 Information bias

Systematic measurement errors may lead to misclassification of variables. If misclassification is non-differential, the result may be an underestimation of the strength of the association between determinant and outcome. If misclassification is differential, measurement errors or differences in information retrieval are associated with the

value(s) of other variables under study. This may significantly influence the results by either over- or underestimating the strengths of associations, and thus affect the internal validity of the study.

As an example of this, a person may appear depressed during the interview, and as a result the investigator may be more inclined to elicit information about possible previous episodes of depression than in subjects whom the researcher believes not to be depressed ('diagnostic suspicion bias') (Bouter & Van Dongen 2000).

Information bias may also play a role on the side of the subject who is interviewed. Depressed subjects may report more negatively about their past, or about their current health status; this is called recall bias (Raphael & Cloitre 1994) or 'rumination bias' (Bouter & Van Dongen 2000). Another example could be that, in studies on gender differences in depression, women may be more inclined to report depressive complaints, and therefore show higher depression scores (Angst & Dobler-Mikola 1984).

Apart from these forms of report bias, cross-sectional studies may also show contamination, as the disorder under study is assessed at the same moment as its possible determinants. A determinant may then be misclassified as a risk factor for developing the disorder, whereas it is actually part of, or a result from the disorder under study.

All of these types of information bias may have affected the results. However, there are a number of arguments against a strong influence on the main findings. First of all, the design of this study, with a fixed set of questions in a fixed order, and psychiatric diagnoses made only after the interview by the computerised algorithm, make diagnostic suspicion bias less likely to occur. As many subjects who were found to be depressed were not recognised and diagnosed as such by the health services, and thus did not define themselves as 'officially depressed', recall bias was also less likely to have significantly affected the results. The possibility of women over-reporting depression is contradicted by the growing consensus that, both in the elderly (Sonnenberg et al. 2000) and in younger age groups (Wolk & Weissman 1995) higher levels of reported depressive symptoms in women reflect actual higher levels of this type of psychopathology in women. In chapter 7, which is concerned with sex differences, it is further argued that, if this type of bias had occurred, it would have led to an overcorrection in multivariate analyses.

The most important argument against these types of information bias however is the longitudinal design of the study, in which many of the determinants were measured before the outcome measure (incident depression, mortality) had occurred. Furthermore, interviewers at follow-up were not aware of answers that respondents had given at the first assessment. Report bias and contamination thus appears to be improbable explanations for the main findings of this study.

11.2.4 Confounding

Confounding is present when the observed association between a risk factor and an outcome is also independently determined by the presence of another factor that is etiologically, prognostically or otherwise (e.g. as a marker of vulnerability) related to that same outcome. If this factor is not corrected for, confounding may lead to either

over- or underestimation of the strength of an association. In order to qualify as a confounder, a risk factor (Bouter & Van Dongen 2000):

1 is an independent predictor of the outcome studied
2 is related to the risk factor under study
3 is not an intermediate factor in the causal relation between risk factor and outcome

The identification of confounders is not an easy task. First of all, the notion that a certain risk factor may act as a confounder has to come from our theoretical understanding of the etiology of the studied condition. Detecting confounding is mainly depending on having a good hypothesis. As good hypotheses are not as manifold as we would like them to be, it may well be that in the future, new factors will be 'discovered' as confounders that today seem completely trustworthy. Secondly, it may be hard to determine whether a factor is an intermediate between a risk factor and the onset of a disease, or an independent predictor. Thirdly, correcting for confounding is simply impossible if the potential confounders are not included in the study design.

The current study has a number of strengths that limit the possibility of confounding, but the above arguments illustrate that this can never be ruled out. Very importantly again, the AMSTEL study is a longitudinal study. The prospective design greatly facilitates the distinction between factors that co-occur with, or antedate and may possibly be etiologically or prognostically related to the object of study. This is a major advantage over cross-sectional studies in which it is impossible to make these distinctions. Another important characteristic of the study is that it incorporates a comprehensive set of risk factors associated with late-life depression. Almost all of the analyses described in this thesis were based on the notion that depression is a disorder determined by the interaction of a longstanding (genetic) vulnerability, a number of social influences and loss events, physical health, disability and, specific for the elderly, cognitive decline. Furthermore, multivariate analytic models were used to control for confounding, and possible interactions between risk factors were investigated. Examples of this approach are the tests for interaction and subsequent stratification according to gender in the studies on course type (Chapter 3) and mortality (Chapter 7), and according to different types of vulnerability (Chapters 2 and 3). Still, as will be discussed in more detail in paragraph 11.2.6, the current study did not include more specific biological and genetic parameters that may prove to be highly relevant to understand, and model the incidence and course of depression.

11.2.5 Measurement of depression

Depression was measured using a computerised version of the Geriatric Mental State schedule (GMS). The GMS was developed from the Present State Examination (Kendell et al. 1968) and the Present Status Schedule (Spitzer et al. 1964) by a group of British and American researchers that performed pilots in London and New York to assess validity and reliability in diagnosing psychopathology in elderly people (Copeland et al. 1976;Copeland, Dewey, & Griffiths-Jones 1986;Gurland et al. 1976). In line with the primary aims of the AMSTEL study, the GMS items relating to

depression, anxiety and cognitive disorders were incorporated in this study.

As GMS-AGECAT has proven reliability for epidemiological studies (Copeland et al. 1988;Hooijer, Jonker, & Dewey 1991), it was possible to validly diagnose large numbers of community living elderly through a computerised method with trained lay interviewers. Another advantage is, that AGECAT attributes levels of caseness signifying increasing severity levels of psychopathology with a clear distinction between cases and subcases. These rather unique diagnostic properties of GMS-AGECAT were well suited for the type of research questions investigated in the AMSTEL study.

Diagnosing depression using GMS-AGECAT also has a few disadvantages, especially when comparing with other diagnostic systems. First of all, diagnoses are calculated from individual item scores using a computerised algorithm known only to its designers. Although this enables valid comparisons between findings and interpretations of depressive symptomatology in different parts of the globe, there is very limited transparency as to how individual items are weighted in order to reach specific diagnoses. This is unlike other diagnostic and classification systems that are currently in use. A second limitation in comparing findings is that, although AGECAT does provide an assessment of depression severity, it does not diagnose Major Depressive Disorder according to DSM or ICD criteria. It is evident that concepts such as minor depression and subthreshold depression are highly relevant when assessing levels of psychopathology in community living elderly, but ideally it should also be possible to distinguish the most severe depressions according to internationally standardised criteria. Still, comparative studies have repeatedly shown that a diagnosis of depression according to GMS-AGECAT shows moderate to fair agreement with the combination of all diagnostic categories of depression according to DSM criteria (described in chapter 1 of this thesis) (Ames & Tuckwell 1994;Copeland, Dewey, & Griffith-Jones 1990;Lobo et al. 1995). Nevertheless, other authors have also stressed the need to be able to adapt the diagnostic threshold in the algorithm depending on the purpose of specific analyses (Schaub, Linden, & Copeland 2003).

11.2.6 Comprehensiveness of the data set

The AMSTEL study was a study on determinants of cognitive decline and depression. The implication of this is, that a relatively large amount of data on physical and cognitive functioning, including a number of cognitive tests, were available for the analyses. Other factors associated with depression, such as living situation / marital status and functional abilities were also included. Independent variables were measured using internationally established and standardised research instruments that are validated for a population of Dutch elderly. These data were obtained using established research instruments such as the CAMDEX-interview(Roth et al. 1986), the Mini-Mental State Examination (Folstein, Folstein, & McHugh 1975), the Activities of Daily Living (ADL) scale (Katz et al. 1963), and the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969).

A number of potential weaknesses of the data set deserve to be discussed here. One is, that the data on medical illnesses were obtained from the respondents themselves, and were not cross-checked with other sources. Ideally, we would have

checked the health status of all subjects with their general practitioners. Earlier studies have however found that patients' self-reports on selected chronic diseases are fairly accurate, with the exceptions of atherosclerosis and arthritis. Differences in reporting were reported to be non-differential with regard to depression status (Kriegsman et al. 1996).

Likewise, more detailed information on the personal and family history of depression or other psychiatric disorders would have yielded valuable additional information on course types and possibly on specific vulnerability profiles. It can not be ruled out that the fact that the associations between family history and depression were not statistically significant is a result of the way this information was obtained.

Another limitation is that data on current and former treatment of depressive disorder were rather crude. We did not obtain information on specific interventions and medication. If more specific data on treatment had been available, these may have demonstrated that subjects with more severe depressions received more intensive treatment. However, even if such data had been available, treatment allocation was not in any way randomised, and no conclusions could be drawn as to the potential beneficial effects of treatment on long-term prognosis and mortality in community living elderly. The low overall levels of treatment that subjects reported are in line with other findings among Dutch elderly (Sonnenberg et al. 2003) and elsewhere (Unutzer et al. 1997), and show that case-finding is still relatively poor in older persons.

The level of social support was determined with a question that would elicit answers on instrumental, rather than emotional support. Social support is often distinguished into instrumental and emotional/psychosocial support, and more elaborate designs and screening methods exist to define these different types of support. According to Cohen and Wills (Cohen & Wills 1985) a detailed assessment of the availability of interpersonal resources that are responsive to the needs elicited by specific stressful events is required to demonstrate a stress-buffering effect. Our question of whether a person receives 'help from family and/or others' mainly refers to instrumental support, which seems appropriate when faced with invalidating circumstances such as chronic illness or a decrease in functional abilities. More specific measures of emotional support might have shown even more pronounced buffering effects with respect to psychological distress and the association with the onset of depression (Tijhuis et al. 1995).

We did not obtain causes of death. As there is growing interest in the pathways between depression, medical conditions and survival described in chapter 8, it would have been highly informative to combine the current data with more specific information on causes of death. In the LASA study, it was found that suicide accounts only for a very small proportion of the excess mortality associated with depression (Penninx et al. 2001) whereas cardiac mortality was significantly increased. It is of considerable interest to examine whether these findings can be replicated in the AMSTEL study.

A number of other factors were also not included in the study that would, ideally, have been. In light of the recent developments in depression research, the most important missing information would be biological correlates of depression. Especially the functioning of the HPA-axis (Pariante 2003;Raison & Miller 2003) and

inflammatory processes (Penninx et al. 2003;Raison, Marcin, & Miller 2002) are rapidly gaining attention as potential determinants or correlates of depression. More detailed information on the functioning of the HPA-axis and inflammatory markers in our subjects would have been useful to develop a more comprehensive understanding of the psychological and biological correlates of depression, and the associations with onset, course and comorbidity with other illnesses. Chapter 8 gives an outline of the biological mechanisms that may be involved.

The same applies for data on the genetic profile of the respondents. A recent meta-analysis on the genetic epidemiology of major depression showed significant familial vulnerability due to additive genetic effects, with a heritability of 37% (Sullivan, Neale, & Kendler 2000). It was concluded that recurrence of depression still is the most important clinical marker of genetic/familial aggregation. However, it also showed strong support for individual-specific environmental effects (63% including measurement error) in the etiology of depression. In line with this, the current study has demonstrated the importance of longstanding vulnerability, exemplified by a previous history of depression, as a factor determining future relapses and a chronic course. Still, ideally it would have been of interest to investigate possible genetic vulnerability profiles in more detail, together with the information we did obtain on previous history and other risk factors for depression. Genes involved with the serotonin transporter system (Caspi et al. 2003) and the functioning of glucocorticoid receptors (Muller, Holsboer, & Keck 2002) have been suggested as possible candidates.

A third domain that was not included in this study is an assessment of personality structure. The availability of factors such as mastery, neuroticism and possibly the presence of personality disorders would have enabled investigating the interplay between life events or long term difficulties, coping style and the onset and course of depression.

Lastly, traumatic (loss) events early in life are another potential predictor of depression. These were also not included in our study and would possibly have differentiated our view on the nature of longstanding vulnerability (through earlier episodes of depression) that we found.

It can thus be concluded that the AMSTEL study incorporated a large, although not fully comprehensive, set of data that enabled the study of a relatively large number of aspects of late-life depression in a longitudinal design. The data set reflects the dominant concepts of determinants of depression at the time this study was started, and also adhered to rules of economy and pragmatism.

11.2.7 Statistical methods

The statistical significance of bivariate associations between risk factors and outcome was calculated using t-test, chi-2 test, anova, Mann-Whitney U test or logistic regression. As depression is the result of the interplay between a larger number of determinants, multivariate analyses were also performed, using logistic regression in risk factor studies and Cox proportional hazards models in the survival analyses. Chapter 8 and 9 use a hierarchical logistic regression model based on theoretical notions. The advantage of this method is that is shows the contribution of different sets of risk factors to the outcome of study (mortality) in a model that is build up stepwise and reflects the main hypothesis of the study. In other chapters (2, 4, 5, 9), parsimonous regression models were chosen to determine which of the risk factors under study showed the strongest associations with outcome. This for example enabled us to determine which symptoms of depression were specifically associated with excess mortality (chapter 9). Also in chapter 9, separate analyses were performed using symptom clusters that were based on both theoretical and statistical (factor analysis) arguments. Investigating both a statistically driven model and a model build on theoretical grounds can be seen as an acknowledgement of the fact that hypotheses may very well miss important associations that can be found with a non-hierarchical and purely statistically driven research method, and vice versa.

The studies described in this thesis have described the strength of the association between risk factors and outcome through odds ratios or relative risk estimates with 95% confidence intervals. In comparison with the 'traditional' p-value ($P<0.05$) dichotomising significant or non-significant results, confidence intervals help to determine the size of difference of a measured outcome between groups, rather than providing a simple indication of whether or not it is statistically significant (Gardner & Altman 1986).

Still, if one also attempts to study the importance of risk indicators for onset or course of disorder on a population level, more information is needed than just the strength of the association. It is necessary to know how many persons are exposed to a certain risk factor, in order to determine the scale of both the problem and of a possible intervention. This can be done by also providing the level of exposure to a risk factor in the population, also called Expected Event Rate (EER). By combining data on relative risk with the level of exposure to a risk factor in the population, the absolute risk of developing a disorder can also be calculated. If a certain risk factor shows a relative risk of 3.0, the chance that persons with this risk factor develop this disorder is three times higher than in persons without this risk indicator. However, if the EER, or baseline risk, is only 0.2%, the actual difference in the risk to develop depression is 'only' 0.4% (0.6-0.2). If the EER would be 10%, the absolute risk difference, with a similar relative risk, would be much greater, namely 20%, and this may lead to different decisions on whether or not to intervene. What counts for individual patients (and hopefully also for clinicians and researchers) is an absolute risk reduction through treatment or prevention. Also in health politics, the scale of health problems in terms of potential costs of illness and benefits of intervention are crucial. Another way to describe these matters is in terms of the Numbers Needed to be Treated (NNT) (Cook & Sackett 1995); how many persons with a certain risk indica-

tor should we treat in order to prevent one case? This approach, of which chapter 10 is an example, adds a public health dimension to epidemiological studies such as ours. By using these methods, target groups can be identified that may profit from specific preventative interventions.

11.3 Relevance and implications for clinical practice

The studies described in this thesis stress the importance of adequate, and timely recognition and treatment of late-life depression for a number of reasons.

First of all, late-life depression carries a high chance of becoming a chronic or chronic intermittent disorder. The NEMESIS study, a large longitudinal epidemiological study in younger adults in the Netherlands, has shown that at least 20% of depressed adults remained depressed for two years, and 43% of new depressions in the study period were relapses or recurrences in subjects with prior depressive episodes (Spijker et al. 2002). The natural history of depression in adults appears to be characterised by incomplete remissions, relapses, recurrences and chronicity and warrants timely interventions that should, ideally, be targeted to those subjects with a high risk of chronicity (Ormel et al. 1993;Spijker, de Graaf, Bijl, Beekman, Ormel, & Nolen 2002). Our data, and also recent findings from the LASA study (Beekman et al. 2002) and the NIMH Collaborative Depression Study (Mueller et al. 2004) suggest that in the elderly, the natural course may even be worse than in younger age groups. As effective treatment is available also in this age group, the arguments in favour of timely intervention are at least as pressing as in younger adults.

Still, as treatment in itself constitutes a considerable investment from both patient and the health care system, is would be of significant use if we were to know which patients would be most in need of treatment, considering their chances of spontaneous recovery or the development of chronic depression. As an advantage over earlier work, the studies described in this thesis have yielded a number of predictors of course type that may prove useful in distinguishing subjects at high risk for developing chronicity or other untoward consequences of depression. An important predictor of both onset and prognosis was a longstanding vulnerability, signified by a personal history of depression. Although this may not seem very surprising, earlier studies on the course of late life depression have often not been able to incorporate this risk factor (Cole 1990;Cole, Bellavance, & Mansour 1999). This finding underlines the clinical importance of a thorough patient history, including an assessment of earlier episodes of psychiatric illness if one is to make predictions for the individual patient. This is further underlined by the finding that, in depressed subjects without a previous history of depression and in depressed men, a chronic course is predicted by the presence of recent life stresses and disability. Actual life circumstances and health characteristics should therefore be taken into account when making projections about the prognosis of depression in an individual patient.

Psychiatric comorbidity, especially generalised anxiety disorder, was also found to be relevant from a clinical point of view. Subgroups with these characteristics deserve special attention from the health services in order to try and prevent the negative consequences of chronic depression. Subjects with mixed anxiety depression have more severe, and more longstanding depression with a poorer chance of

spontaneous recovery (chapters 4 and 5). This would, if replicated, justify a more systematic assessment of anxiety symptoms in elderly patients who present with depression. As elderly subjects with generalised anxiety were shown to develop either depression or mixed anxiety-depression relatively often, it could also be argued that adequate and timely treatment of generalised anxiety disorder may reduce the risk of further deterioration, especially in elderly women. However, the current data do not provide the detailed information one would ideally have in order to be able to decide after how many months the chance of spontaneous recovery would become so small that intervention is warranted. Studies with more frequent measurements are needed to assess these patterns in more detail.

In younger adults, maintenance treatment with antidepressants has been shown to reduce the overall relapse percentage from 41% (placebo) to 18% over a period of at least one year (Geddes et al. 2003). The potential benefits of continued treatment are larger in subjects with a higher risk of relapse. Although, to our knowledge, such data are not specifically available for the elderly, it can be expected that elderly subjects with the above characteristics may especially benefit from continued treatment of their depression. Still, the efficacy of interventions to reduce chronicity in older persons should also be demonstrated in Randomised Controlled Trials (Cairney 2004).

Risk profiles were also delineated for excess mortality. It was shown that overall, more severe and more chronic depressions are associated with excess mortality, suggesting a dose-response mechanism. The finding that depressive thoughts, and especially suicidal ideation and/or death wishes are associated with a higher mortality risk may also be of clinical relevance. Although we were not able to assess causes of death, earlier work in the LASA study (Penninx, Beekman, Honig, Deeg, Schoevers, van Eijk, & Van Tilburg 2001) and findings from other sources (Maris 2002) suggest that the excess mortality is not accounted for by a possible higher suicide risk only, but also by death through a number of other causes. These findings underline the importance of recognising such symptoms in elderly patients with depression.

As has been discussed in chapter 8, there is no consistent evidence that treatment of depression would reduce the associated excess mortality. Still, adequate treatment of depression in elderly subjects, with or without comorbid chronic illnesses, would be hard to advise against.

11.4 Public health implications

Late-life depression, and especially chronic depression, is associated with high levels of disability, functional decline, diminished quality of life, excess mortality, higher demands on caregivers and higher service utilisation (Charney et al. 2003). As has been stated in the introductory chapter, in comparison with other illnesses, depression accounts for the largest amount of non-fatal burden and for 12% of all years lived with disability worldwide (Ustun et al. 2004). A recent meta-analysis showed the overall costs of health care for elderly patients with physical illness to be 50% higher if a comorbid depression is present (Katon et al. 2003). These facts underline the importance of (late-life) depressive disorder for public health. Although depression is much less of a taboo subject in western countries than it was in earlier days, and received substantial attention from the media, preventative strategies have only recently come into focus in psychiatry (Beekman 2004;Cuijpers 2003). Considering the above, this may seem somewhat surprising. After all, if it were possible to prevent the occurrence of depression, or to intervene early in order to change the course of illness, this may have substantial impact for both the individual patient and the health care system. From an economic standpoint, prevention may also be much more cost-effective than actual treatment of the disorder (Smit et al. 2004). Chapter 10 shows how epidemiological data may further our understanding of persons at risk, and offer statistical models that may help to determine the possible health gains of different preventative strategies. Earlier studies described in chapter 2 and 4 have yielded risk factors associated with depression incidence. As case finding is poor, and the risk of chronicity considerable, the idea that this condition could be prevented using these risk indicators appears rather attractive. Future intervention studies may take into account these risk profiles when investigating the potential gains of various preventative measures in terms of a reduction in both the individual and societal burden of depression.

11.5 Theoretical implications

Although the Brown and Harris vulnerability-stress model elegantly integrated their findings and offered an attractive conceptual framework for the occurrence of depression and the interplay between stress and vulnerability factors, it is now becoming obvious that important determinants of depression were not included. Brown and Harris themselves published a paper in 1994, acknowledging that a (relatively small) group of patients with melancholic recurrent depression did not experience a severely threatening event before the onset of depression (Brown, Harris, & Hepworth 1994). They concluded that this might be an explanation for the variability of results in other studies on the association between life events and depression, as samples differed markedly in the numbers of first onset versus recurrent (psychotic) depressions. Brown and Harris suggested that the vulnerability-stress model would therefore apply to all patients except those with recurrent melancholia. Still, 'endogenous' depression, the recurrence of which is not necessarily preceded by threatening life events, was considered to be of limited importance on a population basis. Our

results seem to contradict this, as 29.4 % of subjects with depression at baseline, and 24.6 % of those with a depression at follow-up were shown to have a history of prior depression. In these subjects, both onset and persistence/chronicity of depression were not predicted by threatening events or difficulties. It was only in subjects with first onset depression that such associations could be demonstrated. A meta-analysis of all available studies on depression incidence in the elderly, in which the AMSTEL data were included, also yielded a personal history of depression as one of five remaining statistically significant predictors of onset (Cole & Dendukuri 2003). Of course, one has to take into account the fact that in a cohort of elderly, depression often has had a longer history than in the sample of much younger women studied by Brown and Harris, and it could be argued that the model was not designed to suit all age groups. However, data from cohort studies of younger adults also show that both onset and persistence (Spijker et al. 2001) of depression are in part determined by earlier (and longer) depressive episodes. This suggests that, next to social and psychological determinants of vulnerability, longstanding, most probably genetic vulnerability deserves a more prominent place in the model. As has been discussed in paragraph 11.2.4, another issue that has received little attention in the original vulnerability stress model are the pathophysiological changes underlying both depression and medical illnesses. Nevertheless, also at a later age the majority of depressive illness was found to be of recent onset and associated with actual life stresses that fit well into the vulnerability-stress model.

11.6 Directions for future research

A number of research areas are proposed here that would merit further study. The issue of comorbidity of depression with a large number of medical illnesses, and especially with ischemic heart disease is of high interest to medicine, especially in older patients with high levels of chronic illnesses. Depression is associated with higher incidence of somatic illnesses, with an untoward prognosis of these disorders, and with excess mortality. All of this can be taken to suggest that underlying mechanisms, or common pathways, are responsible for these phenomena. It is increasingly being recognised that vulnerability appears to cluster in individuals, with high levels of comorbidity of depression and medical conditions (Clarke & Kissane 2002;Gallo et al. 1997;Koenig 1997;Lyketsos et al. 2001). The concept of 'allostatic load' was introduced as a measure of the cumulative physiological burden exacted on the body through attempts to adapt to life's demands (McEwen 2002). A combined scale of dysregulations of different biological regulatory mechanisms was found to adequately predict mortality and declines in cognitive and physical functioning in elderly persons (Seeman et al. 2001). Chronic stress has been suggested as a common denominator to account for the dysregulations of various biological mechanisms that make people with depression of post traumatic stress disorder vulnerable to develop disease (McEwen 2003). As described in chapter 8, both the HPA-axis and inflammatory pathways may be involved. Indications for this come from clinical studies (Pariante 2003), and from animal studies in which genetic defects in the CRH limbic area are responsible for 'depression' in mice (Holsboer 2000;Muller, Holsboer, & Keck 2002). Recently it has been shown that epidemiologi-

cal studies may also find associations between depression and higher levels of inflammatory markers (Bremmer et al. 2004;Penninx, Kritchevsky, Yaffe, Newman, Simonsick, Rubin, Ferrucci, Harris, & Pahor 2003). Cognitive deterioration is also associated with higher levels of these markers (Engelhart et al. 2004), and depression may either proceed or co-occur with cognitive deterioration. Specific research questions for old age psychiatry would be whether these types of clustering of disorders can be associated with determinants of biological dysregulation, and whether (specific) biological mechanisms are associated with onset and course of late life psychopathology. The AMSTEL study may provide an interesting option, as blood samples have been drawn from a selected number of subjects with different levels of cognitive deterioration and depression.

Another aspect of comorbidity is that between depression and anxiety disorders. The studies in this thesis have shown that comorbidity stands for higher severity and longstanding vulnerability. Although Kendler's theory of 'same genes, different environments' could not be proven in the sense that specific risk factors were associated with either phenotype, patients with mixed-anxiety depression are suggested as a subgroup with high genetic vulnerability for depression and may prove to be a fruitful subject for further studies.

The studies on depression and excess mortality described in this thesis could be extended to include also causes of death. This could provide relevant additional information on possible pathogenic mechanisms explaining the association between (onset and course of) depression, medical illnesses and survival, and would be even more interesting if biological markers are included in the analyses. Furthermore, recent findings in the LASA study suggest that anxiety disorders are also associated with a higher mortality risk in men (van Hout et al. 2004). Replication of this in the AMSTEL study seems appropriate, taking into account the different severity and comorbidity levels of generalised anxiety disorder and depression.

Drawing from the findings of chapter 10, which delineates profiles of subjects with specific vulnerability to develop depression, it is of the utmost importance to start and test preventative measures that may reduce the number of actual cases of depression. As outlined, more elaborate work is needed in order to develop evidence-based and cost-effective preventative strategies aimed at subjects with a high risk of developing depression.

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Summary

Summary "Epidemiology of Late Life Depression; Longitudinal findings from the Amsterdam Study of the Elderly (AMSTEL)"

In younger adulthood as well as in later life, depression is associated with a diminished quality of life, significantly higher levels of disability, functional decline, demands on caregivers and service utilization. With a prevalence of 13.5% in older persons, the importance of depression in terms of both individual suffering and public health is uncontested. As the population in western countries is rapidly ageing, adequate recognition and, if possible, prevention of the negative consequences of late-life depression is a major public health issue. Studies in the community may provide knowledge on prevalence, course and risk profiles of 'common' types of psychopathology that do not reach through the consecutive filters in health care up to the specialist level of psychiatry.

The Amsterdam Study of the Elderly (AMSTEL) is a longitudinal study among 4051 inhabitants of Amsterdam between the age of 64 and 85, with a three-year follow-up. AMSTEL was designed to study incidence and course of dementia or cognitive impairment, depression and generalised anxiety disorder in elderly people living in the community.

The primary aims of this thesis were to study late-life depression and its longitudinal associations, keeping in mind the "vulnerability-stress model", that clusters variables according to their role in a causal model of the development of depression. In this model, depression is a result of the interplay between stress factors, such as loss events, and a wide array of endogenous/genetic, social and health related characteristics. Keeping in mind the specific characteristics of later life and the vulnerability-stress paradigm, consecutive chapters describe the factors associated with onset of late life depression, the natural course and the associations of risk factors with course types, comorbidity patterns and temporal associations between depression and generalised anxiety disorder, and between depression and cognitive decline, and the associations of depression with excess mortality. The final study presents a research agenda for prevention of depression in primary care according to vulnerability characteristics of community living older persons.

In Chapter 2 the question is put forward whether, in line with the vulnerability-stress concept, depression is the result of 'social stress' factors such as partner loss, relocation and (the occurrence of) chronic diseases or disability, and whether the influence of these is modified by the vulnerability or protective factors distinguished in this study. Higher age, personal history of depression, death of spouse, health related factors and comorbid organic or anxiety syndrome showed significant associations with depression incidence in bivariate analyses. Genetic/familial vulnerability and organic vulnerability did not modify the association between the investigated stress factors and incident depression. Vulnerability by environmental factors, did act as effect modifier. This can be taken as modest support for the vulnerability-stress hypothesis to model the incidence of depression.

Chapter 3 describes the natural course of depression, assesses whether risk factors related to incidence of late-life depression are also related to prognosis, and investigates whether a vulnerability-stress model can also be established for the course of late-life depression. It was concluded that depression often has a chronic course (50%), and that an important predictor of chronicity was a personal history of depression. In subjects without a personal history, more recent life stresses were related to prognosis. Comparing the risk profile for chronicity between sexes, it was found that in women, the development of chronicity was more strongly associated with a personal history than in men, whereas in men recent psychosocial and health related characteristics were more important than in women. The risk profile for depression onset differs from that associated with the development of chronicity, in the sense that chronicity is associated with both longstanding vulnerability and gender.

Chapter 4 reports on a cross-sectional study of risk patterns and comorbidity of depression and generalised anxiety disorder. It was shown that comorbidity of depression and generalised anxiety disorder increases with higher severity levels of either category. Pure depression, pure generalised anxiety disorder or mixed anxiety-depression did not show different associations with risk factors, but longstanding vulnerability showed significantly stronger associations with mixed anxiety-depression than with pure anxiety and pure depression. Comorbidity was twice as likely in women than in men. It was concluded that in the elderly, a dimensional classification is more appropriate than a categorical classification of depression and generalised anxiety.

Chapter 5 describes the course types of pure depression, pure generalised anxiety disorder and mixed anxiety-depression and investigates whether different risk profiles can be distinguished for onset in a prospective design. Remission rates were poor for subjects with mixed anxiety-depression (27%). A pattern of temporal sequencing was established, with anxiety often progressing to depression or mixed anxiety-depression. Onset of depression and mixed anxiety-depression were predicted by loss events, ill health and functional disability. Onset of pure generalised anxiety, and more strongly that of mixed anxiety-depression, was associated with longstanding, possibly genetic vulnerability. It was concluded that, in comparison with either pure depression or pure anxiety, mixed anxiety-depression represents more severe and more chronic psychopathology, associated with longstanding vulnerability.

Chapter 6 examines whether depression may be indicative of subsequent cognitive decline and Alzheimer's disease in older adults with normal cognition. The research question was investigated in two independent samples of older people with normal cognition: AMSTEL and the Longitudinal Aging Study Amsterdam (LASA). In both studies depression was associated with an increased risk of subsequent AD and cognitive decline respectively, but only among subjects with higher levels of education. In a subgroup of more highly educated older persons, depression may be an early manifestation of AD before cognitive symptoms become apparent, rather than a psychological reaction to subjective and subclinical memory cognitive complaints.

Chapter 7 examines the association between depression and excess mortality according to different severity levels of depression and according to gender, control-

ling for potential confounders. It was found that neurotic (mild) depression was associated with a higher mortality risk in men only, whereas psychotic (severe) depression was associated with significant excess mortality in both sexes. In the elderly, major depressive syndromes thus appear to increase the risk of death in both sexes, whereas mild depressive syndromes only show this association in men.

Chapter 8 provides a review article examining mechanisms that may theoretically be responsible for the excess mortality associated with depression. Depression affects behaviour in the sense that depressed patients show more unhealthy living habits, less compliance with medical treatment, and a higher number of accidents and suicides. Biological correlates of depression such as dysregulation of the neuroimmune system; hyperactivity of the HPA-axis, and autonomic dysregulation may all have a negative effect on both the prognosis of somatic illnesses and longevity. Although the literature suggests that treatment of depression positively affects some biological parameters, it remains unclear whether successful treatment of depression may lead to better survival.

Chapter 9 then further examines specific characteristics of depression and associations with excess mortality. Both moderate and severe depression predicted 10-year mortality also after multivariate adjustment. Chronic depression was associated with a significantly higher mortality risk compared to non-depressed subjects, suggesting a dose-response relationship. Somatic depression items were predictive of excess mortality in the full cohort, regardless of the presence of clinical depression. In subjects with depression, only depressive thoughts were specifically associated with excess mortality, albeit in opposing directions. Subjects with suicidal ideation were at higher risk to die, whereas guilt showed a protective effect relative to the other depression symptoms.

Chapter 10 is an attempt to determine which older individuals are at high risk to develop depression, in order to develop a rational model to guide preventative measures to reduce the incidence of depression. A distinction was made between indicated prevention, in subjects with early or subsyndromal symptoms, and selective prevention in persons who are at risk because they have been exposed to certain risk factors. Prediction models for the onset of depression were calculated in terms of Absolute and Relative Risk estimates, Numbers-Needed-to-be-Treated, and Population Attributable Fraction. In the indicated prevention model, subsyndromal symptoms of depression were associated with a risk of almost 40% to develop depression, an NNT of 5.8, and accounted for 24.6% of new cases. Adding more risk factors raised the AR up to 49.3%, with a lower NNT (3.2), but also lower AF values. In the selective prevention model, loss of spouse showed the highest risk (AR 37%, NNT 5.3, AF 8.2%), a risk that became even higher if subjects also had a chronic illness. Considering costs and benefits of both models in the context of the availability of evidence-based preventative interventions, it was concluded that indicated prevention aimed at elderly persons with depressive symptoms is the preferred option.

Chapter 11 discusses the main findings, methodological considerations, and the merits and limitations of the studies. From this study it can be concluded that late life depression is a common disorder, associated with both concurrent life stresses and long-term vulnerability, that often has a chronic course. Depression is often co-occurring with other disorders, both somatic and psychiatric, and comorbidity repre-

sents more severe disorder and a poorer prognosis. The association between depression and excess mortality was confirmed in a community sample and further explored, but more research is needed on possible underlying mechanisms. The last study finishes with the conclusion that the exclusive focus on treatment of depressive disorder should be readdressed, and more attention should be given to the possibilities of prevention in psychiatry. The thesis thus has a relatively optimistic (although not 'happy') ending.

Samenvatting

Samenvatting "Epidemiologie van depressie bij ouderen; longitudinale bevindingen van de Amsterdam Study of the Elderly (AMSTEL)"

Dit proefschrift gaat over depressie. Depressie zoals die voorkomt bij thuiswonende ouderen. Het gaat om vormen van depressiviteit die veelal niet door de gezondheidszorg als zodanig worden herkend en behandeld, maar waar ouderen wel veel nadeel van kunnen ondervinden. Negatieve effecten van depressie zijn o.m. een slechtere kwaliteit van leven, een toename van beperkingen en handicaps in het dagelijks functioneren, een verhoogde belasting voor de omgeving, en een toegenomen gebruik van medische en andere voorzieningen. In vergelijking met andere ziekten, ook lichamelijke, blijkt depressie wereldwijd zelfs de belangrijkste aandoening wanneer wordt gekeken naar het aantal jaren dat mensen leven met beperkingen als gevolg van die aandoening.

Over depressie is al veel bekend. Er zijn verschillende behandelingen met medicatie en met psychotherapie waarvan de effectiviteit uitgebreid is onderzocht en vastgesteld. Dan gaat het veelal over de ernstigste vorm van depressie, de zogenaamde 'depressie in engere zin' volgens het classificatiesysteem van psychiatrische aandoeningen, de DSM-IV. Deze komt voor bij ongeveer 2% van de van de ouderen. Het blijkt echter dat depressieve symptomen veel vaker voorkomen dan deze percentages suggereren. Verder is gebleken dat de negatieve effecten van depressie ook bij deze 'mildere' vormen van depressie, met minder symptomen dan de depressie in engere zin, worden gevonden. Bij ouderen heeft volgens deze definitie ongeveer 13.5% procent van de bevolking een depressie die het leven in ongunstige zin beïnvloedt, die 'klinisch relevant' is, en (therapeutische) aandacht behoeft.

Net als andere aandoeningen komt depressie vaker voor bij mensen met een familiaire, waarschijnlijk genetisch bepaalde kwetsbaarheid. Omgevingsfactoren, en psychologische factoren spelen echter ook een grote rol. Omgevingsfactoren zijn dingen die mensen overkomen, zoals verlies van een dierbare, of het krijgen van een chronische ziekte, maar ook de steun die iemand krijgt vanuit de omgeving. Psychologische factoren zijn bijvoorbeeld karakter- of persoonlijkheidstrekken die van invloed zijn op de manier waarop mensen tegenslagen verwerken. Ook speelt een rol of mensen eerder in hun leven grote verliezen hebben geleden, of traumatische ervaringen hebben meegemaakt. Het blijkt dat dergelijke ervaringen de vatbaarheid voor depressie op latere leeftijd verhogen. Wanneer wordt gepoogd om het ontstaan van depressie in kaart te brengen, wordt vaak een stress-kwetsbaarheid model als uitgangspunt genomen. Hierin vinden zowel uitlokkende factoren (stressoren) zoals verlieservaringen en gezondheidsaspecten, als kwetsbaarheidfactoren zoals een familiaire aanleg, of het ontbreken van een sociaal netwerk, een plaats. Depressie kan dan worden gezien als de resultante van de interactie tussen dergelijke factoren. In dit proefschrift wordt regelmatig gerefereerd aan het stress-kwetsbaarheid model.

Wanneer depressie bij ouderen wordt onderzocht, is het van belang om iets te

zeggen over de specifieke risicofactoren voor depressie in deze leeftijdsgroep. Er is sprake van het verlies van dierbaren, verlies van sociale rollen (o.a. werk), een afname van sociale steun en een toenemende kans op vereenzaming. Verder hebben ouderen veel meer lichamelijke ziektes (64% van de ouderen in de leeftijd van 65-74 jaar heeft een chronische ziekte) en de kans op cognitieve achteruitgang neemt sterk toe na het 65e levensjaar. Dit is geen hoopgevende beschrijving van de oude dag, en het is gelukkig ook niet zo dat men hier automatisch depressief van wordt. Toch is het voor de bestudering van depressie van belang dat de verdeling van risicofactoren in de bevolking op oudere leeftijd verschilt van die bij jongere volwassenen. Opvallend is verder dat depressie vaak samen voorkomt met andere aandoeningen zoals lichamelijke ziekten en andere psychiatrische aandoeningen. Dit wordt co-morbiditeit genoemd, en er zijn aanwijzingen dat patiënten bij wie dit speelt een ongunstiger prognose hebben. Er is veel discussie over de afgrenzing van depressie met angststoornissen, en over de overlap met lichamelijke ziekten en cognitieve achteruitgang. Aangezien psychiatrische aandoeningen veelal gedefinieerd worden door een combinatie van verschijnselen die geen van allen uniek zijn voor die specifieke diagnose, is het niet eenvoudig daar harde uitspraken over te doen.

Bij de start van deze studie was nog niet heel veel bekend over met name de milde depressie zoals die wordt gevonden in de bevolking. Wat zijn aanleidingen om een depressie te krijgen, hoe is het natuurlijk beloop, hoe hangt depressie bij ouderen samen met andere aandoeningen, en beïnvloedt depressie de levensduur? In deze dissertatie wordt, deels aan de hand van het stress-kwetsbaarheidsmodel, onderzoek beschreven naar verschillende aspecten van depressie bij ouderen.

De AMSTEL studie

In 1990 en in 1994 vond een groot bevolkingsonderzoek plaats onder 4051 thuiswonende ouderen in Amsterdam. Alle respondenten werden thuis bezocht door getrainde interviewers. Doel van het onderzoek was het in kaart brengen van een scala aan demografische, somatische en psychiatrische gegevens van deze ouderen. De onderzoeksinstrumenten waren: de electronische versie van de Geriatric Mental State Examination (AGECAT), met daarin alle items betreffende affectieve, angst- en organische stoornissen, de Mini-Mental State Examination, de Activities of Daily Living (ADL) schaal en de Instrumental Activities of Daily Living (IADL) schaal, en het CAMDEX-interview, dat onder andere informatie verschaft over somatische ziekten. Het GMS-AGECAT systeem stelt diagnosen van organische en depressieve aandoeningen. De diagnose dementie werd ook nog bevestigd in een apart diagnostisch onderzoek. In 1996 en in 2001 werden verder bij de burgerlijke stand de overlijdensgegevens verkregen van de gehele oorspronkelijke onderzoekspopulatie.

Het AMSTEL project gaat uit van de vakgroep psychiatrie van de Vrije Universiteit Amsterdam en is ingebed in het onderzoeksprogramma van het EMGO instituut. Het onderzoek werd financieel ondersteund door het S.G.O, programma (Stimulering Gezondheidszorg Onderzoek) vanuit het ministerie van VWS, dit liep af in 1994. Sindsdien wordt verder onderzoek gefinancierd via projectsubsidies van o.a. het Nationaal Fonds Geestelijke Volksgezondheid, en N.W.O.

Onderzoeksvragen

Hoofdstuk 2 beschrijft een onderzoek naar mogelijke subtypen van depressie, te weten; 1) de vroeg ontstane depressie die al eerder in iemands leven is opgetreden, een chronisch beloop heeft gekregen en samenhangt met een genetische/familiale kwetsbaarheid, 2) de laat ontstane depressie als gevolg van bij de oudere levensfase behorende stressfactoren (bv. overlijden van partner, vereenzaming, ziekte) en 3) de laat ontstane depressie die samenhangt met organische stoornissen en cognitieve achteruitgang. Nagegaan werd welke factoren leiden tot depressie, en of een stress-kwetsbaarheid mechanisme kon worden aangetoond waarbij mensen met een reeds bestaande kwetsbaarheid sneller depressief worden als de belasting (stress) toeneemt. Het bleek dat hogere leeftijd, een voorgeschiedenis van depressie, verweduwing, een slechtere gezondheid en cognitieve of angststoornissen ieder waren geassocieerd met het ontstaan van depressie. Het kon echter niet worden aangetoond dat genetische/familiale kwetsbaarheid en organische kwetsbaarheid leidden tot een verhoogd ontstaan van depressie bij toename van de belasting (effect modificatie). Wel bleek dat de omgeving hierop van invloed was; mensen met een partner, en alleenstaanden met sociale steun, werden minder vaak depressief bij negatieve gebeurtenissen zoals het ontstaan van chronische ziekten en handicaps. Zij leken dus weerbaarder te zijn in tijden van tegenspoed. Er werd dus enige steun gevonden voor het stress-kwetsbaarheidsmodel in dit onderzoek.

Hoofdstuk 3 gaat in op de vraag naar het beloop van depressie bij ouderen. Het bleek dat ongeveer 50% van de depressies een chronisch beloop heeft. Tevens werd onderzocht of het risicoprofiel voor ontstaan van depressie hetzelfde is als die voor een ongunstig beloop (chroniciteit). Gezien de negatieve effecten van met name de chronische depressie, kan inzicht in voorspellers van beloop belangrijke praktische consequenties hebben. Geconcludeerd werd dat een voorgeschiedenis van depressie een sterke voorspeller is van een chronisch beloop, andere risicofactoren vielen daarbij in het niet. Alleen bij patiënten met een recent ontstane depressie, zonder een voorgeschiedenis, bleken ongunstige levensomstandigheden en gebeurtenissen van invloed te zijn op een ongunstig beloop (chroniciteit). Ook werd een vergelijking gemaakt tussen depressie bij mannen en vrouwen, o.m. omdat in de literatuur steevast hogere prevalenties van depressie bij vrouwen worden gevonden. Het zou kunnen dat depressie bij vrouwen minder snel opknapt (vaker chronisch wordt), en een ander risicoprofiel heeft. Een verschil in het percentage chroniciteit werd niet gevonden. Het bleek wel dat chroniciteit bij vrouwen vooral samenhing met een voorgeschiedenis van depressie, terwijl bij mannen een chronische depressie werd voorspeld door actuele ongunstige levensomstandigheden.

Hoofdstuk 4 gaat in op de verschillen en overeenkomsten tussen depressie en de gegeneraliseerde angststoornis. In de literatuur is veel discussie over de vraag of dit verschillende aandoeningen zijn, of wellicht verschillende dimensies van eenzelfde ('onderliggende') stoornis. Er werd onderzoek gedaan naar de overlap tussen gegeneraliseerde angst en depressie, naar mogelijke specifieke risicofactoren, en naar verschillen en overeenkomsten in beloop. In dit hoofdstuk wordt aangetoond dat de overlap tussen deze twee psychische aandoeningen sterk toeneemt bij toenemende

ernst van beiden. Tevens werd vastgesteld dat er weinig verschillen waren in risicofactoren voor het ontstaan van 'pure' depressie, 'pure' gegeneraliseerde angststoornis, en de mengvorm, de zogenaamde 'mixed anxiety-depression'. Wel bleek dat een voorgeschiedenis sterk is geassocieerd met de (ernstigste) mengvorm van beide stoornissen. Overlap kwam verder bij vrouwen veel vaker voor dan bij mannen. Geconcludeerd werd dat een dimensionele classificatie van angst en depressie, waarin angst en depressie in elkaars verlengde liggen, beter bij deze bevindingen past dan de huidige categorale, waarin ze als wezenlijk verschillende stoornissen worden gedefinieerd.

Hoofdstuk 5 beschrijft vervolgens het beloop van pure depressie, pure generaliseerde angststoornis, en de mengvorm, en richt zich tevens op de vraag of verschillende risicofactoren geassocieerd zijn met ontstaan en beloop van deze verschillende diagnostische categorieën. De gemengde vorm bleek in maar 27% van de gevallen te zijn opgeknapt na drie jaar, en had daarmee een duidelijk ongunstiger beloop dan pure angst of depressie. Verder bleek dat de angststoornis in de tijd weinig stabiel is, en vaak overgaat in een depressie. Voorspellers van het ontstaan van depressie en 'mixed anxiety-depression' waren verlieservaringen, een slechte gezondheid en functionele beperkingen. Een voorgeschiedenis van depressie en/of angst bleek wederom vooral het ontstaan van de mengvorm in hoge mate te voorspellen. Vastgesteld werd dat, in vergelijking met pure depressie en pure angst, 'mixed anxiety-depression' een ernstiger en meer chronisch verlopende stoornis is, die sterk samenhangt met een al langer bestaande kwetsbaarheid.

Hoofdstuk 6 gaat in op de mogelijke relaties tussen depressie en cognitieve achteruitgang. De vraag was of depressie bij ouderen zonder meetbare geheugenstoornissen vooraf gaat aan het ontstaan van de ziekte van Alzheimer. Deze vraag werd onderzocht in de AMSTEL studie, en in de LASA studie (Longitudinal Aging Study Amsterdam), eveneens een grote Nederlandse bevolkingsstudie onder ouderen. In beide studies bleek depressie geassocieerd te zijn met een verhoogd risico op het optreden van M.Alzheimer, maar alleen bij ouderen met een hoger opleidingsnivo. Een verklaring hiervoor zou kunnen zijn dat depressie een psychologische reactie is op cognitieve achteruitgang die al wel door de (toekomstige) patiënt wordt opgemerkt, maar nog niet meetbaar is bij een cognitieve test. Dit leek om verschillende redenen minder waarschijnlijk. Eerder lijkt depressie een biologische samenhang te vertonen met dementie. Het effect van opleiding zou kunnen liggen in het feit dat dementie bij patiënten met een hoger opleidingsnivo in een verder gevorderd stadium is wanneer een cognitieve functietest afwijkingen laat zien dan bij mensen met minder opleiding. Dit wordt de 'cognitieve reserve hypothese' genoemd; mensen met een hoger opleidingsnivo hebben meer reservecapaciteit die kan worden aangesproken voordat het cognitieve functioneren er duidelijk zichtbaar onder gaat lijden.

Hoofdstuk 7 beschrijft een onderzoek naar het verband tussen depressie en een verhoogd overlijdensrisico, gemeten 6 jaar na de start van het onderzoek. Uit studies onder patiënten in het algemeen ziekenhuis is gebleken dat een bijkomende depressie een verhoogde kans geeft om te overlijden. Daarbij ging het veelal om de meest ernstige vorm van depressie (depressie in engere zin). Het was de vraag of dit verband ook bestaat bij de mildere depressie die in de bevolking veel vaker voorkomt. Ook waren er tegenstrijdige bevindingen over verschillen tussen mannen en

vrouwen waar het gaat om de relatie tussen depressie en overleving. In deze studie werd nagegaan het verband tussen depressie en sterfte afhankelijk is van de ernst van de depressie, en of dit verschilde tussen mannen en vrouwen. Hierbij werd gecontroleerd voor andere mogelijke oorzaken van een vervroegd overlijden. Gevonden werd dat mildere depressies geassocieerd waren met een verhoogd overlijdensrisico bij mannen, terwijl de ernstiger depressies bij beide seksen een verhoogde sterftekans te zien gaven.

Hoofdstuk 8 gaat verder in op mogelijke verklaringen voor het gevonden verband tussen depressie en sterfte. Diverse mechanismen kunnen dit verband verklaren. Op het gebied van het (ziekte) gedrag is depressie geassocieerd met ongezonde leefgewoonten, een slechtere therapietrouw en een hoger aantal ongelukken en suïcides. Ook biologische aspecten van depressie, zoals neuro-immuun dysregulatie, HPA-as hyperactiviteit en sympathoadrenerge dysregulatie, betrokken bij onder meer de stressreacties en de afweer, kunnen verantwoordelijk zijn voor het ongunstige beloop van lichamelijke ziekten en de verhoogde sterftekans. Hoewel gunstige effecten van behandeling van depressie bij (somatische) patiënten zijn beschreven, is nog onduidelijk of de overleving hierdoor wordt beïnvloedt. Geconcludeerd werd dat zowel met depressie verbonden gedrag, als verstoringen in de neuro-immuun regulatie factoren zijn die het verband tussen depressie en sterfte kunnen verklaren. Verder onderzoek is noodzakelijk naar het voorkomen en de onderlinge beïnvloeding van depressie en lichamelijke ziekten, naar mogelijke pathogenetische verbanden die aan beide typen aandoeningen ten grondslag liggen, en naar de effecten van behandeling van depressie op de biologische ontregelingen en de overleving.

Hoofdstuk 9 onderzoekt in meer detail het verband tussen depressie en sterfte, gebruik makend van de gegevens van het 10-jaars beloop. Wederom bleken ernstiger depressies, maar ook chronische depressies (beide metingen depressief) een hogere overlijdenskans te geven, wanneer werd gecorrigeerd voor andere mogelijke doodsoorzaken. Er lijkt dus een dosis-respons relatie te bestaan tussen de hoeveelheid depressie en de verkorting van de levensduur. Ook werd gekeken naar symptoomprofielen, vanuit de gedachte dat 'biologische' depressiesymptomen (zoals slaapstoornissen) zouden kunnen verschillen van psychologische symptomen (zoals suïcidale gedachten) in de associatie met een verhoogd overlijdensrisico. Dit zou een aanwijzing kunnen geven voor het achterliggende mechanisme. Het bleek dat somatische/biologische symptomen op zich sterfte voorspelden, ook wanneer mensen niet aan de criteria voor een depressie voldeden. Het bleek echter dat bij mensen met een depressie vooral de depressieve gedachten geassocieerd waren met een verhoogde kans op overlijden. Patiënten met suicidale gedachten en doodswensen hadden een verhoogde kans om te overlijden. Bij patiënten met veel schuldgevoelens bleek die kans juist kleiner te zijn. Geconcludeerd werd dat psychologische symptomen belangrijke voorspellers waren van overlijden. Het herkennen van doodswensen, of 'niet meer verder willen', lijkt dus van groot belang om patiënten met een verhoogd risico te identificeren.

Hoofdstuk 10 onderzoekt de mogelijkheid van preventie van depressie. Uit ander onderzoek, maar ook uit de AMSTEL studie, is gebleken dat de herkenning en behandeling van depressie in de bevolking niet optimaal is. Verder mag worden aangenomen dat, zelfs wanneer iedereen met een depressie optimaal behandeld zou

worden, niet meer dan 1/3 van de ziektelast ten gevolge van depressie zou kunnen worden weggenomen.

Het is dus verstandig om na te gaan of depressie voorkomen kan worden. Hiertoe werden twee modellen gemaakt met als doel zoveel mogelijk toekomstige depressies te voorspellen aan de hand van relatief simpele, goed herkenbare risicofactoren. In het 'selectieve preventie model' werden personen met een verhoogde kans op het krijgen van een depressie geïdentificeerd aan de hand van blootstelling aan risicofactoren zoals een slechte lichamelijke gezondheid, functionele beperkingen, verlieservaringen e.d. Het 'geïndiceerde preventie model' omvat tevens zogenaamde subsyndromale symptomen, dit zijn symptomen van depressie die te licht zijn om al van een stoornis te kunnen spreken. De sterkte van het verband tussen risicofactoren en het ontstaan van depressie werd op verschillende manieren berekend. Per (combinatie van) risicofactor(en) kan worden aangegeven hoe groot de kans is dat iemand met die kenmerken depressief wordt (bijvoorbeeld 40% bij mensen met subsyndromale symptomen). Tevens kan worden berekend hoeveel van de nieuw ontstane depressies kunnen worden toegeschreven aan die specifieke risicofactor(en). Dat geeft een idee van het belang van een risicofactor voor de volksgezondheid. Ook kan worden berekend hoe groot de kans is op succes, wanneer men middels preventie het effect van een risicofactor zou kunnen blokkeren. Dat wordt uitgedrukt in Number-Needed-to-be-Treated; het aantal mensen dat moet worden behandeld om 1 succes te behalen (hoe lager de NNT, hoe effectiever de interventie). Als laatste is van belang om na te gaan welke 'evidence-based' preventieve interventies op dit moment beschikbaar zijn voor de verschillende risicofactoren. Wanneer in een model deze aspecten in samenhang worden bekeken, blijkt dat het geïndiceerde preventiemodel de meeste toekomstige patiënten identificeert, met de gunstigste balans tussen kosten en baten van preventie. Overigens; de daadwerkelijke effectiviteit van een dergelijke onderneming moet nog middels gerandomiseerd gecontroleerd onderzoek worden aangetoond.

Hoofdstuk 11 omvat een overzicht van de belangrijkste bevindingen, de methodologische overwegingen en de beperkingen van de in deze dissertatie beschreven studies. Er is veel gezegd over de ernst, het ongunstige beloop, de oversterfte en de relatie met andere aandoeningen. Toch eindigt het proefschrift met een relatief optimistisch pleidooi voor verder onderzoek naar preventie. Gesteld wordt dat de exclusieve focus op (onderzoek naar) het behandelen van stoornissen in de psychiatrie kritisch bekeken zou moeten worden. Wellicht is de kosten/baten afweging op individueel en populatienivo veel gunstiger wanneer vroeger in het ontstaan van een stoornis geïntervenieerd kan worden.

Curriculum Vitae

Robert Schoevers, MD, PHD, was born in 1962. He attended medical school at the University of Amsterdam (Academic Medical Centre) and obtained his medical degree in 1990. He specialised as a psychiatrist at the Amsterdam Vrije Universiteit (1997). His thesis (cum laude) was on the epidemiology of late life depression. A 'Master in Epidemiology' degree is expected in december 2006.
He is currently working as director of program training in a large psychiatry teaching hospital in the centre of Amsterdam, and is also affiliated with the department of psychiatry of the VU University Medical Center Amsterdam. His research topics include the epidemiology of depression and the outpatient treatment of depression. He is currently developing a collaborative research program in 'metropolitan psychiatry' consisting of epidemiological and intervention studies of patients with severe mental disorders in an urban environment. He is a member of the board of the Dutch Association of Psychiatry subsection on administrative psychiatry. Apart from scientific articles, he also wrote and directed a number of educational video programs on general medical and psychiatric topics.

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