Depression and comorbidity

General practice-based studies on occurrence and health care consequences

Jasper Nuijen

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Contents

1 Introduction

This thesis is about the co-existence of depression with other health conditions or, to put it briefly, about comorbidity involving depression. It consists of two main parts. The first part presents three studies that concentrate on the occurrence of comorbidity involving depression. In the second part of the thesis, three studies are presented that deal with the health care consequences of the co-occurrence of depression with other health conditions. Before presenting the focus and content of the thesis in more detail the key concepts depression and comorbidity as well as the relevance of comorbidity involving depression will be described.

1.1 Depression and comorbidity

Defining depression

Depressed mood and loss of interest or pleasure are commonly considered the most typical symptoms of depression. In addition, several other symptoms are indicative of depression, such as fatigue or lack of energy, weight change, disturbed sleep, feelings of excessive guilt, agitation, impaired concentration, and recurrent thoughts about death and suicide. In order to be diagnosed with depression (major depression) according to the criteria of the prevailing psychiatric classification system, the Diagnostic Statistical Manual of Mental Disorder (DSM), a person must have one or both of the core symptoms (depressed mood and loss of interest/ pleasure) together with at least four other symptoms for at least two weeks [1]. In addition, the symptoms must cause clinically significant impairment in functioning or distress. A number of other depressive syndromes are distinguished in DSM-IV, among which is dysthymic disorder, a chronic but less severe form of depression. The classification system also includes provisional diagnostic criteria for minor depression, which correspond to the criteria for major depression, except that fewer symptoms are required. Various other criteria have been used to define depressive syndromes that fail to meet the diagnostic threshold for major depression [2]. In the remainder of the introductory text these will be referred

to as subthreshold depression.
Most studies presented in this thesis are based on morbidity data recorded by Dutch general practitioners (GPs). The International Classification of Primary Care [3] is the standard coding system for morbidity used in Dutch general practice, based on the criteria of the third edition of the International Classification of Health Problems in Primary Care [4]. To be diagnosed with depression according to the ICHPPC-2-Defined, one must have at least three of the following six symptoms: (1) sadness or melancholy more than can be explained by psychosocial stress; (2) suicidal thoughts or attempt; (3) indecisiveness, decreased interest in usual activities or diminished ability to think; (4) feelings of worthlessness, self-reproach, or inappropriate/ excessive guilt; (5) early morning wakening, hypersomnia, or early morning fatigue, and (6) anxiety, hyperirritability, or agitation. As compared to the DSM-IV criteria for major depression, a lower number of symptoms is required, which in addition do not necessarily have to be present for a minimum duration of two weeks. Also, a clinical significance criterion is lacking. Accordingly, a broader definition of depression than the standard psychiatric diagnostic definition is being applied in this thesis. A proportion of the persons who are diagnosed with depression by their GP will suffer from dysthymic disorder or subthreshold depression [5].
Since research on depression diagnosed by GPs is relatively scarce, drawing from the extensive literature on major depression, and, to a lesser extent, that on dysthymic disorder and substhreshold depression is essential to lay a foundation for the rationale of the thesis.

Relevance of depression
Major depression has often an early age of onset and a remitting and recurring nature. For instance, a nationally representative survey of psychiatric morbidity in the U.S. showed that in most cases major depression presents for the first time between the age of 19-44 years [6]. Another U.S. study indicated that nearly three quarters of people aged 15-54 years who had ever fulfilled criteria for major depression had suffered from more than one episode [7]. Using data from the only nationally representative psychiatric morbidity survey conducted in the Netherlands to date, the Netherlands Mental Health Survey and Incidence Study (NEMESIS), it has been estimated that Dutch adults meeting criteria for major depression will experience on average about seven

depressive episodes during their lifetime [8]. The duration of major depressive episodes varies widely and follows an asymmetric distribution that is skewed to the right [9]. The NEMESIS study showed that half of affected Dutch adults aged 18-64 years achieved remission within three months, while 20% were still depressed after two year of follow-up [10]. Noteworthy, a substantial proportion does not reach full remission, but suffers from residual symptoms, thereby having an increased risk of relapse [11-12].

It is well established that major depression is associated with substantial functional disability and loss of quality of life. The impact on functioning is wide-ranging, including occupational, social and physical areas of functioning [13-14]. Functional status tends to be restored after remission from a major depressive episode [15], although improvement in functioning may lag behind clinical remission [16]. Being an important correlate of functioning, it is not surprising that self-perceived quality of life is also decreased in major depression [17]. Depressed persons' appraisal of both mental and physical aspects of their current life is worse than that of their non-depressed counterparts, although mental aspects of quality of life have, understandably, been found to be affected to a greater extent [18]. Overall, the degree of impaired functioning and quality of life associated with major depression appears similar to, if not greater than, the level of impairment associated with common chronic somatic disorders [19]. Major depression also seems to shorten the lifespan [20-21]. The increased risk of dying cannot solely be explained by the high rate of suicide among depressed persons [22], but also appears to be related to other factors such as the more unhealthy lifestyle behaviours of depressed persons, their increased risk for being non-adherent to medical treatment recommendations or the direct pathophysiologic effects of depression [23].

The burden of major depression is not only significant at the individual level, but also at the societal level. First of all, major depression is very common. In the Netherlands, it is estimated that major depression afflicts approximately 700,000 people aged 18 years and older every year [24]. The NEMESIS study showed a one-year prevalence of major depression of 5.7% for adults aged 18-64 years. It should be noted that about half of the persons affected annually in this age-group are first-ever cases of depression [25]. Major depression is less prevalent among older persons [26]. Its high prevalence, substantial impact on functioning and quality of life, early onset, relatively long average episode duration, and impact on premature mortality altogether result in major

depression being ranked as one of the most burdensome disorders worldwide in terms of disability-adjusted life years [27]. The same is true when focusing on the Netherlands [28]. Furthermore, it is evident that the economic burden of major depression is substantial [29-30]. The high costs are primarily the result of the increased use of health care services by depressed persons and their greater risk of being absent from work and being less productive at work [31]. The higher level of health care use associated with depression is pervasive, and includes a higher utilization of primary and specialized medical care, more emergency room visits and a greater number of (antidepressant and non-antidepressant) drug prescriptions [32].

All in all, the significance of major depression is clear. Although examined less frequently than major depression, studies point out that dysthymic disorder also is a condition associated with substantial clinical and societal burden [19; 33-38]. Indeed, dysthymic disorder and major depression frequently co-occur [39], a phenomenon referred to as "double depression". Furthermore, evidence is accumulating that subthreshold depression is also clinically and economically relevant [40]. Subthreshold depression is a highly prevalent condition and it has been indicated that a substantial proportion of affected persons experience an unfavourable course [7; 41]. Some will develop major depression given that subthreshold depression has been shown to be a clear risk factor for subsequent major depressive episodes [42]. In addition, subthreshold depression appears to be associated with impairments in functioning, including work impairment, and loss of quality of life [43-45], increased mortality [20], higher use of health care services [46-47], and considerable costs [48].

Defining comorbidity

Four decades ago, the term comorbidity was first coined by Feinstein and he defined it as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" [49-50]. Since its introduction the concept of comorbidity has received increasing attention, not only in research on chronic somatic diseases, but also in psychiatry research, and has evolved in various directions [51-53]. Consequently, numerous definitions of comorbidity have been presented in the literature through the years [54-58]. Basically, all these definitions have in common that they are about patients with a certain index condition who have

or develop one or more other health conditions in a specific time span.* This thesis deals with comorbidity involving depression: in all studies presented an index condition is being appointed, being either depression or a health condition that co-occurs with depression.

In the course of time, several attempts have been made to classify comorbidity. A parsimonious classification is proposed by Van den Akker and colleagues, which is based on the more elaborate categorization of Schellevis[59]. Three categories of comorbidity are being distinguished in this classification[51; 60]:

1 *concurrent* (or *simple*) comorbidity:
The co-occurrence of an index condition with another health condition whether coincidental or not;

2 *cluster* (or *associative*) comorbidity:
The co-occurrence of an index condition with another health condition at a significantly higher rate than expected by chance;

3 *causal* comorbidity:
The causal mechanism underlying the co-occurrence of an index condition and another health condition is known (e.g. ischaemic heart disease and pheripheral disease).

This is a hierarchical classification. Obviously, all instances of comorbidity fulfil the definition of concurrent comorbidity. Some of these comorbidities will occur in numbers greater than expected by chance and hence should be classified as cluster comorbidity. Some of those statistically significant comorbid associations represent known causal relationships and should be defined as causal comorbidity.

Comorbidity research

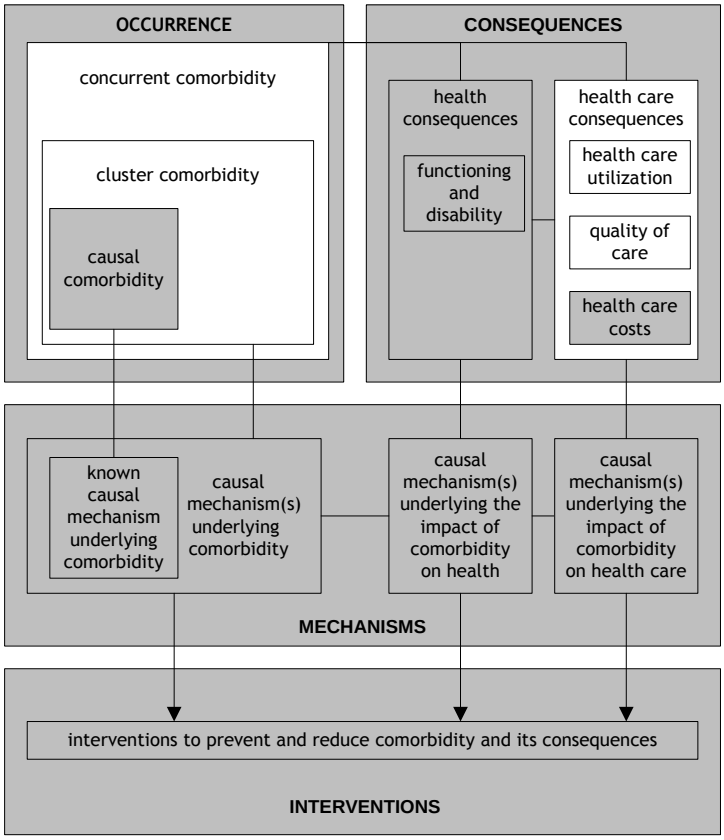
Research on comorbidity, and accordingly research on comorbidity involving depression, can be divided into four broad research areas (see Figure 1): (1) the occurrence of comorbidity; (2) the consequences of comorbidity for health, health care and society; (3) the causal mechanisms underlying the occurrence of comorbidity and its consequences; and (4) the study of interventions to prevent or reduce the occurrence of comorbidity and its associated burden.

* Comorbidity can be distincted from multimorbidity. In the study of multimorbidity the interest is on the co-occurrence of health conditions without appointing an index condition [51].

In general, knowledge of the occurrence of comorbidity is important for clinical practice, health care planning, and for generating new hypotheses for research [61-62]. Clinically, data on the occurrence of comorbid relationships may raise awareness among health care providers of the potential presence of comorbidities in (specific) patient groups, which may facilitate early diagnosis and treatment of comorbid conditions. Information about the pattern of comorbidity in various patient populations can also serve as an important indicator of their health care needs, thereby being relevant for the planning and organisation of health care services. Finally, comorbidity profiles may form a basis for hypothesis-driven research on the causal mechanisms underlying the co-occurrence of health conditions. In this respect, identification of cluster comorbidity, i.e. when an index condition and another health condition occur in combination more often than expected, is of vital interest because concurrent comorbidity represents an index condition and another health condition that co-occur simply by chance, while causal comorbidity implies an already known causal relationship.

A second major research area concerning comorbidity is the study of its associated burden on health, health care, and society [63]. For patients, their relatives, and health care providers, it is important to know whether comorbidity adversely impacts health, for example, by means of increasing the likelihood of poor prognosis, functional impairment and loss of quality of life, and whether it negatively influences the quality of care provided. Such knowledge is also relevant for health care planning and organisation, together with data on the effect of comorbidity on health care utilization and costs. To get a full picture of the economic burden of comorbidity, its consequences for occupational functioning need to be included. Finally, the study of the consequences of comorbidity might generate hypotheses about the mechanisms that underlie the adverse impacts of comorbidity. Noteworthy, whether comorbidity influences health and health care may not be dependent on whether comorbidity represents coincidental or causal co-occurrence. Consequently, all three categories of comorbidity, i.e. concurrent, cluster and causal comorbidity, are relevant when studying the impact of comorbidity [64].

Figure 1 The four main research domains of comorbidity. Uncoloured parts indicate research areas that are being addressed in the thesis



Unravelling the causal mechanisms underlying occurrence of comorbidity and its negative effects on health and health care, the third main research area regarding comorbidity, is vital with respect to the development and refinement of interventions to prevent and reduce comorbidity and its associated burden. As noted above, cluster comorbidity forms a useful starting point from which "etiologic" research can test specific hypotheses about the causal mechanisms that underlie the occurrence of comorbidity. Basically, a certain index condition and another health condition may co-occur more often than expected because (a) the index disease, directly or indirectly, causes or contributes to the development of the comorbid health condition; (b) the comorbid condition, directly or indirectly, causes or contributes to the development of the index disease; and/or (c) both the index disease and comorbid health condition arise from the same underlying cause or risk factor [56; 65-67]. Indeed, with regard to research on the causal mechanisms underlying consequences of comorbidity the focus is not solely on cluster comorbidity, but also on concurrent and causal comorbidity, since these categories of comorbidity can have important impacts on health and health care.
The final major research area of comorbidity is the study of the (cost-) effectiveness of interventions to reduce or prevent comorbidity and its associated burden. These studies may contribute to more (cost-)effective health care.

The relevance of comorbidity involving depression
In the past decade, large-scale studies have established that depression is a highly comorbid condition. Major depression and dysthymic disorder frequently co-occur with each other and with other mental disorders in the general population [39; 68-69] and the primary care population [70-72]. According to the NEMESIS study, for instance, about half of Dutch persons aged 18-64 years with major depression in the past year also experienced an anxiety disorder in the same period [73]. Depression also frequently co-exists with chronic somatic illnesses. Studies indicate that between 47% and 80% of primary care patients with current major depression, dysthymic disorder, or subthreshold depression also suffer from a chronic somatic condition [71; 74]. Conversely, comorbid depression is common in somatically ill patients. For instance, a large-scale health survey of the adult Canadian population found that the annual prevalence of major depression in persons reporting one or more long-term

medical conditions was about 9%, more than twice the prevalence among those not reporting a chronic condition (4%) [62]. Also, various population-based studies using a depression rating scale rather than a diagnostic instrument for major depression, have shown that older individuals with a chronic somatic illness generally have more depressive symptoms than those without a chronic illness [75-78]. Altogether, ample evidence now exists to conclude that depression with comorbidity is the rule, not the exception. This is nicely exemplified by a recent study that examined both psychiatric as well as somatic comorbidity in depression instead of focusing on one "type" of comorbidity [71]. It was found that only 12% of depressed primary care patients had no comorbidity, that is, had no other psychiatric disorder or chronic somatic illness at the same time.

Comorbidity involving depression is also relevant because it is associated with increased personal and societal burden. Studies in the community and the primary health care setting have found that patients suffering from both depression and anxiety have more severe symptoms overall, poorer prognosis, higher rates of chronicity and relapse, increased suicide risk, more functional impairment, greater decrements in quality of life, as well as an increased likelihood of psychiatric hospitalization compared with patients with either disorder alone [79-83]. A similar picture of increased burden emerges from research examining the impact of comorbidity of depression with chronic somatic illnesses. The course of major depression tends to be more protracted in the context of somatic illness [84]. Moreover, a considerable body of evidence points to the adverse impact of comorbid depression in patients with chronic somatic illness [57; 85]. In general, the presence of major depression and depressive symptoms in chronically ill patients have both been found to be associated with increased somatic symptom burden, additive functional impairment, greater loss of quality of life and decreased adherence to self-care and treatment regimens [67; 86-88]. Also, both major depression and depressive symptoms have been suggested to increase the risk of death from somatic conditions such as coronary heart disease and diabetes mellitus [89-91]. Furthermore, comorbid depression has been associated with increased health care utilization and increased absence from work among chronically ill patients [67; 92-96]. Given these observations it is not surprising that studies have found major depression and subthreshold depression both to be associated with markedly increased health care costs, which cannot be explained by the presence of chronic somatic conditions [32; 97].

1.2 Focus and content of the thesis

Although there exists considerable evidence for its relevance, substantial knowledge gaps about comorbidity involving depression remain. This thesis addresses two sets of research questions to extend knowledge about the co-occurrence of depression with other health conditions. The first set of questions pertain to the research domain of the occurrence of comorbidity involving depression (Part A) and the second set of questions relate to the research area of the health care consequences of comorbidity involving depression, specifically consequences for quality of care and health care utilization (Part B) (see Figure 1).

Study data

The studies presented in this thesis are mainly based on data collected within the framework of the second Dutch National Survey of General Practice (DNSGP-2) [98-99] and the National Information Network of General Practice (LINH) (www.linh.nl). LINH was established in 1992 and its database holds longitudinal data on morbidity, prescribing and referrals from a large, representative network of general practices located throughout the Netherlands. Data are extracted twice a year from the electronic medical records systems used by the GPs to record and store information about their patients. Morbidity data concern diagnoses made by GPs during consultations with patients as well as those made by other health care professionals after referral, coded by GPs according to the International Classification of Primary Care (ICPC-1) [3]. The LINH network served as the 'backbone' of the DNSGP-2 which was largely carried out in 2001. During the study period of the DNSGP-2, LINH data collection was temporarily expanded to include, among others, a socio-demographic census of the total population of approximately 385,000 patients registered with the 104 participating practices (response rate: 77%) and the administration of a structured psychiatric diagnostic interview, the Composite International Diagnostic Interview (CIDI) [100], to a sample of about 800 patients from this population (selected by a two-stage sampling procedure).

Part A. Studies on occurrence: research questions addressed

While the occurrence of psychiatric comorbidity in depression has been well-studied in general population samples [39; 68-69; 73], few large-scale population-based studies have examined the pattern of somatic comorbidity in depression. Especially, the identification of chronic somatic illnesses that occur at a rate that exceeds chance, i.e. somatic cluster comorbities, has not often been a topic of research. As pointed out above, ascertaining somatic cluster comorbidity is relevant for clinical practice, health service planning, and generating hypotheses about the aetiology of comorbid relationships between depression and chronic somatic illnesses. It is essential to study cluster comorbidity in a heterogeneous population to avoid bias producing "spurious" cluster comorbidity [101]. Dutch general practice provides a good opportunity to study the pattern of somatic cluster comorbidity in a largely unselected sample of depressed persons. Almost all Dutch noninstitutionalized citizens are registered with a GP. Moreover, in the Netherlands, GPs act as a gatekeeper to other health care facilities. After referral, specialists report back results to the patient's GP. GPs have therefore comprehensive knowledge about the health status of their patients. *Chapter 2* reports on a large cross-sectional study that uses GPs' records of morbidity to answer the following research question:

> *What are the patterns of somatic and psychiatric cluster comorbidity in depression, stroke, multiple sclerosis, Parkinson's disease/ parkinsonism, dementia, migraine and epilepsy?*

Merely determining with which chronic somatic conditions depression tends to co-occur at a rate that is higher than expected is valuable but not sufficient. Information on the temporal order of the relationship between depression and a chronic somatic illness is a critical indicator of possible underlying causal mechanisms [57]. Causal processes that may operate include depression being a contributing factor to the development of the somatic illness or, conversely, the somatic illness being causative of or contributing to the development of depression [67]. In the former case, the onset of depression generally tends to precede the onset of the somatic illness, while in the latter case the development of depression will generally occur after the onset the somatic disease. A theory on the causal role of somatic illness in the development of depression that has received considerable attention in the last decade is the "vascular depression hypothesis", which postulates that cerebrovascular

disease may cause or exacerbate depression with late onset in life [102-103]. Evidence supporting this hypothesis may derive from longitudinal epidemiological studies that demonstrate an association between established risk factors for cerebrovascular disease, such as hypertension, diabetes mellitus and heart disease, and the subsequent development of depression. The premise is that the increase in prevalence of cerebrovascular risk factors (CVRFs) with age contributes over time to the development of small-vessel brain disease, which, in turn, disrupts neurobiological functioning resulting in depression [104-105]. Longitudinal research on the relationship between CVRFs and late-life depression is scarce, however. *Chapter 3* contains a case-control study that further tests the vascular depression hypothesis by addressing the following research question:

> *Is there a relationship between cerebrovascular risk factors (CVRFs) and the subsequent development of depression in older general practice patients?*

Part A finishes with a systematic review. It is important to determine whether the occurrence of comorbid depression in the context of a certain index condition varies depending on sociodemographic and clinical variables. In this way, subgroups of patients with the index disease under study can be identified who are at greatest risk for comorbid depression. Such information may improve the quality of care by means of earlier diagnosis and treatment of comorbid depression. It could also serve as an indicator of treatment need which is relevant to the planning and organisation of health care services and give clues to the underlying mechanisms of the comorbid relationship. In general, however, there exist critical gaps in this type of knowledge [85]. An example concerns the correlates of comorbid depression in Alzheimer's disease (AD). Although it is well-known that depression occurs frequently in patients with AD [106], it remains unclear whether the prevalence of comorbid depression increases, decreases or remains stable with increasing severity of AD [107]. This lack of clarity is not caused by a lack of research. On the contrary, various, mainly cross-sectional, studies have reported on this relationship, but their results are equivocal. *Chapter 4* describes a systematic review of these cross-sectional studies to address the following research question:

> *Is there a relationship between severity of AD and prevalence of comorbid depressive symptoms and depression?*

Part B. Studies on health care consequences: research questions addressed

Consequences for quality of care

The focus is laid on the influence of the presence of other health conditions on the diagnosis and management of depression in Dutch general practice. In the Netherlands, like various other countries, GPs have an important position in the care for persons with depression [108-109]. The majority of depressed persons first consult their GP. Moreover, after being diagnosed as depressed, many will be managed exclusively in general practice, with only a minority being referred to mental health services [110-111].

It is well-established that a substantial proportion of persons with depression are not diagnosed as such by their GP [112-113]. A variety of factors have been found or hypothesized to influence diagnosis of depression in the primary care setting, among which are the presence of comorbid somatic and psychiatric disorders. Studies have suggested that being chronic somatically ill increases the risk of not being diagnosed as depressed. Other studies indicate that the presence of co-existent anxiety exerts an opposite effect and facilitates diagnosis of depression. However, research carried out so far investigated the effects of somatic and psychiatric comorbidity on depression diagnosis separately and did not address their combined effect, despite the fact that a considerable proportion of primary care patients have both types of comorbidity [71]. Therefore, the study described in *chapter 5* attemps to answer the following research question:

> *Is there an interaction effect between psychiatric and chronic somatic comorbidity on diagnosis of depression by GPs?*

As in GPs' diagnosis of depression, there appears to be room for improvement in the adequacy of management of depression by GPs. That is, available evidence points to suboptimal management of depression in the primary care setting, meaning that too often either no treatment is initiated at all or that treatment provided is inadequate (e.g. because of insufficient dosing and/or duration of antidepressant therapy) [113-115]. Whether this less-than-optimal management of depression is associated with the presence of specific chronic somatic illnesses has only been scarcely studied. Most primary-care based studies used a composite measure of chronic somatic morbidity. In *chapter 6* a

prospective study is presented in which two research questions are being addressed:

> *What is the influence of specific chronic somatic conditions on the initiation of any depression care in patients newly diagnosed with depression by their GP?; and*
>
> *Among those being prescribed antidepressants by their GP, what is the influence of these conditions on prescription of continuous antidepressant treatment?*

Consequences for health care utilization

Comorbid depression among somatically ill patients is associated with a higher use of both outpatient and inpatient general (i.e. somatic) health care services [67; 92-95]. There is, however, a notable lack of data on the potential influence of time of onset of depression on this relationship. For instance, in prospective studies of the association between comorbid depression and health care use of patients admitted to hospital for somatic illness, presence of depression was usually assessed in the first week of admission to a hospital [93]. It remains unclear from these studies which proportion of patients were already depressed at the time of onset of (the complications of) their somatic illness leading to hospital admission and which proportion developed their depression afterwards, and whether this characteristic influences health care utilization. Knowledge on the potential role of time of onset of depression is relevant because it could point to possible mechanisms that underlie the increased health care use among hospitalized patients with comorbid depression, which may subsequently help to develop intervention strategies to reduce their use of health care services. *Chapter 7* presents a study that focuses on patients who are already depressed when admitted to a hospital for stroke. Although the influence of comorbid depression on the health care use of patients hospitalized due to stroke has received some attention [116-117], no study to date has focused specifically on patients with pre-existing depression. The following research question is addressed:

> *What is the impact of having pre-existing depression at hospital admission for stroke on the length of acute hospital stay and discharge destination?*

This opportunity became available by linking data from the LINH database with data from a national longitudinal hospital database, the National Medical

Register (www.prismant.nl).

The final chapter, *chapter 8*, summarizes the study findings, and reflects on their relevance for further research and clinical practice, while considering the strengths and weaknesses of the studies.

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Part A

Studies on occurrence

2 Comorbidity was associated with neurologic and psychiatric diseases: A general practice-based controlled study

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Abstract

Background and objective: To comprehensively examine comorbidity in unselected cohorts of patients with depression, stroke, multiple sclerosis (MS), Parkinson's disease/parkinsonism (PD/PKM), dementia, migraine, and epilepsy.
Methods: This cross-sectional study used morbidity data recorded by Dutch general practitioners. Index disease cohort sizes ranged from 241 patients with MS to 6,641 patients with lifetime depression. Thirty somatic and seven psychiatric disease categories were examined to determine whether they were comorbid with the index diseases by performing comparisons with age- and gender-matched control cohorts. Identified comorbidities were classified as either ''possible'' or ''highly probable'' comorbidity.
Results: An extensive range of 26 disease categories was found to be comorbid with lifetime depression. The comorbidity profile of stroke was also wide, including 21 disease categories. The comorbidity patterns of migraine and epilepsy comprised each 11 disease categories. Those concerning MS, PD/PKM, and dementia included a small number of disease categories.
Conclusion: This study provides comprehensive knowledge of the occurrence of somatic and psychiatric comorbidity in general populations of patients with depression, stroke, MS, PD/PKM, dementia, migraine, and epilepsy. The implications of the findings for clinical practice and research are discussed.

2.1 Introduction

Comorbidity, defined as any additional coexistent condition in a patient with a particular index disease [1], has been shown to be a common phenomenon, especially in the older population [2-3]. The phenomenon of comorbidity is relevant because it has in general a negative impact on health outcomes, quality of life, and health care use [4]. Knowledge about the comorbidity of major neurologic and psychiatric diseases like stroke, multiple sclerosis (MS), Parkinson's disease/parkinsonism (PD/PKM), epilepsy, migraine, dementia, and depression is limited. For each of these index diseases, relatively few studies have examined the occurrence of comorbidities while addressing an extensive range of conditions. Most studies have focused on the association between a neurologic/psychiatric index disease and one (e.g. stroke-depression [5]) or a restricted set [6-9] of conditions. Furthermore, studies have mainly concentrated on either somatic [10-12] or psychiatric [13-15] comorbidity, with only a few investigating both types of comorbidity. In addition, most of the studies that have comprehensively examined occurrence of somatic or psychiatric comorbidity did not use a control group and/or were not population based [10-26]. Including a control group for comparison is essential to identify comorbid associations beyond chance. Examining comorbidity in population-based samples is important to minimize the effect of referral bias. Generally, studying samples from secondary or tertiary care settings will probably bias comorbidity findings towards more severe and atypical forms of neurologic and psychiatric disease. The present study used general practice data from The Netherlands to elaborate on previous studies on comorbidity associated with neurologic/psychiatric index diseases. The Dutch general practice setting provides a good opportunity to identify comorbidity among a comprehensive range of somatic and psychiatric conditions for a heterogeneous cohort of patients with a particular index disease. In The Netherlands general practitioners (GPs) act as a gatekeeper to health care facilities. Patients visit their own GP before possible referral to specialist care. Almost all noninstitutionalized Dutch inhabitants are listed to a GP. By being the entry point of the Dutch health care system, GPs come across an almost full morbidity spectrum. Furthermore, after referral, specialists report back results, by which GPs have comprehensive information about a patient's health

status. Using morbidity information recorded by GPs, this cross-sectional study aimed at identifying comorbid disease categories among unselected cohorts of patients with seven different neurologic/psychiatric index diseases, namely depression, stroke, MS, PD/PKM, dementia, migraine, and epilepsy. These index diseases were prioritized in health research in The Netherlands because of their high prevalence, high disease burden, and/or high health care burden [27]. A wide spectrum of somatic and psychiatric disease categories was examined. Comorbid disease categories were identified by comparing rates of disease categories in patients with a particular neurologic/psychiatric index disease with those among matched controls without that index disease.

2.2 Methods

Study setting and morbidity data

The present study utilized morbidity data from a population of 276,921 persons registered with 134 GPs who worked in 75 general practices. Data were collected within the framework of the second Dutch National Survey of General Practice (2001) [28]. The practice population was representative of the Dutch population in terms of age, gender, and type of health insurance. The morbidity data were extracted from the electronic medical records systems of the participating GPs and comprised: (1) diagnoses made by the GPs during contacts with their patients during a 1-year period, and (2) diagnoses recorded by the GPs on so-called ''problem lists'' of relevant health problems of patients, including relevant past health problems. Diagnoses were coded by the GPs according to the International Classification of Primary Care (ICPC) [29] based on the criteria of the International Classification of Health Problems in Primary Care [30]. Different contacts for a same health problem during the contact registration were clustered into episodes of disease and a distinction was made between newly occurring and ongoing (prevalent) episodes.

Study population

Seven index disease cohorts of patients diagnosed with depression, stroke, MS, PD/PKM, dementia, migraine, and epilepsy, were established on the basis of morbidity data from the contact registration and problem lists. Specifically, an

index disease cohort consisted of patients who were diagnosed with a prevalent episode of that index disease according to the contact registration and/or who were diagnosed with that index disease according to the problem list. The specific ICPC codes used were: P76 (depression), K90 (stroke), N86 (MS), N87 (PD/PKM), P70 (dementia), N89 (migraine), and N88 (epilepsy). Noteworthy, this ''lifetime'' cohort definition did also include patients who were diagnosed with an index disease in the past only. The rationale for using a lifetime definition was that for all index diseases, except for depression, the cohorts include patients actually suffering from these diseases or its sequelae due to their persistent nature. A lifetime definition was also used for depression because depression has been found to have a recurrent course in the majority of primary care patients [31]. Nonetheless, a substantial number of patients diagnosed with depression in the past only may not suffer from recurrent, chronic depression. Therefore, as a sensitivity analysis, we examined also comorbidity in a ''current'' depression subcohort consisting of patients who were diagnosed with depression during the observation year. A total of 13,106 patients were selected, of which 12,422 patients were diagnosed with one of the index diseases under study, while 684 patients were diagnosed with two (5%) or more (0.2%) index diseases. The latter patients were included in two or more different index disease cohorts. The cohort sizes ranged from 241 patients with MS to 6,641 patients with lifetime depression. Data regarding gender and age were derived from the practice administration. For each neurologic/psychiatric index disease cohort, 10 control cohorts were randomly selected with replacement from all subjects who were not diagnosed with that specific index disease. Each control cohort was frequency- matched to the index disease cohort concerned for gender and age distribution (categorized into 20 age groups).

Disease categories

Thirty-seven disease categories were examined to determine whether they were comorbid with any of the neurologic/ psychiatric index diseases under study, including 30 somatic and seven psychiatric disease categories. The disease categories comprised a total of 213 ICPC codes (Appendix). For each index disease and control cohort, the occurrence of a disease category was determined by identifying the number of cohort members who had been diagnosed with (at least one of) the condition(s) included in that disease

category according to the contact registration and/or their problem list. Diagnoses from the contact registration concerned only prevalent episodes.

Statistical analyses

For each of the 37 disease categories, multilevel logistic regression analysis was carried out to compare the occurrence of the disease category in a cohort of neurologic/psychiatric patients with the occurrence among a cohort of control subjects. Multilevel analyses were performed because of the two-level structure of the data (i.e. practice level and patient level), thus allowing us to adjust for variation among general practices (e.g. variation regarding registration discipline). In addition, analyses took into account consultation with GP during the contact registration year (represented by a dummy variable: 0 vs. ≥1 contacts) to control for the opportunity to have a health condition diagnosed. As was often the case in the MS cohort and sometimes in other index disease cohorts, the number of cases in an index disease cohort and/or control cohort with a comorbid condition was too small for meaningful analysis. In these cases and when appropriate, a multilevel regression analysis without the covariate GP contact was carried out. Analyses were performed using the MLwiN software version 2.0. Statistical significance was accepted at the 5% level. Each analysis was repeated 10 times, each time using a different control cohort. In this way, the consistency of the outcomes resulting from using 10 different, randomly sampled control cohorts could be examined, thereby avoiding coincidental findings resulting from accidental abnormal characteristics of a control group. The choice of ten sampled control groups was based on other methods that try to control for random error using different samples, like multiple imputation [32,33]. Associations between a neurologic/ psychiatric index disease and a disease category for which at least 6 out of the 10 comparisons resulted in a statistically significant odds ratio (OR) were considered to indicate comorbidity. Identified comorbidities were classified as either highly probable comorbidity (i.e. 9 or 10 significant ORs) or possible comorbidity (i.e. 6 to 8 significant ORs). It should be noted that also statistically lower than expected prevalences of disease categories among patients with a particular index disease could be identified. For convenience, such inverse associations between an index disease and disease category were also termed comorbidity. To present the results in a convenient manner, an estimation of the average OR was calculated for each association between an

index disease and disease category:

$$\text{Average OR} = \exp\left(\frac{\sum_{i=1}^{10} \beta_i}{10}\right)$$

where β_i are the regression coefficients resulting from the 10 index disease cohort–control cohort comparisons. In addition, an estimated 95% confidence interval (CI) of the average OR was calculated using an estimated average standard error (SE):

$$\text{Average SE} = \sqrt{\frac{\sum_{i=1}^{10} SE_i^2}{10}}$$

where SE_i are the SEs resulting from the 10 index disease cohort–control cohort comparisons.

Noteworthy, the pooling of the individual SEs in this way is conservative, meaning that the estimated CIs are wider than would be the case when the ''true'' value of the SE of the average OR is used.

2.3 Results

Table 1 presents age, gender, and GP contact characteristics of the seven neurologic/psychiatric index disease cohorts. Restricting the depression cohort to patients with current depression (*n* = 3,617) did not change mean age (50.6 years; SD = 16.7 years) and slightly increased the proportion of women (69.4%). Also illustrated are the rates of disease categories in the different index disease cohorts. Table 2 shows the associations between each of the index diseases and the various disease categories resulting from the comparisons between index disease cohorts and control cohorts. Associations presented in bold are instances of highly probable comorbidity, and those presented in bold italic are instances of possible comorbidity. The associations are presented as estimated average ORs (hereafter referred to as ORs) with estimated 95% CIs.

Table 1
Characteristics of the seven neurological/psychiatric index disease cohorts. Presented are numbers (percentages)

	Lifetime depression cohort (*n* = 6,641)	Stroke cohort (*n* = 1,701)	MS cohort (*n* = 241)
Gender			
Male	2189 (33.0)	850 (50.0)	73 (30.3)
Female	4452 (67.0)	851 (50.0)	168 (69.7)
Mean age (SD) in years	50.7 (16.5)	69.4 (13.9)	49.1 (12.7)
GP contacts[a]			
0	380 (5.7)	142 (8.3)	24 (10.0)
≥1	6261 (94.3)	1559 (91.7)	217 (90.0)
Disease category (*n* = 37)			
Somatic			
Congenital	74 (1.1)	28 (1.6)	0 (0.0)
Allergy/allergic reaction	420 (6.3)	45 (2.6)	12 (5.0)
Anemia	180 (2.7)	75 (4.4)	3 (1.2)
Gastrointestinal	965 (14.5)	267 (15.7)	15 (6.2)
Liver/gall	155 (2.3)	89 (5.2)	7 (2.9)
Eye	337 (5.1)	216 (12.7)	8 (3.3)
Ear	269 (4.1)	133 (7.8)	4 (1.7)
Ischemic heart	411 (6.2)	376 (22.1)	2 (0.8)
Nonischemic heart	214 (3.2)	221 (13.0)	2 (0.8)
Blood pressure	1055 (15.9)	755 (44.4)	24 (10.0)
Stroke	149 (2.2)	1701 (100.0)	1 (0.4)
TIA	62 (0.9)	120 (7.1)	0 (0.0)
Other vascular	450 (6.8)	261 (15.3)	12 (5.0)
Musculoskeletal	1321 (19.9)	418 (24.6)	25 (10.4)
MS	12 (0.2)	1 (0.1)	241 (100.0)
PD/PKM	36 (0.5)	29 (1.7)	0 (0.0)
Epilepsy	50 (0.8)	55 (3.2)	3 (1.2)
Migraine	242 (3.6)	11 (0.6)	4 (1.7)
Other neurological	177 (2.7)	77 (4.5)	8 (3.3)
Respiratory	737 (11.1)	211 (12.4)	8 (3.3)
Skin/subcutis	798 (12.0)	213 (12.5)	25 (10.4)
Thyroid	271 (4.1)	76 (4.5)	4 (1.7)
Diabetes mellitus	422 (6.4)	337 (19.8)	4 (1.7)
Obesity/lipid metabolism	541 (8.1)	267 (15.7)	11 (4.6)
Kidney	177 (2.7)	72 (4.2)	6 (2.5)
Female genital	368 (5.5)	66 (3.9)	10 (4.1)
Male genital	87 (1.3)	57 (3.4)	3 (1.2)
Cancer	300 (4.5)	171 (10.1)	6 (2.5)
Neoplasms	313 (4.7)	92 (5.4)	7 (2.9)
Other chronic	332 (5.0)	106 (6.2)	9 (3.7)
Psychiatric			
Substance abuse	466 (7.0)	85 (5.0)	6 (2.5)
Dementia	44 (0.7)	45 (2.6)	0 (0.0)
Schizophrenia/psychotic	136 (2.0)	15 (0.9)	1 (0.4)
Depression	6641 (100.0)	150 (8.8)	12 (5.0)
Anxiety	294 (4.4)	27 (1.6)	3 (1.2)
Other mental	348 (5.2)	21 (1.2)	4 (1.7)
Mental retardation	12 (0.2)	7 (0.4)	0 (0.0)

MS, multiple sclerosis; PD/PKM, Parkinson's disease/ parkinsonism; SD, standard deviation; GP, general practitioner;

unless stated otherwise

PD/PKM cohort (*n* = 376)	Dementia cohort (*n* = 528)	Migraine cohort (*n* = 3,067)	Epilepsy cohort (*n* = 1,259)
180 (47.9)	176 (33.3)	654 (21.3)	622 (49.4)
196 (52.1)	352 (66.7)	2413 (78.7)	637 (50.6)
73.7 (10.5)	80.8 (7.9)	43.4 (14.9)	42.3 (21.0)
36 (9.6)	78 (14.8)	215 (7.0)	166 (13.2)
340 (90.4)	450 (85.2)	2852 (93.0)	1093 (86.8)
2 (0.5)	4 (0.8)	37 (1.2)	46 (3.7)
9 (2.4)	10 (1.9)	257 (8.4)	76 (6.0)
16 (4.3)	29 (5.5)	48 (1.6)	30 (2.4)
56 (14.9)	59 (11.2)	334 (10.9)	106 (8.4)
15 (4.0)	22 (4.2)	43 (1.4)	17 (1.4)
39 (10.4)	62 (11.7)	79 (2.6)	56 (4.4)
37 (9.8)	62 (11.7)	77 (2.5)	46 (3.7)
58 (15.4)	106 (20.1)	59 (1.9)	59 (4.7)
36 (9.6)	56 (10.6)	60 (2.0)	49 (3.9)
89 (23.7)	132 (25.0)	322 (10.5)	125 (9.9)
29 (7.7)	44 (8.3)	12 (0.4)	56 (4.4)
13 (3.5)	26 (4.9)	11 (0.4)	14 (1.1)
39 (10.4)	55 (10.4)	148 (4.8)	61 (4.8)
86 (22.9)	123 (23.3)	475 (15.5)	158 (12.5)
0 (0.0)	0 (0.0)	4 (0.1)	3 (0.2)
376 (100.0)	22 (4.2)	2 (0.1)	5 (0.4)
5 (1.3)	7 (1.3)	21 (0.7)	1259 (100.0)
2 (0.5)	0 (0.0)	3067 (100.0)	21 (1.7)
11 (2.9)	9 (1.7)	79 (2.6)	62 (4.9)
43 (11.4)	58 (11.0)	230 (7.5)	105 (8.3)
54 (14.4)	57 (10.8)	356 (11.6)	131 (10.4)
21 (5.6)	22 (4.2)	83 (2.7)	34 (2.7)
46 (12.2)	87 (16.5)	56 (1.8)	51 (4.1)
29 (7.7)	31 (5.9)	168 (5.5)	85 (6.8)
11 (2.9)	19 (3.6)	40 (1.3)	23 (1.8)
13 (3.5)	20 (3.8)	156 (5.1)	29 (2.3)
14 (3.7)	13 (2.5)	17 (0.6)	14 (1.1)
32 (8.5)	54 (10.2)	87 (2.8)	49 (3.9)
12 (3.2)	15 (2.8)	136 (4.4)	55 (4.4)
27 (7.2)	25 (4.7)	70 (2.3)	58 (4.6)
6 (1.6)	9 (1.7)	83 (2.7)	48 (3.8)
22 (5.9)	528 (100.0)	0 (0.0)	8 (0.6)
12 (3.2)	13 (2.5)	10 (0.3)	20 (1.6)
37 (9.8)	47 (8.9)	244 (8.0)	51 (4.1)
7 (1.9)	10 (1.9)	71 (2.3)	19 (1.5)
6 (1.6)	6 (1.1)	96 (3.1)	18 (1.4)
1 (0.3)	1 (0.4)	1 (0.4)	58 (4.6)

TIA, transient ischemic attack. [a] Consultation with GP during the one-year contact registration.

Table 2
Associations between the seven neurological/psychiatric index diseases and disease categories. Associations

Disease category (*n* = 37)	Lifetime depression	Stroke	MS
Somatic	OR (95% CI)	OR (95% CI)	OR (95% CI)
Congenital	1.21 (0.82-1.78)	**2.59 (1.25-5.37)**	-
Allergy/allergic reaction	***1.22 (1.03-1.44)*** [a]	1.02 (0.66-1.59)	-
Anemia	**1.55 (1.19-2.02)** [a]	***1.70 (1.15-2.53)***	-
Gastrointestinal	**1.77 (1.56-2.01)**	**1.34 (1.07-1.66)**	0.80 (0.39-1.64)
Liver/gall	***1.41 (1.06-1.87)*** [a]	***1.91 (1.25-2.92)***	**3.50 (1.78-6.91)** [b]
Eye	**1.41 (1.15-1.72)** [a]	**1.55 (1.20-2.01)**	2.05 (1.00-4.22)
Ear	**1.44 (1.16-1.79)**	1.16 (0.87-1.56)	1.16 (0.48-2.80) [b]
Ischemic heart	***1.22 (1.04-1.44)*** [a]	**1.67 (1.38-2.03)**	0.25 (0.07-0.91) [b]
Nonischemic heart	1.11 (0.89-1.39)	**2.17 (1.68-2.81)**	-
Blood pressure	1.03 (0.93-1.14)	**2.39 (2.05-2.79)**	0.95 (0.52-1.73) [b]
Stroke	**1.96 (1.45-2.65)**	X	-
TIA	1.30 (0.83-2.05)	**3.50 (2.28-5.37)**	-
Other vascular	**1.28 (1.09-1.52)** [a]	**1.97 (1.54-2.51)**	1.80 (0.92-3.54) [b]
Musculoskeletal	**1.31 (1.18-1.45)**	1.07 (0.89-1.28)	0.76 (0.41-1.44)
MS	1.24 (0.68-2.28) [b]	-	X
PD/PKM	***2.48 (1.24-4.96)***	**2.54 (1.26-5.12)**	-
Epilepsy	1.30 (0.83-2.05)	**8.41 (3.66-19.34)**	-
Migraine	**1.81 (1.44-2.29)** [a]	0.73 (0.39-1.36)	0.81 (0.30-2.16) [b]
Other neurological	**1.67 (1.27-2.19)**	**1.96 (1.26-3.07)**	-
Respiratory	**1.46 (1.27-1.67)**	1.09 (0.87-1.36)	0.61 (0.26-1.45) [b]
Skin/subcutis	**1.30 (1.14-1.47)**	1.25 (0.99-1.57)	1.28 (0.69-2.38) [b]
Thyroid	**1.50 (1.22-1.86)** [a]	1.43 (0.99-2.07)	0.78 (0.31-1.92) [b]
Diabetes mellitus	1.03 (0.88-1.20)	**2.05 (1.68-2.51)**	***0.29 (0.13-0.66)*** [b]
Obesity/lipid metabolism	**1.36 (1.17-1.59)**	**2.23 (1.74-2.86)**	1.03 (0.56-1.91) [b]
Kidney	**1.63 (1.22-2.17)** [a]	***1.76 (1.13-2.73)***	-
Female genital	**1.41 (1.15-1.71)** [a]	1.04 (0.69-1.57)	1.54 (0.91-2.62) [b]
Male genital	**2.03 (1.34-3.06)** [a]	1.24 (0.80-1.93)	-
Cancer	1.16 (0.96-1.40)	1.26 (0.98-1.63)	0.99 (0.41-2.38) [b]
Neoplasms	1.24 (1.01-1.51)	***1.56 (1.05-2.30)***	0.92 (0.49-1.71) [b]
Other chronic	**1.47 (1.17-1.85)** [a]	**1.69 (1.17-2.44)**	***3.93 (1.64-9.39)*** [b]
Psychiatric			
Substance abuse	**2.78 (2.26-3.42)**	**1.97 (1.33-2.90)**	0.62 (0.36-1.09) [b]
Dementia	**2.24 (1.25-4.03)**	***2.00 (1.16-3.44)***	-
Schizophrenia/psychotic	**4.07 (2.68-6.19)**	1.74 (0.94-3.24)	-
Depression	X	**2.39 (1.74-3.26)**	1.46 (0.79-2.69) [b]
Anxiety	**3.57 (2.73-4.68)**	1.75 (0.94-3.24)	-
Other mental	**3.46 (2.65-4.51)**	1.06 (0.66-1.69)	-
Mental retardation	1.43 (0.82-2.49) [b]	-	-

Presented ORs and CIs are estimates (see text for the formulas used to calculate these). Empty cells refer to PD/PKM, Parkinson's disease/ parkinsonism; OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack.

[a] Disease categories not comorbid with current depression.

[b] Model without the covariate consultation with general practitioner.

identified as comorbidity are presented in bold (**highly probably comorbidity**) or bold italic (***possible comorbidity***)

PD/PKM	Dementia	Migraine	Epilepsy
OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
-	-	1.33 (0.77-2.28)	**3.09 (1.63-5.85)**
1.15 (0.50-2.64)	-	**1.51 (1.21-1.88)**	1.38 (0.95-2.01)
1.17 (0.58-2.35) [b]	1.27 (0.71-2.27)	1.11 (0.71-1.74)	***2.29 (1.17-4.51)***
1.45 (0.92-2.28)	0.93 (0.62-1.40)	**1.68 (1.38-2.06)**	1.19 (0.86-1.64)
1.39 (0.80-2.40) [b]	1.25 (0.77-2.01)	1.15 (0.70-1.88)	1.12 (0.68-1.85)
1.02 (0.61-1.72)	1.02 (0.67-1.56)	1.21 (0.84-1.75)	1.56 (0.98-2.48)
1.34 (0.78-2.30)	1.47 (0.95-2.26)	1.47 (0.98-2.19)	1.61 (0.94-2.75)
0.92 (0.61-1.39)	1.10 (0.79-1.52)	0.81 (0.55-1.18)	1.08 (0.72-1.61)
1.09 (0.65-1.83)	1.13 (0.74-1.72)	1.22 (0.80-1.85)	***1.76 (1.06-2.93)***
0.74 (0.53-1.05)	0.78 (0.59-1.03)	1.05 (0.88-1.25)	0.94 (0.71-1.23)
3.55 (1.60-7.87)	***2.03 (1.16-3.55)***	0.72 (0.35-1.48)	**5.84 (2.89-11.79)**
1.62 (0.79-3.31) [b]	1.76 (0.89-3.48)	1.27 (0.72-2.22) [b]	-
1.23 (0.73-2.06)	1.25 (0.80-1.96)	1.24 (0.94-1.63)	1.23 (0.81-1.87)
1.08 (0.75-1.55)	1.01 (0.75-1.37)	**1.32 (1.12-1.56)**	1.07 (0.82-1.39)
-	-	-	-
X	**3.84 (1.95-7.55)**	-	-
-	2.41 (0.91-6.38) [b]	1.39 (0.76-2.54) [b]	X
-	-	X	1.41 (0.73-2.72) [b]
1.16 (0.67-2.02)	-	**1.94 (1.28-2.94)**	**4.65 (2.33-9.29)**
0.91 (0.57-1.44)	1.12 (0.74-1.69)	1.20 (0.96-1.49)	1.15 (0.84-1.56)
1.64 (1.02-2.62)	1.05 (0.69-1.59)	***1.26 (1.05-1.51)***	1.17 (0.88-1.55)
1.84 (0.93-3.63)	1.03 (0.55-1.95)	1.17 (0.82-1.66)	1.60 (0.90-2.86)
0.93 (0.60-1.44)	1.29 (0.92-1.82)	**0.50 (0.36-0.70)**	0.94 (0.63-1.42)
1.03 (0.57-1.85)	1.25 (0.71-2.21)	1.22 (0.95-1.58)	***1.41 (0.97-2.03)***
0.88 (0.45-1.71)	1.50 (0.85-2.65) [b]	1.34 (0.79-2.29)	1.28 (0.78-2.10)
0.88 (0.51-1.52)	0.96 (0.55-1.69)	**1.51 (1.14-2.01)**	1.01 (0.59-1.74)
1.52 (0.85-2.72)	0.97 (0.56-1.67) [b]	1.89 (1.04-3.42) [b]	1.55 (0.69-3.50) [b]
0.93 (0.55-1.57)	1.14 (0.74-1.74)	1.16 (0.83-1.62)	***1.64 (1.01-2.67)***
0.94 (0.55-1.61) [b]	0.94 (0.56-1.57)	***1.50 (1.11-2.01)***	**2.04 (1.25-3.32)**
1.74 (0.90-3.37)	0.77 (0.45-1.30)	1.23 (0.83-1.81)	**2.13 (1.30-3.50)**
0.85 (0.50-1.44) [b]	0.91 (0.55-1.52) [b]	0.86 (0.62-1.20)	***1.56 (1.01-2.40)***
3.46 (1.40-8.53)	X	-	-
-	***3.52 (1.25-9.86)***	0.56 (0.30-1.06) [b]	**4.53 (1.45-14.17)**
2.98 (1.52-5.87)	**2.29 (1.34-3.92)**	**1.85 (1.46-2.35)**	1.34 (0.86-2.11)
-	***2.25 (1.20-4.23)*** [b]	***1.59 (1.05-2.41)***	1.64 (0.89-3.04) [b]
2.21 (1.19-4.10)	1.79 (0.78-4.11) [b]	**2.00 (1.37-2.91)**	1.16 (0.65-2.07) [b]
-	-	-	-

associations that could not be meaningfully analyzed due to a low number of cases. MS, multiple sclerosis;

Comorbidity in the index disease cohorts

Depression

For lifetime depression, an extensive range of 26 comorbid somatic and psychiatric disease categories was identified, of which 22 were classified as highly probable comorbidities and three as possible comorbidities. In most cases, ORs for the somatic comorbidities (range: 1.22–2.48) were substantially lower than those concerning psychiatric comorbidities (range: 2.24–4.07). The five highest ORs were found for schizophrenia/other psychotic disorders, anxiety disorders, other mental disorders, substance abuse, and PD/PKM. Fourteen disease categories were found to be comorbid with current depression, with nine classified as highly probable and five as possible comorbidities. Compared to the results using lifetime depression, 12 somatic disease categories were no longer identified as comorbidity (see Table 2, second column). The ORs concerning the vast majority of these categories decreased minimally (between 0.00–0.23), with only those regarding migraine (0.46) and male genital conditions decreasing to a larger extent (0.55). No disease category was found to be comorbid with current depression that was not also comorbid with lifetime depression. Also, the five comorbidities most strongly associated with current depression were the same as when examining lifetime depression.

Stroke

A broad range of 21 somatic and psychiatric disease categories was identified as being comorbid with stroke, with 16 categories being classified as highly probable comorbidities and five as possible comorbidities. The OR of the majority of the comorbidities was around 2.0, while the Ors concerning the associations between stroke and transient ischemic attack (TIA), and especially between stroke and epilepsy, was markedly higher. The five comorbidities with the highest ORs were epilepsy, TIA, congenital abnormalities, PD/PKM, and blood pressure problems.

MS

Three disease categories were found to be comorbid with MS, with liver/gall diseases classified as highly probable comorbidity and other chronic diseases and diabetes mellitus as possible comorbidities. Although the former two

disease categories were positively associated with MS, there was an inverse relationship between MS and diabetes mellitus. Further explorative analysis (data not shown) suggested that the relatively strong comorbid association of MS with the unspecific category other chronic diseases (i.e. OR = 3.93) was mainly determined by the relatively high frequency of vitamin deficiency (code T91) among patients with MS compared to control subjects without MS. Psychiatric comorbidity in the cohort of patients with MS could not be comprehensively examined due to too few cases regarding several sychiatric disease categories.

PD/PKM

PD/PKM was found to be comorbid with four disease categories, of which stroke, dementia, and depression were classified as highly probable comorbidities and other mental disorders as possible comorbidity. The ORs of the comorbidities were relatively high (range: 2.21–3.55) and three of the four concerned psychiatric disease categories. Statistical analysis of the association between PD/PKM and schizophrenia/other psychotic disorders was precluded because of very few cases in the control groups. However, inspection of the frequency distributions strongly suggested a comorbid relationship (i.e. 12 patients with PD/PKM had schizophrenia/other psychotic disorders vs. on average 1.2 control subjects without PD/PKM).

Dementia

Five disease categories were identified as being comorbid with dementia, of which PD/PKM and depression were classified as highly probable comorbidities, and stroke, schizophrenia/other psychotic disorders and anxiety disorders as possible comorbidities. The ORs of the comorbidities were relatively high (range: 2.03–3.84).

Migraine

Eleven comorbid disease categories were found for migraine, with eight classified as highly probable comorbidities and three as possible comorbidities. All these categories were positively associated with migraine, except for diabetes mellitus, which was found to be inversely related to migraine. When only the positive associations were taken into account, it is apparent that the ORs were relatively low (range: 1.26–2.00). The five comorbidities most

strongly positively associated with migraine were a mixture of somatic and psychiatric disease categories: other mental disorders, other neurologic disorders, depression, gastrointestinal disorders, and anxiety disorders.

Epilepsy
Eleven disease categories were identified as comorbidities of epilepsy, with six classified as highly probable comorbidities and five as possible comorbidities. The five comorbidities most strongly associated with epilepsy were stroke, other neurologic disorders, schizophrenia/other psychotic disorders, congenital abnormalities, and anemia. The ORs of the other comorbidities varied between 1.41 and 2.13. The association between epilepsy and mental retardation could not be analyzed due to very few cases in the control groups. However, inspection of frequency distributions strongly indicated a comorbid association (i.e. 58 patients with epilepsy had mental retardation vs. on average 1.3 control subjects without epilepsy). Further explorative analysis (data not shown) did suggest that the relatively high occurrences of carpal tunnel syndrome (code N93) and other diseases of the central nervous system (code N99) among patients with epilepsy in comparison with nonepileptic control subjects underlied the relatively strong comorbid association between epilepsy and the unspecific category other neurologic diseases (i.e. OR = 4.65).

2.4 Discussion

Strengths and weaknesses of the study

Before discussing the results in more detail, strengths and weaknesses of this study need to be noted. A first strength is that comorbidity was examined in largely unselected, heterogeneous cohorts of neurologic/psychiatric patients. Second, a comprehensive range of potential comorbid somatic and psychiatric disease categories was investigated. Third, by repeating each analysis 10 times with different control groups, the consistency of results could be determined, thereby reducing the chance that coincidental comorbidities were identified. A final strength was that most analyses (except those regarding the MS cohort) took into account whether or not subjects had consulted their GP during the contact registration year. In this manner analyses controlled for possible

confounding effects of differences between patients and controls regarding the chance of having a health condition diagnosed. A weakness of this study concerns the adequacy of the GP diagnoses of the neurologic/psychiatric index diseases. Because all these diseases have a major impact on quality of life, a high rate of underdiagnosis is not expected. Furthermore, diagnoses will in most cases be confirmed by a specialist, except for diagnoses of depression and migraine, which are exclusively made by GPs in many patients. However, contrary to the expectation of low misclassification, studies have suggested considerable underdiagnosis of depression [34], dementia [35], and migraine [36], and significant overdiagnosis of stroke [37], PD/PKM [38], and epilepsy [39] in primary care settings. If underdiagnosis and overdiagnosis played a part in the results reported here, both sources of bias would have reduced the chances of finding significant associations between a particular index disease and disease category, either by confounding an index disease cohort with subjects who do not actually have an index condition (overdiagnosis) or by confounding a control cohort with subjects who actually have an index condition (underdiagnosis). A second weakness is that because of the cross-sectional design and the lack of onset data nothing can be said about the temporal association between a particular index disease and a comorbid disease category. Third, some disease categories under study were relatively broad and heterogeneous, which has the disadvantage that, on the one hand, ''true'' comorbid associations might have been masked, and that, on the other, interpretation of observed comorbid associations is sometimes difficult.

Range of comorbidity

Our data showed that, in particular lifetime depression, and to a lesser extent, stroke, were associated with an extensive range of somatic and psychiatric disease categories. The comorbidity patterns of current depression, migraine, and epilepsy were less broad, while those of MS, PD/PKM, and dementia included only a small number of disease categories. It is possible that the restricted range of comorbidity associated with these latter three index diseases was partly due to examining relatively small cohorts, thereby limiting statistical power to detect ''true'', but weaker comorbid associations. This explanation is in line with the finding that, looking at the positive associations, all ORs of the identified comorbidities in the MS, PD/PKM, and dementia

cohorts were relatively high (i.e. >2.0), while in the other larger cohorts several associations with ORs less than 2.0 were identified as comorbidity. An influence of statistical power is also indicated by the finding that, using a subset of the cohort of depressed patients, the comorbidity profile of current depression comprised considerably less somatic disease categories than the broad profile associated with lifetime depression, while at the same time no disease category was comorbid with current depression that was not also comorbid with lifetime depression. An additional potential explanation for the small number of identified comorbidities associated with dementia is that patients with dementia underreport symptoms [3]. Such underreporting could have decreased the likelihood of having comorbid illnesses diagnosed in the demented patients under study, thereby lowering the opportunity to identify comorbidities when making comparisons with controls without dementia. We are not aware of other population-based studies including control group comparisons that have comprehensively examined comorbidity simultaneously in the different neurologic/ psychiatric index diseases. To the best of our knowledge, there are only a few population-based controlled studies that have focused on some of the index diseases under study, mostly examining the range of either somatic or psychiatric comorbidity, and not both types of comorbidity. Our finding of a wide spectrum of somatic comorbidity in patients with lifetime depression seems to contrast with that from a previous population-based study [40]. Although Moldin et al. [40] found rates of all somatic conditions under study to be higher in subjects with treated lifetime major depression (*n* = 512) than in those without lifetime major depression, only a few associations between major depression and somatic conditions were statistically significant. Possibly, this study simply lacked statistical power to detect significant associations. Our comorbidity results concerning lifetime and current depression are generally in line with those of large population-based studies that compared subjects with and without self-reported long-term somatic conditions regarding the 12-month prevalence of major depression as assessed according to a standardized psychiatric interview [41-42]. These studies found that various chronic medical conditions were associated with an increased prevalence of major depression. We found that patients with epilepsy had higher risks of a range of somatic disease categories. Other general population studies either did not find significant differences between patients with epilepsy and control subjects without epilepsy in the occurrences

of somatic disorders [43], or showed that epileptic patients, compared to nonepileptic controls, had increased prevalences of almost all studied broad somatic disease categories or specific somatic conditions [44-45]. The negative findings of the former study [43] might be due to its investigation of a small and selective population, that is, 220 patients with childhood-onset epilepsy. The extensive pattern of somatic comorbidity observed in the latter two studies, which also used general practice data, might be explained by a possible bias towards including more severe epilepsy cases with greater morbidity. That is, in contrast to our study, these studies excluded patients who had not consulted their GP for epilepsy during the study period, thereby excluding patients whose seizures are well controlled. Despite various differences in methodology, our findings support earlier population-based controlled studies showing a relatively broad range of psychiatric comorbidity among patients with lifetime and current depression [46], dementia [47], and migraine [48-49]. No broad range of psychiatric comorbidity was observed in our cohort of patients with epilepsy, a finding that differs from a previous general population study observing higher risks of a wide range psychiatric disorders in epilepsy patients[45]. Although, as stated above, in this study there might have been a bias towards patients with more severe epilepsy.

Specific comorbidity

Apart from differing in range, the comorbidity profiles observed in the different index disease cohorts also varied with respect to the specific disease categories they comprised. Only the comorbidity patterns associatedwith PD/PKMand dementia shared some similarities. That is, PD/PKM and dementia were observed to be comorbid with each other, irrespective of which condition was taken as the index condition, while both disorders were comorbid with stroke and depression. The majority of the identified comorbidities confirms previous research or clinical experience. Noteworthy, post hoc power analysis indicated that some established comorbidities, such as stroke–dementia and dementia–schizophrenia/other psychotic disorders, were most likely not classified as highly probable comorbidities but as possible comorbidities because of insufficient power. Interestingly, some index disease–disease category associations for which previous research has provided strong evidence that they represent comorbidity, were not identified as such in our study, like

MS–depression [50], epilepsy– depression [51], depression–cancer [52], migraine–stroke [53], and migraine–epilepsy [54]. This may suggest that these comorbid associations do not exist in unselected populations. However, some of these relationships have been identified as comorbid in other population-based controlled studies[55-57]. Possible explanations for these discrepancies in findings are differences in study design, characteristics of the study population, and/or criteria and procedures used to diagnose the index disease and comorbid condition(s). For instance, it is possible that underdiagnosis of either the index disease or the comorbid condition by GPs played a role in our failure to confirm comorbidities. This may be particularly relevant regarding diagnosis of depression, because studies have indicated that underdiagnosis of depression by GPs is more pronounced among somatically ill patients [58-59]. This line of reasoning would lead to the hypothesis that depressed patients with epilepsy, cancer, and MS are at special risk of being not diagnosed as depressed by theirGPs. Further studies are needed to evaluate this hypothesis. Also of interest, several specific comorbidities were identified that are not firmly established by earlier population- based research or that have not been previously investigated. These included possible comorbidities, like stroke–liver/gall disease, MS–diabetes mellitus (inverse association), epilepsy–nonischemic heart disease, epilepsy–lipid metabolism disorder, epilepsy–substance abuse disorder, as well as highly probable comorbidities such as MS–lever/ gall disease, migraine–diabetes mellitus (inverse association) and migraine–female genital disease. It is beyond the scope of this study to discuss in detail possible underlying mechanisms for all these comorbidities. Basically, there are several possible explanations for a higher (or lower) than expected association between an index disease and comorbid condition: (1) the index disease and/or its treatment causes (or protects against) the development of the comorbid condition; (2) the comorbid condition and/or its treatment causes (or protects against) the development of the index disease; (3) both the index disease and comorbid disease arise from the same underlying cause; (4) the comorbid association is artificial (e.g. due to bias in the data). Further cross-sectional studies are required to substantiate these ‘‘new’’ comorbid associations and, if they do, subsequent longitudinal research could elucidate the order of onset and mechanism(s) underlying these comorbidities.

Implications for clinical practice and research

Our results should lead to an increased awareness among physicians of the comorbid conditions associated with the neurologic/psychiatric diseases under study, which in turn, may improve diagnosis and treatment of these comorbidities. Improving diagnosis and management of comorbidity is important because evidence is accumulating that its presence results in a poorer course and outcome of these neurologic/ psychiatric index diseases, as well as a poorer quality of life and an increased use of health services [11,60-69]. As far as comorbidities are known to be caused by the index disease or its treatment, raised awareness of them among physicians may lead to improved prevention of comorbidity. Furthermore, our findings can be useful with respect to the planning and organisation of health services for neurologic/psychiatric patients. For instance, the findings that the patients with stroke, PD/PKM, and migraine showed in general a broad range of psychiatric comorbidity and that the depressed patients displayed an extensive spectrum of somatic comorbidity, indicate the need for a closer collaboration between, on the one hand, GPs and neurologists and, on the other, psychiatrists and psychologists. A major role for GPs in the coordination of care for patients with comorbidity seems appropriate, as they are in the best position to detect (adverse effects of) comorbidity [70]. In addition, our results form a descriptive epidemiologic basis for more hypothesis-driven research on the comorbidity of neurologic/psychiatric disease. The identified ''new'' comorbidities are of particular interest in this context. Further detailed investigation of these comorbidities could eventually provide clues to the etiologies of the index diseases as well as the comorbid conditions involved. Also, the finding that depression was comorbid with an extensive range of somatic and psychiatric disease categories underlines the importance of further research that improves our understanding of the mechanisms underlying the interaction between depression and (specific) somatic and psychiatric diseases. Furthermore, our findings provide a starting point for more complex future research that, when examining an association between a neurologic/ psychiatric index disease and a comorbid condition, takes into account interrelationships among comorbid conditions themselves [9]. In sum, this study provides comprehensive knowledge of the occurrence of somatic and psychiatric comorbidity in general populations of patients with depression,

stroke, MS, PD/PKM, dementia, migraine, and epilepsy, which could contribute to efforts to improve the quality of care for these patients.

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Appendix

Disease categories and their corresponding ICPC codes

Disease category	ICPC codes
Somatic	
Congenital	A90;[e] B78; B79;[d,e] D81; F80;[c] F81;[c,d] H80;[e] K73; L82; N85; R89;[c–e] S83; T78;[d,e] T80;[e] U85; X83;[c–e] Y82;[b–e] Y83;[c–e] Y84;[c–e]
Allergy/allergic reaction	A12; R97; S98
Anemia/coagulative defects	B80; B81; B82; B83
Gastrointestinal	D82; D83; D84; D85; D86; D87; D90; D92; D93; D94; D95; D99
Liver/gall	D72; D97; D98
Eye	F82; F83; F84; F91; F92; F93; F94; F95; F99
Ear	H82; H83; H84; H86; H99
Ischemic heart	K74; K75; K76; K77
Nonischemic heart	K78; K79; K80; K81; K82;d K83; K84
Blood pressure	K85; K86; K87; K88
Stroke	K90
TIA	K89
Other vascular	K91; K92; K93; K94; K95; K96; K99
Musculoskeletal	L83; L84; L85; L86; L87; L88; L89; L90; L91; L92; L95; L97; L98; L99
MS	N86
PD/PKM	N87
Epilepsy	N88
Migraine	N89
Other neurological	N90;[e] N91; N92; N93; N94; N99
Respiratory	R91; R93;[c] R95; R96; R99
Skin/subcutis	S86; S87; S88; S90;[d,e] S91; S92;[d] S93; S94; S96; S97; S99
Thyroid	T15; T81; T85; T86
Diabetes mellitus	T87; T88;[c,g] T90
Obesity/lipid metabolism	T82; T83; T93
Kidney	U88; U90;[a–c,e,f] U95; U98;[c] U99
Female genital	X84; X85; X86; X87; X88; X89;[c,d] X99
Male genital	Y85; Y86; Y99
Cancer/malignant neoplasms	A79;[g] B72; B73;[c] B74;[c] D74; D75; D76;[c] D77;[c] N74;[c] R84; R85; S77; T71;[c–e] U75; U76; U77;[c,f,g] W72;[a–e,g] X75; X76; X77; Y77; Y78[c]
Benign neoplasms/unspecified neoplasms	B75;[c,d,g] D78; F74;[c,e] H75;[c–e], K72;[c–e,g] L71;[c] N75; N76;[d,e] R86; S78; S79; S80;[c] S81;[c,e] S82; T72; T73;[c,e] U78;[c] U79;[c] W73;[b–d] X78; X79; X80; X81;[c–e] Y79[c–e]
Other chronic	A99; B99; T91; T92; T99

Disease category	ICPC codes
Psychiatric	
Subtance abuse	P15; P16;[e] P17; P18; P19[e]
Dementia	P70
Schizophrenia/psychotic	P71; P72; P73; P98
Anxiety	P74; P79
Depression	P76
Mental retardation	P85
Other mental	P75; P78; P99

ICPC, International Classification of Primary Care; MS, multiple sclerosis; PD/PKM, Parkinson's disease/ parkinsonism; TIA, transient ischemic attack.
[a] Disease not present in lifetime depression cohort and 10 matched control cohorts.
[b] Idem stroke cohort.
[c] Idem MS cohort.
[d] Idem PD/PKM cohort.
[e] Idem dementia cohort.
[f] Idem migraine cohort.
[g] Idem epilepsy cohort.

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3 Cerebrovascular risk factors and subsequent depression in older general practice patients

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Abstract

Background: This general practice-based case-control study tested the association between cerebrovascular risk factors (CVRFs) and the development of later-life depression by focusing on the impact of exposure duration to CVRFs and the modifying influence of age at depression onset.

Methods: Cases were 286 patients aged ≥50 years with a first diagnosis of depression at age ≥50 years. Nondepressed controls (*n* = 832) were individually matched for age, gender and practice. CVRF diagnoses (hypertension, diabetes mellitus, cardiovascular conditions) prior to depression were determined. Analyses controlled for education, somatic and nondepressive psychiatric disease.

Results: No CVRF variable examined was significantly associated with subsequent depression in the total sample. An unexpected impact of age at onset of depression was observed: the odds ratio associated with having any CVRF was smaller for patients with age at onset ≥70 years than for patients with onset between ages 50–59 years (p = .002) and 60–69 years (p = .067). Subsequent analyses excluding patients with onset at age ≥70 years revealed that CVRF variables, including long-term exposure to CVRFs, significantly increased the odds of subsequent depression with onset between ages 50 and 69 years.

Limitations: Reliance on GPs' records of morbidity may have resulted in bias towards underestimation in patients with depression onset at age ≥70 years.

Conclusions: Our findings suggest that CVRFs play a relevant role in the development of depression with onset between ages 50 and 69 years, but no evidence was found that they contribute to the occurrence of depression with onset at age ≥70 years. Replication is warranted to exclude the possibility of bias.

3.1 Introduction

The vascular depression hypothesis proposes that cerebrovascular disease is an important aetiological factor in late-life depression [1-2]. An implication of this hypothesis is the existence of an association between cerebrovascular risk factors (CVRFs), such as hypertension, diabetes mellitus and cardiac disease, and depression in later life. More specifically, Lyness et al. [3-4] have suggested that the increase in prevalence of CVRFs with age contributes over time to the development of small-vessel brain disease, which, in turn, disrupts neurobiological functioning resulting in depression. Most studies testing the link between CVRFs and later-life depression have been cross-sectional and used predominantly samples of psychiatric patients. These reports have yielded mixed results [3-12]. A major limitation of these studies is their transversal design. Given that depression may also contribute to the development of CVRFs [13-16], it is essential to perform longitudinal studies that specifically address the hypothesized causal pathway of CVRFs leading to the development of depression. To the best of our knowledge, only two prospective studies have directly examined this association and their results are equivocal. In older primary care patients, Lyness et al. [17] detected no relationship between baseline severity of CVRFs and depression symptoms and diagnoses at 1-year follow-up after controlling for overall medical burden. Conversely, Mast et al. [18] investigated geriatric rehabilitation patients and found an association between a higher number of CVRFs at baseline and the manifestation of depressive symptoms at 6 and 18 months follow-up, also after adjusting for baseline depression scores, limitations in activities of daily living and general medical comorbidity. It is unclear what explains this inconsistency in findings, but differences in patient characteristics may play a role, as well as limitations within the studies. The study by Lyness et al. included patients who were depressed at baseline, rather than focusing exclusively on newly onset depression. Mast et al. examined a specific clinical sample, which was potentially subject to referral bias and focused on a restricted set of three CVRFs (i.e. hypertension, diabetes and atrial fibrillation). Both longitudinal studies did not examine the impact of the duration of exposure to CVRFs as well as the potential moderating influence of age at onset of depression. Since the theoretical model by Lyness et al. [3-4] postulates that CVRFs produce

depression through the development of small-vessel brain disease *over time*, exposure duration to CVRFs is an essential factor to be taken into consideration. In addition, age at depression onset may modify the relationship between CVRFs and the subsequent development of depression. Given that the prevalence of, and consequently exposure duration to, CVRFs generally will increase with age, one would expect the association between CVRFs and subsequent depression to be stronger in patients with an older age at depression onset compared with patients with a younger age at onset. The aim of the present case-control study was to further test the association between CVRFs and the subsequent development of depression in older general practice patients. Besides investigating the influences of having any CVRF, specific CVRFs and the number of CVRFs, we examined the effect of exposure duration to CVRFs on the development of depression in later life. In addition, the potential modifying influence of age at depression onset on the relationship between CVRFs and subsequent later-life depression was investigated.

3.2 Methods

Study setting and data

This study was a sub-study of the second Dutch National Survey of General Practice [19] and utilized morbidity data recorded by general practitioners (GPs). In the Netherlands, GPs act as a gatekeeper to health care facilities. After referral, specialists report back results, by which GPs have comprehensive information about the health status of a patient. The majority of Dutch GPs keep electronic medical records of their patients as part of daily medical practice. An important element of these records, initially formulated by Weed[20], are the so-called "problem lists." A problem list contains diagnoses of all relevant past and current health problems of a patient, with a health problem defined as "anything that has required, does or may require health care management and has affected or could significantly affect a person's physical or emotional well-being" [21]. The dates of establishing the diagnoses are also recorded. Health problems are coded by the GPs according to the International Classification of Primary Care (ICPC) [22] based on the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2-Defined) [23]. For the present study, eight practices, comprising 14 GPs, were

selected on the basis of their fulfillment of quality criteria relating to the accuracy of dates of diagnoses recorded on the problem lists, as well as the completeness of the registration. These practices took part in a procedure to increase the completeness of the problem lists concerning diagnoses of depressive disorder (ICPC code P76) and heart failure (code K77). This procedure involved running a computer search program that, by searching the entire electronic medical record system for markers (e.g. relevant ICPC codes, certain text strings, specific medication), traced potential cases of depression and heart failure. Subsequently, for each identified possible diagnosis of depression or heart failure, the GP made a decision to add the diagnosis to the problem list.

Study population

The population registered at the eight practices consisted of 28,307 persons in 2001 and was representative of the Dutch population in terms of age, gender and type of health insurance. The practice population formed the source population. Cases were defined as patients aged 50 years or older in 2001 who were diagnosed with depressive disorder (ICPC code P76) or depressive feelings (code P03) for the first time at age 50 years or older according to their problem list. The ICHPPC-2- Defined criteria for depressive disorder correspond largely to those of the DSM-IV for major depression [14]. The P03 code is used for patients with depressive symptomatology who do not fulfill criteria for depressive disorder. Cases diagnosed with stroke or transient ischaemic attack (TIA) and/or dementia before the date of depression diagnosis were excluded (*n* = 20) to minimize the influence of clinically overt cerebrovascular disease and dementia on the relationship between CVRFs and subsequent depression, leaving 286 cases. Controls comprised those patients who had never received a diagnosis of depression or depressive feelings, but who had at least one other diagnosis on their problem list. This latter requirement was imposed to minimize selectivity due to the degree of attention a GP pays to a patient. For each depressed case, three control patients matched on age (using 5 year age bands), gender and practice were randomly selected. Each matched control was assigned a virtual “exit date” marking the end of the observation period, which was identical to the date of depression diagnosis of the case with whom the control was matched. Controls with a diagnosis of stroke or TIA and/or dementia before the exit date were excluded. A small number of cases were

matched to less than three control patients because the number of eligible controls was not sufficient, resulting in 832 control patients.

Cerebrovascular risk factors (CVRFs)

The current study investigated the following wellestablished CVRFs [24-25]: hypertension (ICPC codes K86 or K87), diabetes mellitus (code T90) and several cardiovascular conditions, including atrial fibrillation (code K78), chronic ischemic heart disease (code K76), angina pectoris (code K74), myocardial infarction (code K75), heart failure (code K77), and intermittent claudication (code K92). Diagnoses of hypertension, diabetes mellitus, and chronic ischemic heart disease made by GPs have been shown to agree well with the diagnostic criteria of the ICHPPC-2-Defined, with a highest false positive rate of 4% being observed in diabetes mellitus [26]. For each case (control), the presence of each CVRF diagnosis prior to the date of depression diagnosis (assigned exit date) was determined, as well as the time periods between the date of each CVRF diagnosis and depression diagnosis date (assigned exit date). The influence of the following CVRF variables on the development of subsequent depression was examined: a basic variable "any CVRF" (i.e. any CVRF diagnosis), individual CVRFs (i.e. three CVRF diagnosis categories: hypertension, diabetes mellitus and cardiovascular conditions), the number of CVRFs (i.e. the number of diagnoses belonging to a different CVRF category; possible range= 0–3) and the duration of exposure to CVRFs. Regarding this last variable, if a case or control had CVRF diagnoses in more than one category, the time periods between each CVRF diagnosis within the category and depression diagnosis were summed (e.g. hypertension and diabetes mellitus diagnosed, respectively, 7.7 and 3.0 years before depression diagnosis resulted in a total exposure duration of 10.7 years). Subsequently, this variable was categorized into 0, >0–10, >10–20, and >20 years of exposure. Of note, atrial fibrillation was included in the cardiovascular category and not considered separately because the number of cases with this condition was too small for meaningful analysis.

Covariates

We took into account other factors that might influence the associations between the CVRF variables and subsequent depression, including attained educational level, other psychiatric disorder and the number of chronic somatic disorders present prior to the development of depression [27].

Educational level was categorized into low (none, elementary school), middle (high school) and high (college or university). Also, a separate category of missing data was created because education data were missing for a substantial number of cases (16.4%) and controls (18.5%). The presence of psychiatric disease was defined as having at least one psychiatric diagnosis other than depression or depressive feelings diagnosed before depression diagnosis date (for cases) or "exit date" (for controls), respectively. The following psychiatric diagnoses were taken into account: anxiety disorders, schizophrenia and other psychotic disorders, and a rest category of other mental disorders. The number of chronic somatic conditions prior to depression was established in a similar fashion, while considering a comprehensive range of conditions relating to various body systems [28]. This variable was categorized into four categories, i.e. 0, 1, 2 and ≥3 conditions.

Statistical analysis

Separate conditional logistic regression analyses were performed using SPSS version 11.5 for Windows (www2.chass.ncsu.edu/garson/PA765/logit.htm) to examine the association between each of the CVRF variables and the subsequent development of depression in the total sample. The potential confounding effects of attained educational level, presence of other psychiatric disease and the number of chronic somatic conditions prior to depression were controlled for in multivariate models. Next, to examine the potential modifying influence of age at onset of depression, three "age at depression onset" groups were formed consisting, respectively, of cases with depression onset between ages 50 and 59 years (n = 149) and their matched controls (n = 439), of cases with onset between ages 60 and 69 years (n = 70) and their matched controls (n = 202), and of cases with onset at age 70 years or older (n = 67) and their matched controls (n = 191). This categorization was based on the most commonly employed cut-off points, i.e. 50 and 60 years of age, to define late-onset depression [29]. To investigate whether there existed a different relationship between having any CVRF and subsequent depression for the three age at depression onset groups, an interaction term of any CVRF and age at depression onset group was added to the multivariate model. Interaction was tested by comparing the log likelihood of this model with that of the model without the interaction term (i.e. likelihood ratio test). In case of a significant interaction effect, the odds ratio of developing depression for

patients with any CVRF in each of the three age at depression onset groups were assessed using multivariate conditional logistic regression analysis. Finally, as a sensitivity analysis, all analyses were repeated while excluding cases that were diagnosed with depressive feelings (*n* = 16) and their matched controls (*n* = 48) to evaluate the effect of possible misclassification of depression. Also, the modifying influence of age at depression onset was examined using a more detailed classification of age at onset groups (i.e. onset between ages 50–54, 55–59, 60–64, 65–69, 70–74 years and onset at ≥75 years) to evaluate the influence of definition of age at onset categorization. Statistical significance was accepted at the 5% level.

3.3 Results

Table 1 illustrates the demographic and clinical characteristics of the depressed patients (*n* = 285) and their matched controls (*n* = 831). Table 2 shows the results of the conditional logistic regression analyses examining the association between each of the CVRF variables and the subsequent development of depression. None of the CVRF variables was significantly linked to subsequent depression. Additionally controlling for educational level, other psychiatric disease and number of chronic somatic conditions only minimally affected the odds ratios. Next, the potential modifying influence of age at depression onset on the relationship between having any CVRF and subsequent depression was examined. Noteworthy, the proportion of cases and controls with any CVRF differed across the age at depression onset groups, suggesting a modifying role of age at depression onset. Specifically, in the groups with onset between ages 50 and 59 years (mean age: 61.3, SD: 6.9, 58.9% females) and 60 and 69 years (mean age: 70.5, SD: 5.0; 71.7% females) having any CVRF was more common among cases than controls (22.3% vs. 13.7% and 32.9% vs. 27.7%, respectively). In contrast, in the group with onset at age 70 years or older (mean age: 80.3, SD: 5.9; 80.5% females), a lower proportion of cases than controls had any CVRF (35.8% vs. 46.8%).

Table 1
Demographic and clinical characteristics of depressed cases and matched nondepressed controls

Characteristic	Depressed patients (*n* = 285)	Control patients (*n* = 831)
Age in 2001 (years): mean (SD), range	68.1(10.1), 51-92	67.8(10.0), 51-95
Female gender, *n* (%)	191 (67.0)	557 (67.0)
Educational level, *n* (%)		
High	27 (9.5)	71 (8.5)
Middle	106 (37.2)	337 (40.6)
Low	105 (36.8)	269 (32.4)
Missing	47 (16.5)	154 (18.5)
Other psychiatric disease prior to depression, *n* (%)	30 (10.5)	27 (3.2)
Number of somatic diseases prior to depression, *n* (%)		
0	75 (26.3)	229 (27.6)
1	67 (23.5)	223 (26.8)
2	49 (17.2)	148 (17.8)
≥ 3	94 (33.0)	231 (27.8)
Any CVRF prior to depression, *n* (%)	80 (28.1)	205 (24.7)
Individual CVRF prior to depression, *n* (%)		
Hypertension	53 (18.6)	131 (15.8)
Diabetes	19 (6.7)	43 (5.2)
Any cardiovascular condition	28 (9.8)	81 (9.7)
Number of individual CVRFs prior to depression, *n* (%)		
1	61 (21.4)	158 (19.0)
2	19 (6.7)	47 (5.7)
Exposure duration to CVRFs prior to depression (sum of years), *n* (%)		
> 0-10	55 (19.3)	144 (17.3)
> 10-20	9 (3.2)	30 (3.6)
> 20	16 (5.6)	31 (3.7)

CVRF, cerebrovascular risk factor.

Table 2
Association between cerebrovascular risk factor (CVRF) variables and subsequent depression using separate conditional logistic regression analyses

	Bivariate		Multivariate	
	OR (95% CI)	p^a	OR (95% CI)	p^a
Any CVRF	1.18 (0.85-1.64)	.33	1.18 (0.80-1.59)	.49
Individual CVRF				
Hypertension	1.23 (0.84-1.80)	.30	1.18 (0.80-1.75)	.41
Diabetes	1.28 (0.73-2.26)	.39	1.20 (0.67-2.13)	.55
Any cardiovascular condition	0.96 (0.60-1.54)	.86	0.85 (0.52-1.40)	.53
Number of CVRFs	1.13 (0.88-1.44)	.34	1.07 (0.83-1.38)	.63
Exposure duration to CVRFs (sum of years)				
> 0-10	1.15 (0.78-1.69)	.48	1.15 (0.78-1.71)	.48
> 10-20	0.91 (0.42-1.96)	.80	0.83 (0.38-1.82)	.65
> 20	1.56 (0.82-2.97)	.17	1.32 (0.67-2.60)	.42

Bivariate analysis controlled for the matching variables gender, age and practice. Multivariate analysis additionally controlled for educational level, presence of other psychiatric disease and number of somatic diseases prior to depression. The reference category for exposure duration to CVRFs is 0 years.
OR, odds ratio; CI, confidence interval.
[a] Wald chi-square test.

Table 3
Association between having any cerebrovascular risk factor (CVRF) and subsequent depression in three "age at depression onset" groups using multivariate conditional logistic regression analysis

	OR (95% CI)	p^a
Any CVRF with age at depression onset 50-59 years	1.88 (1.12-3.14)	.016
Any CVRF with age at depression onset 60-69 years	1.23 (0.64-2.35)	.542
Any CVRF with age at depression onset ≥ 70 years	0.53 (0.28-0.99)	.045

Analysis controlled for educational level, presence of other psychiatric disease and number of somatic diseases prior to depression. The reference category is patients without CVRFs.
OR, odds ratio; CI, confidence interval.
[a] Wald chi-square test.

Indeed, a significant interaction between any CVRF and age at depression onset group (likelihood ratio test: p = .010) confirmed that the influence of having any CVRF differed by age at depression onset group. A subsequent multivariate logistic regression (Table 3) showed that, relative to patients without CVRFs, having any CVRF significantly increased the odds of developing depression in the group with onset between ages 50 and 59 years. In the group with onset between ages 60 and 69 years, having any CVRF also increased the likelihood of subsequent depression, although this relationship was not significant. In contrast, in the group with onset at age 70 years or older, having any CVRF was associated with a significantly decreased odds of developing depression compared to patients without CVRFs. Furthermore, the odds ratio associated with having any CVRF in this oldest age at depression onset group was significantly smaller than that observed in the group with depression onset between ages 50 and 59 years (p = .002) and tended to be significantly smaller than the odds ratio for the group with onset between ages 60 and 69 years (p = .067). The odds ratios associated with having any CVRF did not differ significantly between the two younger age at depression onset groups (p = .31). Using a more detailed classification of age at depression onset yielded essentially similar results.

Given these results, we repeated our analyses concerning the CVRF variables under study while excluding the cases with an age at depression onset of 70 years or older and their matched controls. The demographic and clinical characteristics of the sub-sample are shown in Table 4, and Table 5 presents the regression results.

Having any CVRF significantly increased the odds of developing depression with onset between ages 50 and 69 years. Regarding individual CVRFs, the influence of having hypertension tended to be significant in both the bivariate and the multivariate model. Having diabetes significantly increased the likelihood of onset of depression between ages 50 and 69 years, while having any cardiovascular condition did not. Furthermore, a higher number of CVRFs was found to exert a significant effect. Additionally, patients who were exposed to CVRFs for more than 20 years were significantly more likely to have subsequent depression with onset between ages 50 and 69 years than patients who had no exposure to CVRFs. Finally, repeating all analyses after excluding cases with depressive feelings and their matched controls yielded basically similar results.

Table 4
Demographic and clinical characteristics of depressed cases with depression onset between ages 50 and 69 years and matched nondepressed controls

Characteristic	Depressed patients (*n* = 218)	Control patients (*n* = 641)
Age in 2001 (years): mean (SD), range	64.2(7.6), 51-87	64.2(7.7), 51-90
Female gender, *n* (%)	137 (62.8)	404 (63.0)
Educational level, *n* (%)		
High	23 (10.6)	66 (10.3)
Middle	91 (41.7)	282 (44.0)
Low	66 (30.3)	176 (27.5)
Missing	38 (17.4)	117 (18.3)
Other psychiatric disease prior to depression, *n* (%)	23 (10.6)	23 (3.6)
Number of somatic diseases prior to depression, *n* (%)		
0	67 (30.7)	198 (30.9)
1	52 (23.9)	187 (29.2)
2	34 (15.6)	116 (18.1)
≥ 3	65 (29.8)	140 (21.8)
Any CVRF prior to depression, *n* (%)	56 (25.7)	116 (18.1)
Individual CVRF prior to depression, *n* (%)		
Hypertension	36 (16.5)	74 (11.5)
Diabetes	17 (7.8)	24 (3.7)
Any cardiovascular condition	15 (6.9)	37 (5.8)
Number of individual CVRFs prior to depression, *n* (%)		
1	44 (20.2)	97 (15.1)
2	12 (5.5)	19 (3.0)
Exposure duration to CVRFs prior to depression (sum of years), *n* (%)		
> 0-10	37 (17.0)	84 (13.1)
> 10-20	8 (3.7)	19 (3.0)
> 20	11 (5.0)	13 (2.0)

CVRF, cerebrovascular risk factor.

Table 5
Association between cerebrovascular risk factor (CVRF) variables and subsequent depression with onset between ages 50 and 69 using separate conditional logistic regression analyses

	Bivariate		Multivariate	
	OR (95% CI)	p^a	OR (95% CI)	p^a
Any CVRF	1.61 (1.08-2.39)	.019	1.56 (1.03-2.35)	.034
Individual CVRF				
Hypertension	1.59 (0.99-2.55)	.057	1.57 (0.96-2.55)	.071
Diabetes	2.17 (1.12-4.18)	.022	2.02 (1.03-3.96)	.040
Any cardiovascular condition	1.16 (0.62-2.19)	.64	1.02 (0.53-1.98)	.95
Number of CVRFs	1.47 (1.09-1.99)	.013	1.42 (1.03-1.94)	.032
Exposure duration to CVRFs (sum of years)				
> 0-10	1.45 (0.90-2.32)	.12	1.42 (0.88-2.31)	.15
> 10-20	1.36 (0.57-3.26)	.49	1.30 (0.53-3.17)	.57
> 20	2.80 (1.20-6.54)	.018	2.64 (1.10-6.35)	.031

Bivariate analysis controlled for the matching variables gender, age and practice. Multivariate analysis additionally controlled for educational level, presence of other psychiatric disease and number of somatic diseases prior to depression. The reference category for exposure duration to CVRFs is 0 years.
CVRF, cerebrovascular risk factor; OR, odds ratio; CI, confidence interval.
[a] Wald chi-square test.

3.4 Discussion

In this general practice-based case-control study, none of the CVRF variables examined, including exposure duration to CVRFs, was significantly associated with the subsequent development of depression in later life. In addition, the results refuted our hypothesis that the relationship between having any CVRF and subsequent depression would be stronger in patients with an older age at depression onset compared with patients with a younger age at onset. That is, the odds ratio associated with having any CVRF was significantly smaller in the group with age at depression onset at age 70 years or older than in the group with onset of depression between ages 50 and 59 years and tended to be significantly smaller than the odds ratio observed in patients with onset of depression between ages 60 and 69 years. Subsequent analyses excluding the oldest age at depression onset group showed significant associations between CVRF variables, including long-term exposure duration to CVRFs, and subsequent depression with onset between ages 50 and 69 years. An

interpretation of these findings is that CVRFs play a relevant role in the development of depression with onset between ages 50 and 69 years, but that no evidence was found that CVRFs contribute to the occurrence of depression with onset at age 70 years or later.

However, strengths and limitations of the reliance on morbidity data recorded by GPs must be considered when interpreting our findings. A strong point was that the data allowed us to examine the influence of exposure to CVRFs over a lengthy period of time, rather than merely investigating the impact of presence or severity of CVRFs at a given time point. Another strength was that a largely unselected group was studied because almost all non-institutionalized Dutch citizens are registered with a GP. Therefore, potential referral bias was minimal. Furthermore, a possible influence of recall bias concerning onset data was minimized because these were ascertained on the basis of dates of diagnosis recorded by GPs instead of based on patient recall. Relying on GPs' records of morbidity has also limitations.

First, it is likely that the problem lists were not entirely complete regarding diagnoses of depression and CVRFs despite the implemented procedure to increase their completeness. Theoretically, this could have resulted in spurious significant results when the degree of completeness of the recorded CVRF diagnoses was substantially greater among cases than controls. However, we minimized this potential bias towards overestimation by including only controls who had at least one record of a health condition on their problem list. Second, only a limited range of CVRFs could be studied because the available data did not allow us to examine the influence of other risk factors (e.g. smoking, dyslipidemia), though not taking into consideration other CVRFs would most likely have attenuated a true relationship between CVRFs and depression rather than producing a spurious one. Third, examining diagnosis of depression made by GPs and not diagnosis based on a standardized assessment procedure may have led to a substantial misclassification of subjects who actually developed depression as not having had this disorder (i.e. underdiagnosis) and visa versa (i.e. overdiagnosis). At least, the rather low incidence of “depressive feelings” does suggest considerable underdiagnosis of subthreshold depression. If there is a true relationship between CVRFs and depression, misclassification of depression and/or depressive feelings would have resulted in an underestimation of the associations under study, though, in case of differential misclassification, there is also the possibility of

overestimating effects. For instance, underdiagnosis of depression may occur less frequently among patients with CVRFs because GPs have raised awareness of depression in these patients. However, we consider this unlikely for two reasons. First, as our study concerned older patients and only control patients were included who had been diagnosed with at least one health problem, the majority of the patients not suffering from CVRFs (i.e. 71%) had at least one somatic disease before the date of depression diagnosis (cases) or assigned "exit date" (controls). Given this high number together with the fact that these health problems in general concern conditions that require health care management and significantly affect a person's physical or emotional well-being [21], it is likely that most patients without CVRFs were also subject to increased vigilance by GPs. Second, it remains to be seen whether having CVRFs, or more broadly having a chronic somatic illness, leads to increased detection of depression by GPs. In fact, studies have suggested an opposite effect; that is, they have found that somatically ill patients who have comorbid major depression have a higher risk of not being diagnosed as depressed by GPs than those without a somatic illness [30-31]. A final limitation of our study is that only patients who were alive at the time of data collection were examined. There is growing evidence that depression significantly increases the risk of death in adults with diabetes [32], cardiovascular disease [33-34] or hypertension [35]. If so, differential mortality would have resulted in the non-participation of more cases than controls with CVRFs, which, in turn, would have led to an underestimation of the associations under study.

Having addressed potential sources of bias, we cannot rule out the possibility that bias towards underestimation explains the "failure" to find any of the CVRF variables to be significantly associated with the development of later-life depression in our total sample. That is, it is possible that particularly in the oldest age at depression onset group (onset ≥70 years) a significant bias towards underestimation was present because (1) the rate of overdiagnosis and especially underdiagnosis of depression by GPs may be higher in older age groups than among younger age groups [36-37], and/or because (2) the mortality rate of patients with CVRFs and comorbid depression may be higher in patients with an older age at depression onset relative to patients with a younger age at depression onset [38]. Such pronounced conservative bias in the oldest age at depression onset group could have masked "true" relationships between CVRFs and subsequent later-life depression in our total sample, which only came into

sight when this group was excluded from analysis. Further longitudinal research that circumvents the potential biases addressed above is needed to settle the role of CVRFs in the development of depression with onset at age 70 years or older. Anyhow, our findings may help explain why Lyness et al.[17] did not find significant associations between CVRF variables at baseline and subsequent depression symptoms and diagnoses at 1-year follow-up after controlling for overall medical burden. They examined a sample of primary care patients aged 60 years or older and also conducted separate analyses using a subset of patients with onset at age 60 years or later. However, no analyses were performed excluding patients with depression onset at age 70 years or older.

This is the first study that examined the association between duration of CVRFs exposure over time and the development of later-life depression. We found that patients who were exposed to CVRFs for more than 20 years were significantly more likely to develop depression with age at onset between 50 and 69 years than patients without CVRFs. In the context of the proposed model of Lyness et al. [3-4], this suggests that a long-term exposure to CVRFs is required before they contribute via the development of small-vessel brain disease to the occurrence of depression in later life. It should be noted that our measure of exposure duration to CVRFs weighted each individual CVRF (hypertension, diabetes, cardiovascular disease) equally and also did not take into account treatment of CVRFs. Additionally, in case of exposure to more than one specific CVRF, the exposure duration to each CVRF was simply summed. It is possible that the association between CVRFs and subsequent later-life depression varies with (the exposure duration to an) individual CVRF and that, consequently, each individual CVRF has to be given a specific weight. Our findings concerning specific CVRFs suggest that diabetes and hypertension may play a more important role than cardiovascular conditions in the development of depression in later life. Only a limited number of previous longitudinal studies have examined the association between a specific CVRF and the development of depression and their results are inconsistent [17; 39-41]. Also, the influence of age at depression onset was not considered in these studies. Further prospective studies are needed to determine whether long-term exposure to CVRFs exerts its effect on the development of later-life depression regardless of type of CVRF or that specific (combinations of) CVRFs do matter.

In sum, although our findings were essentially negative using the total sample of older general practice patients, results of subsequent analyses excluding the patients with onset of depression at age 70 years or older offered support for a longitudinal relationship between CVRFs and subsequent depression in later life. Replication is needed to exclude the possibility that our findings were substantially influenced by biases inherent to relying on morbidity data recorded by GPs. Ideally, such future research should take into account several other variables that appear to moderate the association of CVRFs with later-life depression, including executive functioning [42], severe life stress preceding onset of depression [43; 28] and physical symptoms and limitations [44].
Ultimately, subgroups of patients could be identified for whom the vascular depression concept is particularly relevant, which, in turn, may guide prevention of depression in later life through modification of CVRFs.

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4 The relationship between severity of Alzheimer's Disease and prevalence of comorbid depressive symptoms and depression: a systematic review

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Abstract

Objectives: To gain more insight into the association between severity of Alzheimer's Disease (AD) and prevalence of comborbid depression.

Methods: A systematic literature review based on the Cochrane methodology was performed. PubMed, PsychINFO and EMBASE databases were searched for existing studies that fulfilled predefined inclusion criteria. The studies were divided into: (1) those that analysed the association between severity of AD and prevalence of depressive symptoms ("continuous" approach) and (2) those that investigated the association between severity of AD and diagnosed depression ("categorical" approach). The quality of existing studies was rated and the results were synthesized with a best evidence synthesis.

Results: Twenty-four studies fulfilled the inclusion criteria. Nineteen reported results for a continuous approach and seven for a categorical approach.

Three of the four high quality studies within the continuous approach did not find a significant association between severity of AD and prevalence of depressive symptoms. None of the three high quality studies using the categorical approach found a significant association between the severity of AD and the prevalence of diagnosed depression.

Conclusions: There is evidence for a lack of association between the severity of AD and the prevalence of comorbid depressive symptoms or diagnosed depression. Until new studies contradict this conclusion, prevention and intervention strategies for comorbid depression in AD should be aimed at all patients irrespective their disease severity.

4.1 Introduction

According to recent studies up to 50% of patients with Alzheimer's Disease (AD) suffer from depression at least once during their disease course [1]. Comorbid depression in patients with AD has been associated with decreased quality of life [2], increased need for institutionalization [3], greater health care utilization[4], higher mortality rates [5] and decreasing caregiver's well being [6; 2]. These serious consequences ask for the development of strategies for prevention, early recognition and intervention for depression in AD. Diagnostic and preventive services should be targeted at those at greatest risk which means that it is important to understand who is most likely to develop depression. In addition, this tells us something about the underlying causes of depression and may help develop preventive and intervention strategies. Within this context, it is important to expand knowledge regarding the relationship between severity of AD and comorbid depression. The results of studies that have examined this relationship are inconsistent [7-9]. Explanations for these diverging results could be multiple, because the studies and study samples differ on many points.

One of the differences between the existing studies is the method used to determine the prevalence of depression: "continuous" or "categorical". Within the continuous method the number of prevalent depressive symptoms is determined without establishing a diagnosis of depression. According to the categorical method, diagnostic criteria for depression are used to determine if a patient suffers from comorbid depression or not. There are various other differences between existing studies that could possibly offer explanations for the diverging results:

1. Many studies group different types of dementia together,
2. Diagnostic procedures for AD differ between studies,
3. The assessment instruments for the severity of AD differ,
4. The instruments used to assess the prevalence of depression are multiple, also within the continuous and categorical approach and
5. Study samples differ in many relevant aspects, such as severity of AD, living situation, history of depression, or use of psychotropic medication.

In order to gain more insight into the relationship between the prevalence of depression and severity of AD we conducted a systematic literature review by systematically analysing the differences, similarities and methodological

quality of existing empirical studies. The division into studies that use a continuous or a categorical approach forms the main structure around which the results of the review are presented and discussed.

4.2 Methods

The systematic review was conducted in accordance with a predefined research protocol following the guidelines of the Cochrane Collaboration [10] that prescribed the following steps: (1) inclusion criteria, (2) search method, (3) selection method, (4) data extraction, (5) assessment of methodological quality, (6) data synthesis. Steps 3 to 6 were performed independently by the first two authors (RV, JN).

Inclusion criteria

Type of research. This review included naturalistic studies that conducted cross-sectional analyses on the relationship between severity of AD and prevalence of comorbid depressive symptoms or depression.

Patients. Studies had to involve patients who had been diagnosed with AD according to established diagnostic methods and criteria (e.g. NINCDS-ADRDA[11], ICD-10 [12], DSM-III-R or DSM-IV [13-14] criteria.)

Measurement of AD severity. Only studies using a validated measure for AD severity were included. Scales that just measure degree of cognitive impairment as a measure for the severity of AD (e.g. Minimal Mental State Examination (MMSE) [15]) as well as scales that also take non-cognitive aspects of AD into account (e.g. Global Deterioration Scale (GDS) [16]) were included.

Measurement of depression. In the case of continuous studies: only studies using an established, validated rating scale for measuring depressive symptomatology were included, regardless of whether the rating scale used was specifically developed to assess depressive symptoms in patients with dementia, e.g. the Cornell Scale for Depression in Dementia (CSDD) [17,] or not, e.g. the Hamilton Depression Rating Scale (HDRS) [18]. In the case of categorical studies: those studies were included that either employed established diagnostic criteria for major depressive disorder (MDD) (e.g. DSM-III-R/-IV or ICD-10 criteria) or used an empirically validated cut-off score on a rating scale for depressive symptoms specifically devised for patients with dementia (e.g.

CSDD score >12 [19; 17]).
Statistical analysis. Only studies were included that tested the relationship between severity of AD and prevalence of depressive symptoms or depression for statistical significance.

Search method
In March 2006 we searched in three international bibliographical databases, i.e. PubMed, PsychINFO and EMBASE, for all studies that were published in English until that date and potentially fulfilled all five inclusion criteria. The databases were searched using the following strategy that was formulated in PubMed and adapted to the other databases: Dementia [MESH] AND (Depression [MESH] OR Depressive Disorder [MESH]). All literature lists of possibly relevant studies were also screened for additional references.

Selection method
A first selection for inclusion was performed by the first author (RV). On the basis of titles and abstracts all studies that clearly did not meet one of the five inclusion criteria were excluded from the review. If a study appeared to meet the inclusion criteria or if there was any doubt, the full article was read. A second selection was made by two reviewers independently (RV, JN). Based on the full articles both reviewers checked if the studies satisfied all five criteria. Disagreements regarding inclusion status were resolved by discussion. In three cases no consensus could be met and a third reviewer (AF) was consulted.

Data extraction
After the selection procedure, the two reviewers (RV, JN) independently documented the following characteristics of each study:

1. the diagnostic criteria employed to establish presence of AD;
2. the characteristics of the study sample of patients with AD (i.e. size, inpatients or outpatients, socio-demographics, and, if reported, other relevant characteristics such as duration of AD, presence of depression prior to the onset of AD);
3. the rating scale used to measure severity of AD;
4. the rating scale used to measure depressive symptoms OR the diagnostic procedure used to establish presence of depression;
5. the dependent and independent variable studied and the statistical

technique used to examine their relationship. If a multivariate technique was employed, the included covariates were also documented;

6. a short description of the results (i.e. significant or non-significant relationship, and, if reported, descriptive statistics, test statistics, *p*-value);
7. the direction of the association (in case a significant relationship was found).

The findings of the two researchers were compared and disagreements were resolved by discussion. The extracted data is presented for continuous and categorical studies in two separate tables.

Assessment of quality

After the data extraction, the quality of each included study was rated independently by the two researchers (RV, JN), using a set of five predefined criteria (box 1). Criteria one to three concerned the internal validity and four and five are statistical criteria. The criteria cover the key domains (1) comparability of subjects (between studies) (2) outcome measurement and (3) statistical analyses that are formulated by the U.S. Agency for Healthcare Research and Quality for observational studies (AHRQ)[20]. Studies were considered to be of "high quality" if at least three quality criteria were met.

Several studies examined the relationship between severity of AD and prevalence of depressive symptoms or depression in more than one way - either by employing different statistical techniques or by performing the same analytical technique using the scores of different rating scales for measuring depression symptomatology and/or severity of AD. These so-called "sub-studies" were evaluated independently.

For each of the five quality criteria scoring positively, a (sub-)study received one "quality" point. The methodological quality of a (sub-)study was operationalized simply as the sum of all criteria scoring positively and thus potentially ranged from 0 to 5. There were no disagreements between the two researchers regarding the methodological quality ratings.

Box 1

Quality criteria

1. The diagnosis of AD is established according to the 'golden standard', the NINCDS-ADRDA criteria [11];
2. Severity of AD is assessed using a clinical instrument that besides cognitive capabilities also takes account of functional and/or clinical factors: (a) CDR [21] or (b) GDS [16];
3. Regarding studies that use a continuous approach, depressive symptoms are assessed using a rating scale specifically developed for patients with dementia. In studies with a categorical approach this type of rating scale should be used in combination with established diagnostic criteria for major depressive disorder. The following depression rating scales are specifically developed for demented populations: (a) the CSDD [17], (b) the NPI depression subscale [22], (c) the Dementia Mood Assessment Scale (DMAS) [23], (d) the Revised Memory and Behavior Problem Checklist (RMBPC) [24];
4. The statistical analysis controls for the possible influence of at least two of the following confounders known to be associated with comorbid depression: (a) gender, (b) history of depression, (c) history of other psychiatric disorder, (d) current other psychiatric disorder, (e) current use of antidepressant or psychotropic medication, (f) degree of functional impairment;
5. The sample size of patients with AD is at least as large as the median sample size of all included studies in the review (n = 78).

Best evidence synthesis

A "best evidence synthesis" [25] was conducted to determine the existing evidence for a relationship between severity of AD and prevalence of depressive symptoms and diagnosed depression. Levels of evidence were based on an earlier review of observational studies [26]. Box 2 shows the principles of the best evidence synthesis.

Box 2

Principles of Best Evidence Synthesis

Evidence:
Provided by consistent outcomes in at least 75% of the studies with a quality score ≥ 3

Insufficient evidence:
If less than 75% of the studies with a quality score ≥ 3 have consistent outcomes OR

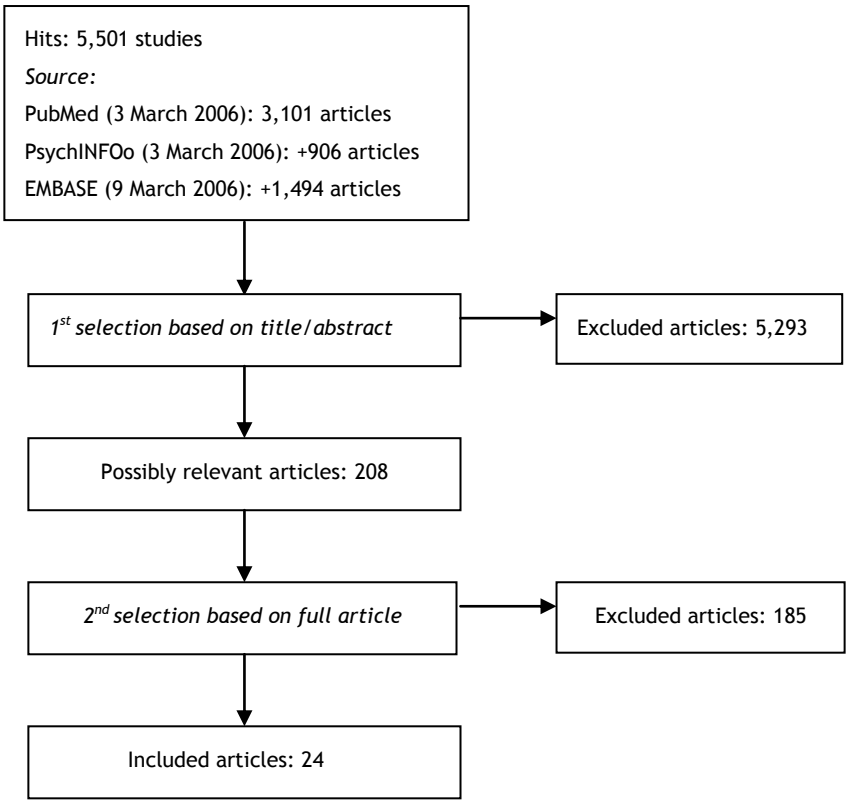
If no studies received a quality score ≥ 3

4.3 Results

Search results and selection of studies

Figure 1 shows the results of each phase in the search method and selection of studies.

Figure 1
Results of database searches and selection methods



Searching the specified databases according to the strategy described above resulted in 5,501 hits. Of these, 208 articles were judged by the first author to be possibly relevant on the basis of titles and abstracts. Based on full articles found, the first two authors agreed that 21 studies met the four inclusion criteria. A screening of reference lists of all 208 articles resulted in the inclusion of three additional studies. Of the total of 24 included studies, 19 reported results of analyses on the relationship between severity of AD and prevalence of depressive symptoms (continuous approach) and seven on the association between severity of AD and prevalence of diagnosed depression (categorical approach). Two studies used both approaches.

Data extraction

The extracted data and quality rating of each included study are presented in table 1 (continuous approach) and 2 (categorical approach). Studies were ordered by their methodological quality rating. The 19 "continuous" studies included 34 (sub-)studies, and the seven "categorical" studies included nine (sub-)studies.

The last column of table 1 and 2 indicates whether or not a significant association was found between the severity of AD and the prevalence of comorbid depressive symptoms or diagnosed depression and, if so, the direction of the association. In studies with a continuous approach eight times a positive association was found, two times a negative association and 24 times no association. In studies with a categorical approach two times a negative association was found and seven times no association.

Best Evidence Synthesis

Only four studies within the continuous approach and three studies within the categorical approach were rated as being of high methodological quality. Three of these four "continuous" studies found no association between severity of AD and depressive symptoms and all three "categorical" studies demonstrated found no relationship between severity of AD and prevalence of diagnosed depression.

Following the principles of the best evidence synthesis within both approaches we found scientific evidence for a lack of association between the severity of AD and the prevalence of depressive symptoms or diagnosed depression.

Table 1
Studies on the association between severity of dementia and prevalence of depressive symptoms in patients with Alzheimer's Disease (AD)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD
Piccininni *et al.*, 2005	3	NINCDS-ADRDA criteria for probable AD	*n* = 50; Outpatients; Female gender: 76%; Age: M(SD)= 69.3(7.5), Range= 53-84; Education: M(SD)= 6.5(3.9) Duration AD (months): M(SD)= 57.7(37.3) *Exclusion criteria*: history of alcoholism or psychiatric disturbances prior to the onset of dementia; drug abuse or dependence	(1) GDS: Mild (score: 2-3): 28%; Moderate (score: 4-5): 54%; Severe (score: >5): 18% (2) MMSE: M(SD)= 16.8(5.6)
Harwood *et al.*, 2000a	3	NINCDS-ADRDA criteria for possible/ probable AD	*n* = 114; Outpatients; Female gender: 63% Age: M(SD)= 78.8(6.5), Range= 59-92; Education: M(SD)=11.9(3.5); Range= 2-20; Hispanic: 44%; Duration AD: M(SD)= 3.4(2.5); Range= 1-11	MMSE: M(SD)= 17.8(7.2)
Harwood *et al.*, 1998	3	NINCDS-ADRDA criteria for probable AD	*n* = 137; Outpatients; Female gender: 70% Age: M= 78.2, Range= 63-95; Education: M= 10.4, Range= 0-20; Hispanic: 50.4%; Duration AD: M= 4.1; Range= 0-14	MMSE: M=15.6, Range= 0-29
Brodaty and Luscombe, 1996	3 & 2[c]	NINCDS-ADRDA criteria for AD	*n* = 208; Outpatients *Total sample of patients with dementia* (*n* = 288)[d]: Female gender: 55%; Age: M(SD)=71.4(7.7); Education: M(SD)=9.7(3.4)	*Total sample of patients with dementia*[d]: (1) MMSE: M(SD)= 18.2(7.2); Mild (score: ≥22); Moderate (score: <22) (2) CDR: score 0.5: 30.0%; score 1: 48.3%; score 2: 15.7%; score 3: 6.0%
Müller-Thomsen *et al* ., 2005	2	NINCDS-ADRDA criteria for probable AD	*n* = 316[f] ; Outpatients *Patients with MMSE ≥18* (*n* = 157): Female gender: 65% Age: M(SD)= 72.7(8.7) *Patients with MMSE<18* (*n* = 159): Female gender: 74% Age: M(SD)= 72.6(9.0)	MMSE: Mild (score: ≥18): 49.7%; Moderate-severe (score: <18): 50.3% Mild: M(SD)= 22.3(2.8); Moderate-severe: M(SD)= 11.6(4.4)
Levy *et al.*, 1998	2	NINCDS-ADRDA criteria for probable AD	*n* = 30; Outpatients; Female gender: 63%; Age: M=74, Range= 54-85	MMSE: M(SD)= 17.5(7.0)
Bungener *et al.*, 1996	2	NINCDS-ADRDA criteria for possible/ probable AD	*n* = 118; Outpatients; Female gender: 64% Age: M(SD)= 70.1(7.8), Range= 52-86; Education: <6: *n* = 49, 7-11: *n* = 38, ≥12: *n* = 29; Early-onset AD: *n* = 61, Late-onset AD: *n* = 55	(1) MMSE: M(SD)=19.1(5.8); Range= 3-29 (2) DRS: M(SD)= 104.8(20.5)

Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
NPI depression subscale: M(SD)= 3.3(3.7)	ANOVA: Comparison between mildly, moderately and severely impaired groups regarding NPI-depression score	Mildly impaired group: M(SD)= 3.7(4.0); Moderately impaired group: M(SD)=2.7(3.1); Severely impaired group: M(SD)=4.7(5.0); Overall comparison: p = 0.35	No significant association
RMBPC 9-item depression scale: M(SD)= 8.4(7.8)	Pearson correlation between RMBPC and MMSE scores	r= 0.02, n.s.	No significant association
CSDD: M= 5.2, Range= 0-25; Mild (8-12): 9.5%; Moderate (>12): 11.7%	Pearson correlation between CSDD and MMSE scores	r= -0.25, p < 0.01	More severe depressive symptoms in more severe AD
HDRS (21-item version): M(SD)= 6.7(5.3)[e] *Total sample of patients with dementia*[d]: MDD (DSM-IV criteria): 6.3%	(1) Spearman correlations with Bonferroni correction between (a) HDRS and MMSE scores; (b) HDRS and CDR scores (2) t test: comparison between mildly and moderately impaired groups (based on MMSE) regarding HDRS scores	(1a) significant negative correlation; (1b) n.s. (2) mildly impaired group had a significantly lower HDRS score	(1a&2) More severe depressive symptoms in more severe AD (1b) No significant association
(1) GDS (15-item version) (2) MADRS (3) CSDD	ANOVAs: Comparison between mildly and moderately-severely impaired groups (based on MMSE) regarding: (1) GDS score (2) MADRS score (3) CSDD score	A: Mildly impaired group B: Moderately-severely impaired group (1) A(n = 140): M(SD)= 4.5(3.3); B(n = 101): M(SD)= 4.6(2.6), n.s. (2) A(n = 120): M(SD)= 10.1(6.7); B(n = 76): M(SD)= 12.8(8.8), p < 0.10 (3) A(n = 31): M(SD)= 6.7(5.0); B(n = 16): M(SD)= 8.1(5.1), n.s.	(1-3) No significant association
NPI depression subscale: M(SD)= 1.2(1.6)	Spearman correlation between NPI-depression and MMSE scores	Nonsignificant trend toward a negative correlation	No significant association
(1) HDRS (17-item version): M(SD)= 8.1(4.6), Range= 0-22 (2) RRS: M(SD)= 9.3(4.0), Range= 3-29	Pearson correlations between (1) HDRS and MMSE scores (2) HDRS and DRS scores (3) RRS and MMSE scores (4) RRS and DRS scores	(1) n.s. (2) n.s. (3) r = -0.27, p = 0.003 (4) r = -0.31, p < 0.001	(1&2) No significant association (3&4) More severe depressive

Table 1 *continued*

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD
Haupt *et al.*, 1995	2	ICD-10 draft criteria for mild to moderate dementia in AD	*n* = 78; Outpatients; Female gender: 73%; Age: M(SD)= 74.3(7.5), Range= 57-90; Age at symptom onset: M(SD)= 69.4(7.3); Past history of depression: 0%; Antidepressant medication within the 2-year study period: 32%; no patient had to stay on antidepressant medication for >3 weeks	(1) MMSE (2) CAMCOG: M(SD)= 36.2(24.4) (3) GDS: score 5: 54%; score 6: 35%; score 7: 11%
Verhey *et al.*, 1995	2	NINCDS-ADRDA criteria for possible or probable AD	*n* = 48; Outpatients; Female gender: 65%; Age: M(SD)= 72.9(7.6); Education [1(primary school) – 7(university grade)]: 3.6(1.3); Duration AD: M(SD)= 3.28(2.4)	GDS: M(SD)= 4.8(0.9); Very mild (score: 3): 8.3%; Mild (score: 4): 25.0%; Moderate (score: 5): 45.8%; Severe (score: 6): 20.8%; Very severe (score: 7): 0%
Feher *et al.*, 1992	2	NINCDS-ADRDA criteria for probable AD	*n*=83; Outpatients; Female gender: 49% Age: M(SD)= 65.6(5.7); Education: M(SD)= 13.3(2.8) *Exclusion criteria*: Current psychiatric diagnosis (DSM-III-R criteria); HDRS score >16	MMSE: M(SD)= 19.4(2.9), Range= 12-23
Gottlieb *et al.*, 1988	2	NINCDS-ADRDA criteria for probable AD	*n*=43; Outpatients; Female gender: 67%; Age: M(SD)= 72.8(7.3), Range= 55-88; Education: M(SD)= 11.9(3.6), Range= 4-18 *Exclusion criteria*: evidence of other psychiatric disorder; history of significant psychiatric disorder; requiring acute psychiatric intervention at the time of initial presentation	GDS: Low (score: 3-4): 55.8% High (score: ≥5): 44.2%
Weiner *et al.*, 1997	1	NINCDS-ADRDA criteria for AD	*n* = 30; Outpatients Age: M(SD)=72.5(6.4), Range= 6-28; Education: M(SD)=12.6(4.0), Range= 3-20	MMSE[h]: M(SD)=17.3(6.4), Range= 6-28
Fitz and Teri, 1994	1	DSM-III-R criteria for AD	*N* = 91; Outpatients; Female gender: 55%; Age: Range= 46-90	DRS: M(SD)=102(18.8), Range= 56-139; Mild (score: <102): 50.5%; Moderate (score: >103): 49.5%
Troisi *et al.*, 1993	1	NINCDS-ADRDA criteria for probable AD	*n* = 26; Outpatients; Female gender: 54%; Age: M(SD)= 74.0(5.5), Range= 65-84; Education: M(SD)=7.15(5.0), Range= 0-19	(1) MMSE: mild-moderate (score: 16-23): 50%; severe (score: ≤15): 50% (2) DSM-III-R: Mild: 26.9%; Moderate: 42.3%; Severe: 30.8%

Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
DMAS mood subscale: M(SD)= 14(6.6), Range= 2-31	Correlations between[g]: (1) DMAS and MMSE scores (2) DMAS and CAMCOG scores	(1) 0.02, n.s. (2) 0.04, n.s.	(1&2) No significant association
HDRS (17-item version): M(SD)= 9.4(9.4) MDD (DSM-III-R criteria): 6.3%	Spearman correlation between HDRS and GDS scores	r = 0.04, n.s.	No significant association
(1) HDRS (17-item version): M(SD)= 4.0(3.1) (2) GDS (30-item version): M(SD)= 7.8(5.4)	Correlations between: (1) HDRS and MMSE scores; (2) GDS and MMSE scores (3) multivariate linear regression: Dependent: GDS score; (a) hierarchical: HDRS scores were entered first; followed by MMSE, memory test and self-awareness scores (b) simultaneous entry	(1) -0.15, n.s. (2) -0.15, n.s. (3a&b) MMSE score was not a significant predictor of GDS score, $p > 0.10$	(1-3) No significant association
(1) HDRS (17-item version) (2) SDS	t tests: Comparison between low- and high-impaired groups (based on GDS) regarding (1) HDRS score and (2) SDS score	A: High-impaired group B: Low-impaired group (1) A: M(SD)= 2.2(3.0), Range=0-10; B: M(SD)= 3.3(6.1), Range=0-28, t < 1, n.s.	(1&2) No significant association
HDRS (21-item version): (a) Patient's report: M(SD)= 5.7(3.6), Range= 1-12; (b) Caregiver's report: M(SD)= 9.3(5.2), Range= 0-21	Correlations between (1) patient's report HDRS and MMSE scores; (2) caregiver's report HDRS and MMSE scores	(1) n.s. (2) n.s.	(1&2) No significant association
HDRS (17-item version) MDD (DSM-III-R criteria): 50.5%	(1) Pearson correlation between HDRS and DRS scores; (2) Comparison between mildly and moderately impaired groups (based on DRS) regarding HDRS score	(1&2) n.s.	(1&2) No significant association
HDRS (17-item version): Mild-moderate (score: 10-16): 30.8%; Marked (score: ≥17): 7.7% MDD (DSM-III-R criteria): 23.1%	ANOVA and PLSD posthoc tests: (1) comparison between mildly- moderately and severely impaired groups (based on MMSE) regarding HDRS score; (2) comparison between mildly, moderately and severely impaired groups (based on DSM-III-R) regarding HDRS score	(1) Overall: $p < 0.05$; Posthoc: severely impaired group had significantly higher HDRS score ($p < 0.05$); (2) Overall: $p = 0.01$; Posthoc: severely impaired group had significantly higher HDRS score than mildly ($p < 0.01$) and moderately impaired ($p < 0.05$) groups	(1&2) More severe depressive symptoms in more severe AD

Table 1 *continued*

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD
Sultzer *et al.*, 1992	1	NINCDS-ADRDA criteria for probable AD	*n* = 61; Outpatients (majority) and inpatients; Female gender: 5%; Age: M(SD)=73.0(7.8), Range= 53-88 Education: M(SD)= 13.0(3.2), Range= 7-20 Duration: M(SD)= 5.8(3.7), Range= 1-20 *Exclusion criteria*: history of psychotic disorder prior to onset of dementia; evidence of psychoactive substance use	MMSE: M(SD)= 10.0(8.5), Range= 0-28
Fischer *et al.*, 1990	1	NINCDS-ADRDA criteria for probable AD	*n* = 55; Inpatients; Female gender: 87%; Age: M(SD)=79.4(8.8), Range= 58-93; No patient received antidepressants at the time of investigation or for 2 weeks previously	MMSE: M(SD)= 11.5(9.1), Range= 0-23; Mild (score: 16-23): 41.8%; Moderate (score: 6-15): 23.6%; Severe (score: <6): 34.5%
Shuttle-worth *et al.*, 1987	1	NINCDS-ADRDA criteria for AD	*n* = 22; Outpatients; Female gender: 59%; Age: M= 67.1; Education: M= 14.5	MMSE: Mild (score: 20-25): 31.8%; Moderate (score: 15-19): 36.4%; Severe (score: 5-14): 31.8%
Galynker *et al.*, 1995	0	DSM-III-R criteria for AD	*n* = 26; Outpatients; Female gender: 58%; Age: M(SD)=78.8(6.45), Range 63-89; Antipsychotic medication: 26.9% Benzodiazepines: 23.1% Antidepressants: 15.4%	MMSE: M(SD)=16.8 (7.52), Range= 1-28
Teri and Wagner, 1991	0	DSM-III-R criteria for AD	*n* = 75; Outpatients; Female gender: 68%; Age: M(SD)=74.0(7.4), Range= 46-89 Education: ≤12th grade: 72%, >12th grade: 28%	(1)MMSE: M(SD)= 18.1(5.7), Range= 4-27; Mild (score: >21): 30.7%; Moderate (score: 21-16): 37.3%; Severe (score: <16): 32.0% (2) GDS: M(SD)=4.6(1.0), Range= 2-6

CAMCOG, Cambridge Cognitive Examination; CDR, Clinical Dementia Rating Scale [27]; CSDD, Cornell Scale for Depression in Diagnostic and Statistical Manual of Mental Disorders, third revised (DSM-III-R) or fourth (DSM-IV) edition [13-14]; GDS, Geriatric Classification of Diseases, tenth edition (World Health Organization, 1987)[12]; MADRS, Montgomery and Åsperg Depression Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association [11]; NPI, Memory and Behavior Problem Checklist [24]; RRS, Retardation Rating Scale [33- 34]; SDS, Zung Self-Rating Depression Scale [35].
[a] Data concerning education and duration of AD are presented in years, unless stated otherwise. Only psychiatric exclusion criteria are presented.
[b] If available data on prevalence of major depression or dysthymia are also presented.
[c] This study had two different quality scores because separate analyses were performed using scores on different scales to assess severity of AD.
[d] No (further) data concerning the sample of patients with AD were reported.
[e] Missing data for 6 patients, *n* = 202.
[f] Depression scales were not performed in every patient with AD for various reasons.
[g] Results concern those at baseline.
[h] Missing data for 2 patients, *n* = 28.

Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
HDRS (17-item version): M= 10.3, Range= 1-22	Pearson correlation between HDRS and MMSE scores	r = -0.38, p = 0.003	More severe depressive symptoms in more severe AD
HDRS (17-item version): M(SD)= 12.4(5.8), Range= 2-27	(1) Kruskal-Wallis rank test: comparison between mildly, moderately and severely impaired groups (based on MMSE) regarding HDRS score; (2) Spearman correlation between HDRS and MMSE scores	(1) Mildly impaired group: M(SD)= 13.1(6.5); Moderately impaired group: M(SD)= 14.3(5.2); Severely impaired group: M(SD) = 9.9(3.9) Overall: p < 0.05 (2) r = 0.27, p < 0.05	(1&2) Less severe depressive symptoms in more severe AD
SDS: M= 41.2 MDD (DSM-III criteria): 41%	ANOVA: comparison between mildly, moderately and severely impaired groups (based on MMSE) regarding SDS score	Mildly impaired group: M= 41.4; Moderately impaired group: M= 41.6; Severely impaired group: M= 40.6; Overall: F= 0.98, d.f. = 2 and 19, n.s.	No significant association
HDRS (17-item version): M(SD)= 10.5(5.73), Range= 2-24	Pearson correlation with Bonferroni correction between HDRS and MMSE scores	r = -0.33, n.s.	No significant association
HDRS (17-item version): (a) patient's report: M(SD)= 5.0(5.2), Range= 0-26 ; (b) caregiver's report: M(SD)= 7.6(6.9), Range= 0-30; (c) clinician's evaluation: M(SD)= 8.2(6.9), Range= 0-30 MDD (DSM-III-R criteria): 29%	3(source) x 3(severity of AD) repeated measures MANOVA: Dependent: HDRS score; *Severity of AD*: mild, moderate, severe (based on MMSE); *Source*: patient, caregiver or clinician	No significant effect of severity of AD	No significant association

Dementia [17]; df, degrees of freedom DMAS, Dementia Mood Assessment Scale [23]; DRS, Mattis Dementia Rating Scale [28]; DSM, Depression Scale [29-30]; GDS, Global Deterioration Scale [16]; HDRS, Hamilton Depression Rating Scale [18,31]; ICD-10, International Scale [32]; MDD, Major Depressive Disorder; MMSE, Mini-Mental State Examination [15]; NINCDS-ADRDA, National Institute of Neuropsychiatric Inventory [22]; n.s., not significant; PLSD, Fisher's Protected Least Significant Difference; RMBPC, Revised

Table 2
Studies on the association between severity of dementia and prevalence of diagnosed depression in patients with Alzheimer's Disease (AD)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD
Harwood *et al.*, 2000b	3	NINCDS-ADRDA criteria for possible/ probable AD	*n* = 96; Outpatients; Female gender: 70%; Age: M(SD)= 74.9(6.8); Education: M(SD)= 9.9(5.2); Cuban American: 100%; Functional status (BDS): M(SD)= 5.8(4.2) Presence of delusions/hallucinations: 32.3%	MMSE: M(SD)= 15.9(6.5)
Lyketsos *et al.*, 1997	3	NINCDS-ADRDA criteria for probable AD	*n* = 109 Outpatients Female gender: 79% Age: M(SD)= 74.4(7.9) History of depressive disorder: 17.4%.	(1) CDR: Early (score: 0.5): 9.8%; Mild (score: 1): 38.2%; Moderate (score: 2): 29.4%; Severe (score: 3): 21.6% (2) MMSE: M(SD)= 15.0(6.5), Range= 0-28
Ballard *et al.*, 1996	3	NINCDS-ADRDA criteria for possible/ probable AD	*n* = 88; Outpatients *Total sample of patients with dementia* (*n* = 124)[c]: Female gender: 73% ; Age: M= 79.6 *Exclusion criteria*: fulfilment of the CAMDEX criteria for severe dementia	CAMCOG: *Total sample of patients with dementia*[c]: M= 43.9
Lopez *et al.*, 2003	2	NINCDS-ADRDA criteria for probable AD	*n* = 1,155; Outpatients; Female gender: 70%; Education: M(SD)= 12.0(3.0); Duration AD: M(SD)= 4.0(2.7); African Americans: 6.3% ; BDS: M(SD)= 6.1(4.2) Antidepressants: 19.0% Sedatives, hypnotics and anxiolytics: 6.3% Antipsychotics: 7.7%	(1) MMSE: M(SD)=16.9(6.1); Mild (score: ≥20): 37.9%; Moderate (score: 10-19): 48.7%; Severe (score: ≤9): 13.3% (2) DRS: M(SD)= 107.4(22.9) (3) CDR: M(SD)= 1.3(6.8)
Payne *et al.*, 1998	2	NINCDS-ADRDA criteria for possible or probable AD	*n* = 151; Outpatients; Female gender: 81%; Age: M(SD)=78.1(7.9); Caucasian: 80.7%; Functional status (PGDRS-P): M(SD)= 7.5(7.5)	MMSE: M(SD)=14.7 (7.3)

Prevalence of depression[b]	Statistical analysis	Results	Direction of association
Depression (CSDD score: ≥7): 39.6% CSDD (all AD patients): M(SD)= 7.4(6.9), Range= 0-28	Multivariate logistic regression: Dependent: depression (0/1); Independent: MMSE score; Covariates: age, education, gender, marital status, functional status and psychosis	OR(95% CI)= 0.9 (0.9-1.0), p = 0.25	No significant association
(a) MDD (DSM-IV criteria): 22%; (b) Minor depression (depressed mood, crying spells, or anhedonia according to CSDD and CSDD score: >6): 27%; (c) remaining patients: 51% CSDD (all AD patients): M(SD)= 8.0(7.2), Range= 0-28	Chi-square test: Distribution of the 3 depression groups across CDR scores	X^2= 5.86, d.f.= 4, p = 0.21	No significant association
MDD (depressive symptoms were rated using the CSDD; next, diagnosis was made according to the RDC criteria): 17.0% CSDD (all AD patients): M= 9.2	Bivariate logistic regression: Dependent: depression (0/1); Independent: CAMCOG score	Wald chi-square test= 0.63, p = 0.43	No significant association
MDD (depressive symptomatolo-gy was rated using the BRSD, HDRS and BDS; next, diagnosis was made according to DSM-III/ -III-R/ -IV criteria): 17.0% HDRS (all AD patients; 17-item version): M(SD)= 6.4(4.4)	Chi-square test: Comparison between mildly, moderately and severely impaired groups (based on MMSE) regarding frequency of MDD	MDD: Mildly impaired group: 11.5%; Moderately impaired group: 10.0%; Severely impaired group: 4.5%; X^2= 6.03, d.f.= 2, p = 0.04	Lower likelihood of depression in more severe AD
Depression (CSDD score: >12): 17% CSDD (all AD patients): M(SD)= 6.6(6.1), Range= 0-25	(1) bivariate logistic regression: Dependent: depression (0/1); Independent: MMSE score (2) multivariate logistic regression: Covariate: functional status	(1) OR(95% CI)= 1.03 (0.97-1.09) (2) OR(95% CI)= 1.09 (1.01-1.19)	(1) No significant association (2) Lower likelihood of depression in more severe AD

Table 2 *continued*

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD
Fitz and Teri, 1994	1	DSM-III-R criteria for AD	*n* = 91; Outpatients; Female gender: 55% Age: Range: 46-90	DRS: M(SD)= 102(18.8), Range= 56-139; Mild (score: <102): 49.5%; Moderate (score: >103): 50.5%
Troisi *et al.*, 1993	1	NINCDS-ADRDA criteria for probable AD	*n* = 26 Outpatients Female gender: 54% Age: M(SD)= 74.0(5.53), Range= 65-84 Education: M(SD)=7.15 (5.03), Range= 0-19	(1) MMSE: mild-moderate (score: 16-23): 50%; severe (score: ≤15): 50% (2) DSM-III-R: Mild: 26.9% Moderate: 42.3% Severe: 30.8%

ADRDA, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Registry for Alzheimer's Disease (CERAD) [37]; CAMCOG, Cambridge Cognitive Examination [34]; CAMDEX, Cambridge Mental for Depression in Dementia [17]; df, degrees of freedom; DRS, Mattis Dementia Rating Scale [28]; DSM, Diagnostic and Statistical Depression Rating Scale 18; MDD, Major Depressive Disorder; NINCDS--MMSE, Mini-Mental State Examination [15]; n.s., not Diagnostic Criteria [40].

[a] Data concerning education and duration of AD are presented in years, unless stated otherwise. Only psychiatric exclusion criteria are presented.

[b] If available scores on depression rating scales for the sample of patients with AD are also presented.

[c] No (further) data concerning the sample of patients with AD were reported.

Prevalence of depression[b]	Statistical analysis	Results	Direction of association
MDD (DSM-III-R criteria): 50.5%	Comparison between mildly and moderately impaired groups (based on DRS) regarding frequency of MDD	MDD: Mildly impaired group: 56.5%; Moderately impaired group: 44.4%; n.s.	No significant association
MDD (DSM-III-R criteria): 23.1%	Chi-square tests: (1) comparison between control, mildly-moderately and severely impaired groups (based on MMSE) regarding frequency of MDD (2) comparison between control, mildly, moderately and severely impaired groups (based on DSM-III-R criteria) regarding frequency of MDD	(1) MDD: mildly-moderately impaired group: 7.7%; severely impaired group: 38.5%; control group: 11.5%; X^2= 5.51, d.f.= 2, p = 0.06 (2) MDD: Mildly impaired group: 0%; Moderately impaired group: 11.5%; Severely impaired group: 11.5%; Control group: 11.5%; X^2= 5.11, d.f.= 3, n.s.	(1&2) No significant association

Association [11]; BDS, Blessed Dementia Scale [36]; BRSD, Behavioral Rating Scale for Dementia of the Consortium to Establish a Disorders in the Elderly Examination [34]; CDR, Clinical Dementia Rating Scale [27]; CI, Confidence Interval; CSDD, Cornell Scale Manual of Mental Disorders, third (DSM-III), third revised (DSM-III-R) or fourth (DSM-IV) edition [38, 13-14]; HDRS, Hamilton significant; OR, Odds Ratio; PGDRS-P, Psychogeriatric Dependency Rating Scale- Physical dependency scale [39]; RDC, Research

4.4 Conclusion and discussion

The main conclusion of this systematic review is that, based on current knowledge, evidence exists for a lack of association between the severity of AD and the prevalence of comorbid depressive symptoms or depression.

Earlier non-systematic literature reviews [e.g. 41] often stated that no conclusions about the relationship between the severity of AD and the prevalence of comorbid depression could be drawn due to large differences between existing studies. In this review we used various methods to overcome this problem: in the first place selection criteria were formulated that make sure that (1) all study samples consisted of people with AD and, (2) valid assessment methods for depression and severity of AD were used. Secondly, selected studies were categorized into two groups: those that focused on the prevalence of depressive symptoms (continuous approach) and those that examined the prevalence of diagnosed depression (categorical approach). In addition the quality of all selected studies was rated, in order to select the studies with the highest validity.

Limitations of this review are that only studies published in English were included and studies that did not have depression or depressive disorder as a keyword were not identified. We do however not consider it very likely that high quality studies were missed because of this.

The finding that comorbid depressive symptomatology or diagnosed depression is not more prevalent in early, mild or severe AD contrasts with what is often theorized in physiological and psychological theories. These theories hypothesize that the prevalence of depression either decreases (psychological theories) or increases (physiological and psychological theories) with the increasing severity of AD. Interactive theories [42] do however offer a possible explanation for the current findings. According to these theories the neurological and psychosocial factors can reinforce or diminish each other, depending on the specific situation of a patient. Only a longitudinal study could give more insight into the mechanisms underlying the aetiology of depression in AD.

Following the systematic approach of this review and using current knowledge, such a longitudinal study should ideally meet the following criteria: (a) establishing diagnosis of AD according to NINCDS-ADRDA criteria [11]; (b)

assessing severity of AD with a clinical instrument (e.g. CDR [21] or GDS [16]); (c) assessing symptoms of depression with an instrument specifically developed for people with dementia or specifically AD (e.g. CSDD [17] or NPI-depression subscale [22]); (d) establishing diagnosis of depression according to criteria specifically developed for people with AD, such as the Provisional Diagnostic Criteria for Depression of Alzheimer's Disease [41]; (e) using multivariate analytic techniques to control for known potentially important confounders (e.g. gender, history of depression, current use of antidepressant or psychotropic medication).

For clinical practice the conclusion of the review shows that the development of specific interventions for signalling, preventing and treating comorbid depression in the different severities of AD should continue.

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Part B

Studies on health care consequences

5 Accuracy of diagnosing depression in primary care: The impact of chronic somatic and psychiatric comorbidity

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Abstract

Background: Depression is highly comorbid with both psychiatric and chronic somatic disease. These types of comorbidity have been shown to exert opposite effects on underdiagnosis of depression by general practitioners (GPs). However, past research has not addressed their combined effect on underdiagnosis of depression.

Methods: Comorbidity data of 191 depressed primary care patients selected by a two-stage sampling procedure were analysed. Diagnoses of major depression and/or dysthymia in the last 12 months were assessed using a standardised psychiatric interview (CIDI) and compared with depression diagnoses registered by GPs in patient contacts during the same period. Presence of psychiatric and chronic somatic comorbidity was determined using the CIDI and contact registration, respectively.

Results: Regression analysis showed a significant interaction between psychiatric and chronic somatic comorbidity, while taking into account the effects of sociodemographic variables, depression severity and number of GP contacts. Subsequent stratified analysis revealed that in patients without chronic somatic comorbidity, a lower educational level, a less severe depression, and less GP contacts all significantly increased the likelihood of being not diagnosed as depressed. In contrast, in patients with chronic somatic comorbidity only having no psychiatric comorbidity significantly decreased the likelihood of receiving a depression diagnosis.

Conclusions: Our results indicate that there are differential effects of psychiatric comorbidity and other factors on underdiagnosis of depression by GPs among depressed patients with and those without chronic somatic comorbidity. Efforts to improve depression diagnosis by GPs seem to require different strategies for depressed patients with and those without chronic somatic comorbidity.

5.1 Introduction

Major depressive disorder (MDD) is a common disorder associated with significant disability, poorer quality of life, increased morbidity and mortality, and increased use of health services [1-2]. MDD does not occur frequently in pure form, but is often comorbid with other psychiatric disorders, in particular anxiety disorders [3-4], and a wide range of long-term medical conditions, including endocrine, neurological, cardiac, digestive, and respiratory disorders, cancer, diabetes mellitus, arthritis, hypertension, and acquired immunodeficiency syndrome [5-7].

Most depressive disorders are managed exclusively by general practitioners (GPs) [8]. However, despite being one of the most prevalent disorders in primary care [1], depression is poorly recognised and diagnosed by GPs, with most studies reporting a rate of underdiagnosis falling in the 60% to 70% range [9-10]. Although the clinical significance of this underdiagnosis has been argued [8], several lines of research underline that is worthwhile to improve the diagnosis of depression in primary care. First, a substantial proportion of undetected depressed patients have persistently poor outcomes over the course of one year [11-12]. Second, there is evidence for the efficacy of both pharmacological and psychotherapeutic interventions for the treatment of MDD in primary care [13-14]. The third and most important evidence is provided by recent systematic reviews of primary care trials, which have concluded that, compared with usual care, quality improvement efforts aimed at improving detection of depression can improve patients outcomes provided that those recognized receive adequate treatment and follow-up [15-16]. To improve the detection rate of depression by GPs, it is important to have detailed knowledge about the barriers to the diagnosis of depression. In this respect the impact of the frequent presence of comorbidity on underdiagnosis of depression should be more thoroughly examined.

Previous studies have shown that patients with MDD have a higher risk of being not diagnosed as depressed by GPs if they have additional somatic illness(es) [17-21]. In contrast, the co-occurrence of MDD and anxiety has been found to facilitate recognition of depression [22] or psychiatric caseness [21, 23-25]. However, these studies examined the effects of psychiatric and somatic comorbidity on underdiagnosis of depression separately and did not address their combined

effect at all. Because a substantial proportion of depressed primary care patients is expected to have both somatic as well as psychiatric comorbidity [6, 26] it is important to examine their combined effect, in particular in the context of their suggested opposite effects on underdiagnosis of depression. Therefore, the current study examines whether there is an interaction effect between psychiatric and chronic somatic comorbidity on GPs' diagnosis of depression, while accounting for the effects of factors that are frequently reported to be associated with depression diagnosis (i.e. sociodemographic factors, severity of depression, and number of contacts with GP). If so, then the effects of psychiatric comorbidity and the other factors will be studied in subgroups of depressed patients with and without chronic somatic comorbidity. The results could lead to a more precise identification of barriers to the diagnosis of depression and thereby contribute to improved quality of GP care and outcomes of MDD in primary care.

5.2 Method

Study setting

Data collection took place within the framework of the second Dutch National Survey of General Practice (2001; DNSGP-2 [27]), a nationwide study of morbidity and interventions in general practice in the Netherlands. The DNSGP-2 was carried out in 104 practices comprising of 195 GPs, who served approximately 390000 persons. The participating GPs were representative for all GPs in the Netherlands regarding age, gender, region of residence and urbanisation. Dutch GPs are gatekeepers for secondary health care and nearly all non-institutionalised persons are listed to a GP. Three datasets were used, i.e. data from (a) a health interview survey; (b) a standardised psychiatric interview, and (c) a contact registration.

Participants

A random sample of the practice population (n = 12,699) participated in an extensive health interview survey (response rate = 64.5%), spread over a whole year to avoid seasonal patterns. In total 1379 patients aged 18 and older had an indication of psychopathology as measured by two screening instruments

included in the health interview (see below). These patients were approached for follow-up psychiatric assessment using the Composite International Diagnostic Interview (CIDI) [28] , and 58.8% (*n* = 811) were actually assessed. CIDI data of 235 patients were not examined in this study because: (1) the data were either incomplete (*n* = 11) or obtained by using erroneously an earlier version of the CIDI (*n* = 6); (2) patients were diagnosed by their GP as either having dementia (*n* = 2) or a psychotic illness (*n* = 2) and presence of these disorders was not assessed using the CIDI; (3) patients had no contact with their GP within the time frame covered by the CIDI (*n* = 214). The remaining 576 patients did not differ significantly from the eligible patients who were not examined (*n* = 803) regarding age, educational level, GHQ-, and CAGE- scores, though, a higher proportion was female ($p < .01$). Of the 576 patients those were included in the final study population who fulfilled the DSM-IV criteria for MDD and/or dysthymia according to the CIDI (*n* = 191).

Measures

The Dutch version of the 12-item General Health Questionnaire (GHQ-12) was administered as a screener for nonpsychotic psychiatric morbidity [29]. Scores of ≥4 (first half of 2001) or ≥3 (second half of 2001) were used as thresholds for follow-up psychiatric assessment. The cut-off score was lowered to enlarge the group of eligible patients. A three/four threshold has a high sensitivity (84.6%) and specificity (89.3%) in a primary care setting [30]. Additionally, the Dutch version of the CAGE questionnaire was used to identify patients with alcohol problems [31]. The maximum score of four positive answers was used as a threshold for further psychiatric assessment. Although this criterion is highly specific for detecting alcohol abuse/dependence in primary care patients, it has a low sensitivity (23%) [32]. However, since this study examined patients with MDD who were already detected by the highly sensitive GHQ-12, falsely low prevalence rates of alcohol related disorders due to this low sensitivity were avoided.

The CIDI is a fully structured interview that allows administration by trained lay interviewers. The Dutch version of the computerised CIDI-auto 2.1 was used [33]. The fully specified structure does not allow judgement of the interviewer to intervene. Standardized probe questions establish that psychiatric symptoms are clinically significant and not due to medication, drugs or alcohol or to a physical illness or injury. After completion of the interview, computerized

algorithms provide diagnoses according to the DSM-IV. The presence of the following psychiatric disorders in the past 12 months was determined: phobic and other anxiety disorders, depressive disorders and dysthymic disorder, manic and bipolar affective disorder and disorders resulting from the use of alcohol. During the interview, respondents are asked about the first and last occurrence of psychiatric symptoms, on the basis of which the period during which a psychiatric disorder was present was estimated for each patient.
During one year, all GPs electronically recorded each diagnosis made during their contacts with a patient, coded according to the International Classification of Primary Care (ICPC) [34]. Contacts belonging to the same health problem were clustered into disease episodes.

Definitions

DSM-IV diagnoses obtained from the CIDI were considered as the reference standard. Patients were regarded to be depressed in case of a diagnosis of MDD and/or dysthymia (hereafter referred to as "depressed patients"). For all patients the diagnosis was considered positive when all diagnostic criteria (inclusion as well as exclusion criteria) were fulfilled, with the exception of two patients with dysthymic disorder for whom only inclusion criteria were met.
A GP diagnosis of depression could be coded under depression (ICPC code P76), which is based on the criteria of the International Classification of Health Problems in Primary Care [35]. These criteria are largely consistent with those of DSM-IV. In addition, depressive symptoms could also be coded under depressive feelings (ICPC code P03). Therefore, patients having an episode P76 and/or P03 were considered to be diagnosed as depressed by their GP, while patients without such episodes were considered to be not.
The presence of psychiatric comorbidity was determined on the basis of the CIDI data and was defined as having at least one CIDI diagnosis other than MDD/dysthymia. Psychiatric comorbidity had to be present during at least one GP-patient contact. The following three categories of psychiatric comorbidity were formed: alcohol abuse/dependence, bipolar disorder, and anxiety disorder, including the five subcategories panic disorder, agoraphobia (without panic), social phobia, generalized anxiety disorder (GAD), and simple phobia.
The presence of chronic somatic comorbidity was determined on the basis of ICPC coded diagnoses of chronic conditions recorded by GPs and defined as having at least one episode of chronic disease. It was ascertained that chronic

somatic comorbidity was present during the period of MDD and/or dysthymia. The following eight categories of chronic somatic comorbidity were created, based on the body systems involved: neurological conditions (migraine or regular serious headache, dizziness, Parkinson's disease, multiple sclerosis, epilepsy), musculoskeletal conditions (chronic rheumatism, rheumatic complaints of hips and knees, serious or persistent neck/shoulder, back, and hands/elbow/wrist disorder), circulatory conditions (hypertension, vascular disorder, myocardial infarction, other serious heart disorders, stroke), respiratory conditions (asthma/chronic bronchitis or chronic nonspecific lung disease), skin conditions (chronic eczema, psoriasis), endocrine, metabolic, and nutritional conditions (diabetes mellitus, hyperthyroidism, hypothyroidism), digestive conditions (serious disorders of the intestine longer than three months, e.g. Crohn's disease), and a rest category (incontinence, cancer, HIV infection, glaucoma).

Other explanatory variables included sociodemographic and clinical variables which frequently have been found to be associated with GPs' diagnosis of depression [10, 36]. Sociodemographic data (age, gender, highest educational level attained) were derived from the health interview survey. Educational level was categorised into three classes: low (none, elementary school), middle (high school), and high (college or university). Severity of depression was derived from the CIDI and was operationalised as the number of depressive symptoms with scores ranging from 5 to 9 (DSM-IV criterion A for MDD). Patients who had a diagnosis of dysthymia alone (n = 7) were given a score of four on this measure. Annual number of GP-patient contacts was categorised by quartiles, which resulted in the categories 1-3, 4-6, 7-10, and ≥ 11 contacts.

Statistical analyses

Rates of GPs' depression diagnosis in subgroups of depressed patients based on comorbidity characteristics were calculated to explore the relationship between comorbidity status and depression diagnosis. In a second explorative analysis, the bivariate relationships between comorbidity, sociodemographic (age, gender, educational level) and clinical (depression severity and GP contact rate) variables and depression diagnosis were examined using simple logistic regression analyses. Next, multivariate logistic regression analysis was conducted in three steps. The first model entered psychiatric comorbidity and chronic somatic comorbidity. In addition to the comorbidity variables, model 2

entered the sociodemographic and clinical variables. The final multivariate model included model 1 and 2 variables, plus the interaction term between psychiatric and chronic somatic comorbidity. In case of a significant interaction effect, separate multivariate analyses were carried out in patient subgroups stratified by presence or absence of chronic somatic comorbidity.
Additional regression analyses were performed to explore the effects of the number of comorbidities (categorised into three categories: no, 1, and ≥ 2) and the specific comorbid disease categories. Also, a number of supplementary analyses were performed to test the robustness of the multivariate logistic regression results. First, several studies have reported an association between depression severity and psychiatric comorbidity, in particular anxiety comorbidity [e.g. 37]. To examine a possible collinearity effect between these variables multivariate regression analyses were repeated without the variable depression severity. Second, to examine whether the possible inclusion of unexplained symptoms affected the results analyses were repeated after excluding patients with symptom diagnosis only and no somatic disease diagnosis. Third, to test whether lowering the GHQ-12 cut-off score influenced the results analyses were repeated including a dummy variable GHQ threshold. Finally, all analyses were repeated in multi-level models to examine whether the results were affected by variations among the general practices.
Analyses were conducted using SPSS version 11.0 for Windows, except for the multilevel analyses, which were performed using the MLwiN software version 1.1. Significance was accepted at the 5% level.

5.3 Results

Study population characteristics and depression diagnosis rates

Table 1 illustrates the characteristics of the 191 depressed patients. According to the CIDI, 157 patients had MDD alone, seven had dysthymia alone, and 27 had both MDD and dysthymia. Psychiatric comorbidity was present in just over half of the depressed patients, about the same prevalence rate as chronic somatic comorbidity. Anxiety disorder was by far the most common comorbid psychiatric disorder, with GAD being the most frequent specific anxiety disorder, and the most prevalent comorbid chronic somatic disease category was musculoskeletal, followed by the circulatory and neurological categories.

Table 1

Characteristics of the depressed patients (percentages unless stated otherwise)

	Total group (*n* = 191)	
Age (years): mean (SD)	45.4	(14.1)
Gender		
Male	27.7	
Female	72.3	
Educational level		
Low	38.2	
Middle	35.6	
High	26.2	
Depression severity: mean (SD)	6.6	(1.2)
Annual number of GP contacts		
1-3 contacts	19.4	
4-6 contacts	25.7	
7-10 contacts	28.3	
≥ 11 contacts	26.7	
No comorbidity	20.4	
Psychiatric comorbidity	53.4	
Chronic somatic comorbidity	51.8	
Psychiatric and somatic comorbidity	25.7	
Number of psychiatric comorbidities:		
no comorbidity	46.6	
1 comorbidity	31.4	
≥ 2 comorbidities	22.0	
Number of chronic somatic comorbidities:		
no comorbidity	48.2	
1 comorbidity	26.2	
≥ 2 comorbidities	25.7	
Categories of psychiatric comorbidity:		
anxiety disorder	49.2	
alcohol abuse/ dependence	7.9	
bipolar disorder	1.0	
Categories of chronic somatic comorbidity:		
musculoskeletal	29.3	
circulatory	16.2	
neurological	10.5	
skin	9.4	
endocrine/ metabolic/ nutritional	4.7	
digestive	3.7	
respiratory	3.1	
rest category	1.6	

About a quarter of the patients had both psychiatric and chronic somatic disease in addition to their depression, while two-fifths had no comorbidity. As shown in Table 2, fifty-five of the 191 depressed patients were diagnosed as depressed by GPs (ICPC code P76: *n* = 41; ICPC code P03: *n* = 11; both codes: *n* = 3), while 136 depressed patients were not diagnosed, resulting in an overall rate of underdiagnosis of 71.2%.

Table 2
Rate of GPs' diagnosis of depression in subgroups of depressed patients based on comorbidity characteristics

	GPs' depression diagnosis rate
All depressed patients (*n* = 191)	28.8%
Subgroups by comorbidity status:	
Patients with psychiatric comorbidity (*n* = 102)	35.3%
Patients without psychiatric comorbidity (*n* = 89)	21.3%
Patients with chronic somatic comorbidity (*n* = 99)	26.3%
Patients without chronic somatic comorbidity (*n* = 92)	31.5%
Subgroups stratified by chronic somatic comorbidity:	
Patients without chronic somatic comorbidity and	
- with psychiatric comorbidity (*n* = 53)	34.0%
- without psychiatric comorbidity (*n* = 39)	28.2%
Patients with chronic somatic comorbidity and	
- with psychiatric comorbidity (*n* = 49)	36.7%
- without psychiatric comorbidity (*n* = 50)	16.0%

Interestingly, the depression diagnosis rates in patient subgroups based on comorbidity characteristics suggest a possible interaction effect between psychiatric and chronic somatic comorbidity on depression diagnosis. That is, the difference in depression diagnosis rate between depressed patients with psychiatric comorbidity and those without psychiatric comorbidity was small in the subgroup of patients without chronic somatic comorbidity as compared to the substantial difference observed in the subgroup of patients with chronic somatic comorbidity.

Logistic regression results

As shown in Table 3, bivariate analyses revealed that having no psychiatric comorbidity, having fewer contacts with a GP, and being less severely depressed all significantly increased the risk of underdiagnosis of depression.

Table 3
Results of bivariate logistic regression for GPs' depression diagnosis in depressed patients

	OR (95.0% CI)
Psychiatric co-morbidity[a]	2.01 (1.05 - 3.85)[d]
Chronic somatic co-morbidity[b]	0.77 (0.41 - 1.45)
Age	0.99 (0.97 - 1.02)
Gender[c]	0.81 (0.41 - 1.60)
Educational level	1.31 (0.88 - 1.94)
Annual number of GP contacts	1.41 (1.08 - 1.86)[d]
Depression severity	1.71 (1.24 - 2.35)[e]

OR, odds ratio; CI, confidence interval.
[a] Reference group: those without psychiatric co-morbidity. [b] Reference group: those without chronic somatic co-morbidity. [c] Reference group: males. [d] $p < .05$; [e] $p < .001$

The multivariate results are also presented in table 4. Shown are the main effects of psychiatric and chronic somatic comorbidity on depression diagnosis when considered jointly in the same model (model 1) and when all other explanatory variables were entered (model 2). As a last step, the interaction between the two comorbidity types was entered. Importantly, this final multivariate model showed a significant interaction effect between psychiatric and chronic somatic comorbidity on depression diagnosis. Subsequent stratified analysis (see table 5) revealed that psychiatric comorbidity had no significant effect on depression diagnosis in patients without chronic somatic comorbidity. Having a lower educational level, having a lower annual number of GP contacts and having a less severe level of depression all significantly increased the risk of underdiagnosis of depression in this patient subgroup. In contrast, in patients with chronic somatic comorbidity, psychiatric comorbidity was significantly associated with depression diagnosis: depressed patients with chronic somatic comorbidity but no psychiatric comorbidity were more likely to receive no depression diagnosis than those with both psychiatric and chronic somatic and comorbidity. None of the other variables was significantly associated with depression diagnosis in this patient subgroup.

Table 4
Results of multivariate logistic regression for GPs' depression diagnosis in depressed patients

	Multivariate		
	Model 1	Model 2	Final Model
	OR (95.0% CI)	OR (95.0% CI)	OR (95.0% CI)
Psychiatric co-morbidity[a]	1.98 (1.03 - 3.80)[d]	1.32 (0.63 - 2.76)	0.55 (0.19 - 1.58)
Chronic somatic co-morbidity[b]	0.81 (0.43 - 1.54)	0.65 (0.30 - 1.42)	0.24 (0.07 - 0.78)[d]
Psychiatric x chronic somatic co-morbidity			5.32 (1.23 - 22.98)[d]
Age		0.99 (0.97 - 1.02)	0.99 (0.96 - 1.02)
Gender[c]		0.56 (0.25 - 1.22)	0.57 (0.26 - 1.27)
Educational level		1.72 (1.07 - 2.77)[d]	1.84 (1.13 - 2.98)[d]
Annual number of GP contacts		2.13 (1.44 - 3.18)[e]	2.34 (1.54 - 3.54)[e]
Depression severity		1.34 (0.99 - 1.82)	1.39 (1.02 - 1.90)[d]
Nagelkerke R square	0.037	0.19	0.23

OR, odds ratio; CI, confidence interval.
[a] Reference group: those without psychiatric comorbidity. [b] Reference group: those without chronic somatic comorbidity. [c] Reference group: males. [d] p < .05; [e] p < .001

Table 5
Results of logistic regression analysis for GPs' depression diagnosis in depressed patients stratified by presence of chronic somatic comorbidity

	No chronic somatic comorbidity (*n* = 92)	Chronic somatic comorbidity (*n* = 99)
	OR (95.0% CI)	OR (95.0% CI)
Psychiatric comorbidity[a]	0.33 (0.093-1.18)	2.99 (1.06-8.39)[c]
Age	0.98 (0.94-1.03)	0.99 (0.95-1.03)
Gender[b]	0.32 (0.088-1.15)	0.70 (0.24-2.11)
Educational level	3.04 (1.23-7.24)[c]	1.39 (0.73-2.63)
Annual number of GP contacts	3.80 (1.92-7.53)[d]	1.72 (0.95-3.11)
Depression severity	1.88 (1.15-3.07)[c]	1.13 (0.72-1.76)
Nagelkerke R square	0.36	0.16

OR, odds ratio; CI, confidence interval.
[a] Reference group: those without psychiatric comorbidity. [b] Reference group: males.
[c] *p* < .05; [d] *p* < .001

Additional multivariate analyses: number and category of comorbidity

The number of psychiatric comorbidities exerted no significant effect in patients without chronic somatic comorbidity, whereas among patients with chronic somatic comorbidity a lower number of psychiatric comorbidities decreased the likelihood of receiving a depression diagnosis (OR = 2.40; 95% CI: 1.26 to 4.59; $p < .01$). Again, significant effects of education, number of GP contacts, and depression severity were confined to patients without chronic somatic comorbidity. Regarding specific comorbidity categories, patients with a comorbid musculoskeletal condition but no comorbid GAD were more likely to receive no depression diagnosis than patients with both a comorbid musculoskeletal condition and a comorbid GAD (OR = 6.17; 95% CI: 1.39 to 27.41; $p < .05$). In contrast, in patients without a comorbid musculoskeletal condition no effect of comorbid GAD was found. Again, only in these latter patients significant effects were present for education, contact rate and depression severity. The effects of other specific categories were not analysed, because patient numbers were too small for meaningful analysis.

Additional multivariate analyses: robustness of findings

Supplementary multivariate analyses underlined the robustness of the findings. That is, a model excluding depression severity, a model taking into account lowering of the GHQ-12 threshold, and a model allowing for the variation among practices, all yielded basically identical results. Exclusion of the 17 patients who were diagnosed only with (possible unexplained) symptoms revealed also essentially the same results, except that the effect of psychiatric comorbidity on depression diagnosis was no longer significant among the patients with chronic somatic comorbidity (OR= 2.64; 95% CI: 0.92 to 7.54; $p < .10$).

5.4 Discussion

About half of our sample of patients who had depression as assessed according to the CIDI had either comorbid psychiatric or comorbid chronic somatic disease. Nearly a quarter of the depressed patients exhibited both types of comorbidity, and this high rate underlines the importance of studying the

impact of having both chronic somatic as well as psychiatric comorbidity on underdiagnosis of depression by GPs. Previous studies examined the effects of psychiatric and somatic comorbidity only separately. Our study elaborated on the past research and showed that there is an interaction effect between psychiatric and chronic somatic comorbidity on depression diagnosis. Only in depressed patients with a comorbid chronic somatic condition did having no psychiatric comorbidity increase the risk of being not diagnosed as depressed. Furthermore, none of the other factors under study were found to exert significant effects in this subgroup of patients, while in those without chronic somatic comorbidity, a lower educational level, a lower annual number of GP contacts and a less severe level of depression all increased the likelihood of being not diagnosed as depressed.

It should be noted that the effect of psychiatric comorbidity in patients with chronic somatic comorbidity was no longer significant after excluding patients with only symptom diagnoses. Further research is needed to determine whether this was caused by reduced statistical power or that it indicates that the significant psychiatric comorbidity effect in our total group of patients with chronic somatic comorbidity is a coincidental finding. A possible explanation for a facilitating effect of psychiatric comorbidity on depression diagnosis is that GPs' may be better able to detect a mental problem in chronic medically ill patients when nondepressive psychiatric symptoms, i.e. symptoms more specific to anxiety and/or alcohol-related disorders, are also present. This higher detection rate might result in an increased likelihood of diagnosing depression, because GPs are probable more acquainted with depression than other psychiatric disorders encountered in primary care and therefore will interpret any mental distress as indications of depression [21]. Another possible explanation is that a specific comorbidity pattern accounted for the facilitating effect on diagnosing depression in patients with concomitant chronic somatic disease. Explorative analysis suggested that having a comorbid GAD facilitated depression diagnosis in patients with a comorbid musculoskeletal condition. However, the effects of other specific comorbidity patterns remained unclear, because too few cases precluded meaningful analysis.

The higher annual GP contact rate among depressed patients with chronic somatic comorbidity compared to those with no concomitant chronic somatic condition could explain the differential effect of contact rate in the two

subgroups. Because almost all depressed, chronic somatically ill patients had already contact with their GP on a regular basis (i.e. ≥ 4 contacts: 92%; ≥ 7 contacts: 64%), it is probable that a higher frequency of contact will not have much influence on diagnosing depression. In contrast, a substantial number of depressed patients without somatic comorbidity consulted their GP only once or a few times during the last year (i.e. ≤ 3 contacts: 32%; 1-2 contacts: 22%). Accordingly, GPs have little opportunity to recognize depressive symptoms in these patients, and the likelihood of depression diagnosis will be increased in the non-chronically ill patients with a higher contact rate.

One could question the clinical relevance of the finding that less severe depression decreased the likelihood of receiving a depression diagnosis in patients with no chronic somatic comorbidity. Diagnosis may not be needed in all patients with relatively mild forms of depression, because quite a large number of these patients seem to recover spontaneously without being detected as depressed [38-39]. On the other hand, it has been indicated that a substantial number of undetected depressed primary care patients have persistently poor outcomes over the course of one year [11-12]. Of concern is that a more severe level of depression did not facilitate diagnosis among patients with chronic somatic comorbidity, particularly in the context that most of these patients had regular contact with their GPs. It is of special importance to diagnose major depression in chronic medically ill patients, because its presence has been demonstrated to lead to amplification of chronic medical illness symptoms, additive functional impairment, and poorer self-care and adherence [40-41]. Also, depression comorbid with chronic somatic disease may have poorer course and outcome than depression without comorbidity [6; 26]. For these reasons, it is widely advocated that major depression must be appropriately and aggressively treated in patients with chronic somatic disease [41; 40; 42]. Indeed, appropriate treatment has been found to improve both the course and outcome of depression and the comorbid somatic disease as well as patient quality of life [26; 43-44].

It should be kept in mind that the discussed results were obtained by using a multivariate model that included both psychiatric comorbidity and depression severity. In the vast majority of cases psychiatric comorbidity implied comorbid anxiety disorder(s), with GAD being the most prevalent specific comorbid anxiety disorder. As anxiety disorders in general, and GAD particularly, share several common symptoms with major depression, one

might question whether anxiety comorbidity and depression severity are distinct. Indeed, some researchers view them not as distinct entities, but rather conceptualize anxiety-depression comorbidity as an indicator of severity of psychopathology [45-47]. However, we consider anxiety comorbidity and depression severity as related but distinct constructs. This position was based on reviews of research on the most common anxiety-depression comorbidity, i.e. major depression-GAD comorbidity, which argue against the view that GAD should be conceptualized as a severity marker for major depression rather than as an independent disorder [48-49]. Several lines of evidence point to this conclusion, including reports that the symptoms of GAD form an empiric cluster distinct from the symptoms of major depression. Viewing psychiatric comorbidity and depression severity as distinct entities is supported by the finding that the effects of psychiatric comorbidity on depression diagnosis remained essentially the same after dropping depression severity from the multivariate model. If psychiatric comorbidity and depression severity were indistinguishable entities, one would expect the model excluding depression severity to show a significant effect of psychiatric comorbidity on depression diagnosis among depressed patients without chronic somatic comorbidity, which was not the case. Anyhow, further longitudinal research is needed to disentangle the concepts psychiatric comorbidity and depression severity and their relationship with depression diagnosis.

Some limitations of our study must be noted. First, the generalisability of the findings might be restricted by the relatively high attrition rate. The significant difference between participant and nonparticipants regarding gender seemed to be of no major influence given that gender consistently did not exert a significant effect in our analyses. However, it cannot be ruled out that other differences between participants and nonparticipants could have affected the findings. Second, not all sections of the CIDI were administered, which may have confounded assessment of psychiatric comorbidity. For instance, the assessment of somatoform disorders was lacking, which are known to be common in primary care and comorbid with depression [26]. Finally, only small numbers of patients had certain specific diseases, which precluded meaningful analysis of the effects of specific (combinations of) psychiatric and chronic somatic comorbidity categories.

In conclusion, the results of our study indicate that the factors that are associated with underdiagnosis of depression by GPs are different for

depressed patients without chronic somatic comorbidity compared to depressed patients with chronic somatic comorbidity. This implies that efforts to improve GPs' diagnosis of depression require different approaches for depressed patients with and without comorbid somatic illness. Our results suggest that GPs need to be more alert to symptoms of depression in the less well-educated, non-chronic somatically ill patients. The awareness of (the importance to diagnose and treat) depression in chronic somatically ill patients should be raised among GPs. Educating GPs in overcoming the diagnostic challenge of differentiating depressive symptomatology from comorbid chronic somatic disease and/or to refer chronic somatically ill patients to mental health specialists if they suspect a depression could increase the quality of care for these patients.

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6 The influence of specific chronic somatic conditions on the care for comorbid depression in general practice

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Abstract

Background: Limited information exists on the relationship between specific chronic somatic conditions and care for comorbid depression in primary care settings. Therefore, the present prospective, general practice-based study examined this relationship.

Methods: Longitudinal data on morbidity, prescribing, and referrals concerning 991 patients newly diagnosed with depression by their general practitioner (GP) were analyzed. The influence of a broad range of 13 specific chronic somatic conditions on the initiation of any depression care as well as the prescription of continuous antidepressant therapy for 180 days was examined. Multilevel logistic regression analysis was employed to control for history of depression, psychiatric comorbidity, socio-demographics and inter-practice variation

Results: Multilevel analysis showed that patients with pre-existing ischemic heart disease (72.1%) or cardiac arrhythmia (59.3%) were significantly less likely to have any depression care being initiated by their GP than patients without chronic somatic morbidity (88.0%). No other specific condition had a significant influence on GP initiation of any care for depression. Among the patients being prescribed antidepressant treatment by their GP, none of the conditions was significantly associated with being prescribed continuous treatment for 180 days.

Conclusions: Our study indicates that patients with ischemic heart disease or cardiac arrhythmia have a lower likelihood of GP initiation of any care for depression after being newly diagnosed with depression by their GP. This finding points to the importance of developing interventions aimed at supporting GPs in the adequate management of comorbid depression in heart disease patients to reduce the negative effects of this comorbidity.

6.1 Introduction

Depression is known to be comorbid with a wide and diverse range of chronic somatic conditions, including heart disease, gastrointestinal, neurological, and respiratory conditions [1-2]. In general, the presence of comorbid depression in chronically ill patients is associated with increased symptom burden, additive functional impairment, decreased quality of life, increased health-care use, as well as decreased self-care and adherence to treatment regimens [3-4]. Also, evidence is accumulating that depression comorbid with chronic somatic disease may be associated with increased mortality, particularly in patients with heart disease and diabetes [5-6]. Given the negative impacts of comorbid depression, active treatment of depression among patients with chronic somatic illness is recommended [7-8]. This approach is further substantiated by recent evidence that depression in somatically ill patients can be treated effectively [9-10].

Because most depressed patients are cared for in primary care settings, it is important to have knowledge of the primary care management of depression in patients with pre-existing chronic somatic disease. Most primary care based studies that examined the influence of having chronic somatic disease on depression care used a composite measure of chronic somatic morbidity and found conflicting results [11-15]. Possible explanations for this discrepancy in findings may include differences in study settings and patient characteristics, focusing on different outcome measures of depression care, and considering different sets of specific conditions to establish a composite measure of chronic somatic morbidity.

There is reason to believe that the relationship between chronic somatic conditions and depression management in primary care varies by type of condition. Having chronic somatic morbidity may influence care for depression in several, not mutually exclusive, ways. A pre-existing condition may impede depression management because it exerts a strong competing effect on physicians' limited attention and time [16], or because physicians and/or patients erroneously believe that there is little reason to initiate any care for depression because it is a "normal" consequence of having that illness [17], or because physicians are reluctant to prescribe antidepressant drugs because of potential adverse side effects or drug interactions, or to avoid polypharmacy [18]. Alternatively, having a chronic somatic condition may also positively impact

depression management because it implicates frequent physician-patient contacts and thus more opportunities for depression care [19]. It is likely that the relevance of each of the mechanisms described above varies by type of condition, and therefore differential effects of specific chronic somatic conditions on depression care are expected.

However, to the best of our knowledge, only two primary care based studies have looked at the impacts of individual chronic somatic conditions. Bogner et al. [18] investigated the role of cardiovascular conditions and found that older primary care patients with heart failure had a significantly lower likelihood of receiving "active" management for depression (i.e. receiving counselling/supportive listening, referred to a mental health specialist, or prescribed psychotropic medication) than those without heart failure. Other types of cardiovascular disease were not significantly related to depression management. An earlier study by Dunn et al. [20] indirectly suggests no large differential effects of chronic fatigue syndrome, cancer, coronary heart disease, stroke, diabetes, and fibromyalgia on "adequate" duration of antidepressant treatment (i.e. prescribed at least 120 days of antidepressant therapy at an adequate daily dose within the first six months after initiation of therapy) in general practice patients aged 18 years or older.

The aim of the present prospective study was to examine the influence of specific chronic somatic conditions on the management of newly diagnosed episodes of depression in general practice. Unlike previous research, this study considered a broad range of conditions and was not restricted to older patients. The following two research questions were addressed: (1) what is the influence of specific chronic somatic conditions on the initiation of any depression care in patients newly diagnosed with depression by their general practitioner (GP)?; and (2) among the patients being prescribed antidepressants by their GP, what is the influence of these specific conditions on prescription of continuous antidepressant treatment?

6.2 Method

Study setting

Morbidity, drug prescription, and referral data were extracted from the electronic medical record systems of 103 general practitioners (GPs) working in

60 practices. These data were collected within the framework of the second Dutch National Survey of General practice (DNSGP-2) [21] and the National Information Network of General Practice (LINH) [22]. The DNSGP-2 was a nationwide study of morbidity and interventions in general practice in the Netherlands carried out in 2001. Established in 1992, the LINH database holds longitudinal data on morbidity, prescribing, and referrals from participating general practices. The LINH data served as the "backbone" of the DNSGP-2. Because the 60 practices took part in the DNSGP-2 and continued participation in the LINH, follow-up data were available after the end of the one-year DNSGP-2 study period, allowing us to examine depression care provided by GPs during a one-year period after they have diagnosed a depression.

Morbidity data comprised: (1) diagnoses made during contacts with a patient, and (2) diagnoses of all relevant health problems of a patient, including those developed in the past, recorded on a so-called "problem list" [23]. Diagnoses were coded according to the International Classification of Primary Care (ICPC) [24] based on the criteria of the International Classification of Health Problems in Primary Care (ICHPC-2-Defined) [25]. During the contact registration, GPs recorded whether a health problem concerned a new or ongoing problem and different contacts for the same health problem were clustered into episodes of disease. Prescription records were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [26].

Study population

The total practice population registered with the 60 practices (*n* = 236,829) in 2001 was representative of the Dutch population in terms of age, gender, and type of health care insurance.

Potential participants were patients who were diagnosed at the age of 18 years or older with a new episode of depression (ICPC code P76) during the one-year contact registration of the DNSGP-2 (*n* = 1,110). The ICHPPC-2-Defined criteria for depression correspond largely to those of the DSM-IV for major depression [27]. To ensure that new depressive episodes were investigated, patients were required to have not received a prescription for any antidepressant (ATC code N06A) or lithium (code N05AN01) nor were referred to a mental health specialist in the three months before depression diagnosis. Patients who died during the one-year follow-up study period (*n* = 26) and those who were no longer registered with the same practice at the end of the study period (e.g.

because of moving, nursing home admission; *n* = 83) were excluded.
The total study population (*n* = 991) was utilized to answer the first research question concerning initiation of any depression care in the year following depression diagnosis. The second research question on prescription of continuous antidepressant therapy was examined using a subset of this population, namely the patients who received at least one prescription for an antidepressant during the study period (*n* = 790). To ensure that antidepressant treatment provided by GPs was investigated, we excluded patients who received a prescription for lithium and/or were referred to a mental health specialist during the study period (*n* = 93). Also, thirty patients were excluded because either the first antidepressant drug was prescribed 180 days or more after depression diagnosis or because specific prescription data were missing, leaving a study population of 667 patients to examine continuity of antidepressant treatment.

Dependent variables

Any depression care was considered to be initiated following depression diagnosis if the patient received at least one prescription for any antidepressant or lithium, and/or was referred at least once to a mental health professional for depression, and/or had at least one follow-up face-to-face contact for depression with their GP within four weeks after diagnosis. The last part of our definition was incorporated to ensure that patients were included whose depression was being managed by a GP by means of a (short-term) psychological intervention or a "watchful waiting" approach.
To measure prescription of continuous antidepressant treatment a "continuous multiple-interval measure of medication availability" (CMA) was employed [28]. This measure represents the sum of the days covered by all prescriptions in a specific period divided by the total number of days during the specified period, and can potentially range from 0% to values exceeding 100% (in case of oversupply). The number of days covered by each prescription was estimated by multiplying the quantity of a drug prescribed by its corresponding defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (www.whocc.no). Subsequently, for each patient, a CMA score for a 180-day period was calculated and used to define presence (CMA ≥ 80%) or absence (CMA < 80%) of being prescribed continuous antidepressant therapy. A 180 days period was

examined because clinical practice guidelines for the treatment of depression [e.g. 29-30], including the guideline of the Dutch College of General Practitioners [31], recommend continuing antidepressant treatment for at least six months after remission. A CMA cut-off score of 80% is used conventially to define a treatment episode as continuous or discontinuous based on prescription data [32].

Independent variables

The primary independent variable of interest was having a specific chronic somatic condition at the time of newly diagnosed depression. Diagnoses recorded during patient contacts as well as diagnoses recorded on the problem lists were used to identify patients with pre-existing specific chronic conditions. Thirteen conditions were studied because they are highly prevalent in general practice and/or known to be frequently comorbid with depression [1-2] (see Appendix for a description of the included diagnoses): colon conditions, stomach/duodenal conditions, hypertension, cardiac arrhythmia, ischemic heart disease, osteoarthritis/rheumatoid arthritis, migraine, neurological disease, chronic lung conditions, skin conditions, diabetes mellitus, thyroid conditions, and cancer. Also, by considering a comprehensive range of other diagnoses of possible chronic somatic conditions [2], a broad and heterogeneous category of "any other chronic condition" was established. Patients were defined as having no chronic somatic morbidity if they were not diagnosed with any of the conditions considered.

Other variables were taken into account that could potentially influence depression care, including history of a previous depressive episode, psychiatric comorbidity, and socio-demographic variables (age, gender, highest educational level attained) [33]. A prior depressive episode was considered to have occurred when a patient had a depression diagnosis on his or her problem list. Presence of co-existent psychiatric morbidity at the time of depression diagnosis was derived from diagnoses recorded during the contact registration and those recorded on the problem lists. Two categories were formed: comorbid anxiety disorder and other psychiatric comorbidity (i.e. substance abuse disorder, schizophrenia/other psychotic disorder, or other mental disorder). Age was categorized into five groups (18-24, 25-44, 45-64, 65-74, and ≥75) and educational level into three (low: none/ elementary school, middle: high school, and high: college/ university). Also, a separate category of missing educational data was created because the attained level of education

was unknown for a substantial number of patients (23.9%).

Statistical analysis

Multi-level logistic regression analysis using MLwiN version 2.0 was carried out to examine the first research question on the association between specific chronic somatic conditions and initiation of any depression care. Multi-level analysis was employed because the data had a two-level hierarchical structure (i.e. practice level and patient level) and allowed us to adjust for variation due to differences between general practices. A random intercept logistic model was performed, yielding the odds of initiation of any depression care for each group of patients with a specific chronic somatic condition compared to patients without chronic somatic morbidity controlling for the potential influence of the measured covariates as well as inter-practice variation. Parameters were estimated using the second order predictive quasi-likelihood procedure with extra-binomial variation at level one [34].

The second research question regarding prescription of continuous antidepressant therapy was addressed in a similar way. Sensitivity analyses were conducted to test whether the results concerning continuous prescription were robust to using a more (90%) or a less (70%) stringent CMA threshold value.

Of note, as both initiation of any depression care and continuous antidepressant prescription are common outcomes, the odds ratio estimated by logistic regression may substantially overestimate the relative risk. To prevent misinterpretation of odds ratios as meaning the same thing as relative risks in our study, regression coefficients and their confidence intervals are presented.

6.3 Results

Initiation of depression care

The study sample of 991 patients with a new episode of depression had a mean age of 49.0 years (SD= 16.9; Range: 18-93) at the time of depression diagnosis and 66.7% of the patients were female. Table 1 shows that 648 patients (65.4%) had pre-existing chronic somatic morbidity, with hypertension (18.8%) being the most prevalent specific chronic condition and migraine (3.5%) the least prevalent. Table 1 further presents the clinical and socio-demographic

Table 1

Characteristics of patients newly diagnosed with depression by their general practitioner according to presence or absence of chronic somatic morbidity

Characteristics	Patients with chronic somatic morbidity (*n* = 648) *n* (%)	Patients without chronic somatic morbidity (*n* = 343) *n* (%)
Socio-demographic variables		
Gender		
Male	212 (32.7)	118 (34.4)
Female	436 (67.3)	225 (65.6)
Age (years): mean (SD)	52.0 (17.5)	43.1 (13.9)
Age groups		
18-24	28 (4.3)	25 (7.3)
25-44	234 (36.1)	182 (53.1)
45-64	213 (32.9)	105 (30.6)
65-74	87 (13.4)	22 (6.4)
≥ 75	86 (13.3)	9 (2.6)
Educational level		
Low	139 (21.5)	36 (10.5)
Middle	290 (44.8)	165 (48.1)
High	76 (11.7)	48 (14.0)
Unknown	143 (22.1)	94 (27.4)
Previous depressive episode	143 (22.1)	58 (16.9)
Psychiatric comorbidity variables		
Comorbid anxiety	78 (12.0)	18 (5.2)
Other psychiatric comorbidity	104 (16.0)	51 (14.9)
Type of chronic somatic condition[a]		
Hypertension	122 (18.8)	
Chronic lung	84 (13.0)	
Skin	81 (12.5)	
Diabetes mellitus	58 (9.0)	
Colon	55 (8.5)	
Stomach/duodenal	55 (8.5)	
Neurological	46 (7.1)	
Osteoarthritis/rheumatoid arthritis	46 (7.1)	
Ischemic heart	43 (6.6)	
Thyroid	41 (6.3)	
Cancer	28 (4.3)	
Cardiac arrhythmia	27 (4.2)	
Migraine	23 (3.5)	
Any other	471 (72.7)	

[a] Not mutually exclusive.

characteristics of the total groups of patients with and without chronic somatic illness.

The unadjusted rate of initiation of any depression care in the year after depression diagnosis by each characteristic is shown in Table 2. Also shown are the unadjusted rates for the three measured "types" of depression care. Overall, 86.6% of the patients received any care for depression. Of these 858 patients, 81.5% was prescribed an antidepressant or lithium, 3.3% was referred to a mental health professional, and 10.6% received both types of care. Forty patients (4.6%) were neither prescribed antidepressants nor referred but had at least one face-to-face contact with their GP for depression within four weeks after diagnosis. In 85.8% of the patients with chronic somatic morbidity management of depression was initiated, a slightly lower percentage than among the patients without chronic somatic disease (88.0%). The unadjusted rate of initiation of any depression care varied by type of condition, ranging from 59.3% for patients with cardiac arrhythmia to 92.7% for patients with a thyroid condition.

From the multi-level logistic analysis we learned that, as compared to patients without chronic somatic illness, patients with ischemic heart disease or cardiac arrhythmia were significantly less likely to receive any depression care from their GP following a diagnosis of new depressive episode (Table 3). The odds of initiation of any depression care tended to be decreased for patients with migraine (p = .078).

Table 2
Unadjusted rates of patients receiving any depression care from their general practitioner as well as the rates for the three types of depression care

		Type of depression care[a]		
Characteristics	Any depression care	≥1 anti-depressant prescription	≥1 mental health referral	≥1 follow-up contact <4 weeks
Without chronic somatic condition	88.0	81.3	13.7	50.4
With chronic somatic condition	85.8	78.9	11.1	47.4
Type of chronic somatic condition[a]				
Thyroid	92.7	82.9	9.8	48.8
Colon	89.1	76.4	16.4	45.5
Stomach/duodenal	89.1	83.6	5.5	45.5
Skin	87.7	84.0	11.1	51.9
Chronic lung	85.7	79.8	11.9	44.0
Cancer	85.7	78.6	0.0	42.9
Osteoarthritis/rheumatoid arthritis	84.8	76.1	0.0	45.7
Neurological	82.6	78.3	4.3	50.0
Diabetes mellitus	82.8	77.6	6.9	43.1
Hypertension	82.0	75.4	6.6	44.3
Migraine	78.3	73.9	17.4	47.8
Ischemic heart	72.1	67.4	7.0	39.5
Cardiac arrhythmia	59.3	59.3	7.4	29.6
Any other	86.4	79.8	11.5	48.8
Previous depressive episode				
No	85.4	78.0	11.4	47.6
Yes	91.0	86.6	14.4	51.7
Psychiatric comorbidity variables				
Comorbid anxiety				
No	85.9	78.8	11.8	47.5
Yes	92.7	88.5	13.5	57.3
Other psychiatric comorbidity				
No	86.7	79.4	12.2	48.1
Yes	85.8	81.3	11.0	50.3
Socio-demographic variables				
Gender				
Male	87.3	82.4	13.6	47.3
Female	86.2	78.4	11.2	49.0
Age groups				
18-24	77.4	64.2	18.9	47.2
25-44	89.7	81.5	18.5	49.8
45-64	85.2	80.5	8.2	47.5
65-74	83.5	79.8	1.8	45.9
≥ 75	86.3	77.9	1.8	49.5
Educational level				
Low	89.1	81.7	7.4	50.3
Middle	86.8	80.9	12.5	50.1
High	84.7	77.4	16.1	50.8
Unknown	85.2	77.2	12.2	42.6

[a] Not mutually exclusive.

Table 3
Results of multi-level logistic regression for initiation of any depression care. Values shown in bold indicate significant effects

	B	95% CI
Type of chronic somatic condition		
Thyroid	0.86	-0.41 to 2.14
Colon	0.36	-0.58 to 1.30
Stomach/duodenal	0.47	-0.53 to 1.46
Skin	0.17	-0.59 to 0.92
Chronic lung	-0.095	-0.80 to 0.61
Cancer	-0.14	-1.35 to 1.08
Osteoarthritis/rheumatoid arthritis	-0.084	-1.04 to 0.87
Neurological	-0.095	-0.99 to 0.80
Diabetes mellitus	-0.058	-0.87 to 0.75
Hypertension	-0.27	-0.86 to 0.33
Migraine	-0.95	-2.00 to 0.11
Ischemic heart	**-1.04**	**-1.86 to -0.22**[a]
Cardiac arrhythmia	**-1.77**	**-2.69 to -0.86**[d]
Any other	-0.0035	-0.42 to 0.41
Previous depressive episode		
No	reference	
Yes	**0.88**	**0.29 to 1.49**[c]
Psychiatric comorbidity variables		
Comorbid anxiety		
No	reference	
Yes	0.63	-0.23 to 1.49
Other psychiatric comorbidity		
No	reference	
Yes	-0.098	-0.64 to 0.45
Socio-demographic variables		
Gender		
Male	reference	
Female	-0.23	-0.66 to 0.21
Age groups		
18-24	**-1.01**	**-1.76 to -0.26**[b]
25-44	reference	
45-64	-0.33	-0.81 to 0.15
65-74	-0.51	-1.22 to 0.21
≥ 75	-0.16	-1.07 to 0.75
Educational level		
Low	reference	
Middle	-0.55	-1.19 to 0.080
High	-0.64	-1.42 to 0.15
Unknown	-0.64	-1.33 to 0.054

B, regression coefficient; CI, confidence interval.
[a] $p < .05$; [b] $p < .01$; [c] $p < .005$; [d] $p < .001$ (determined by Wald chi-square tests)

Prescription of continuous antidepressant treatment

The mean age at the time of depression diagnosis of the 667 patients being prescribed antidepressant therapy was 50.3 years (SD= 16.9; Range: 18-90) and 65.7% were female. Table 4 shows the characteristics of the sample by presence and absence of chronic somatic morbidity. Among the 437 (65.5%) patients with pre-existing chronic illness, hypertension (19.0%) was the most common specific condition and cardiac arrhythmia (2.7%) the least common.

Overall, 37.8% of the patients were prescribed continuous antidepressant therapy for 180 days. As illustrated in Table 5, the unadjusted proportion of patients with continuous antidepressant prescription was somewhat lower in the group with chronic somatic morbidity (37.1%) than in the group without chronic somatic morbidity (39.1%). The unadjusted rate of being prescribed continuous therapy for 180 days differed according to type of condition. Patients with cardiac arrhythmia showed the highest rate of continuous prescription (50.0%), whereas the lowest rate was found among patients with a thyroid condition (23.3%).

Subsequent multi-level logistic regression analysis did not yield a significant influence of any specific chronic somatic condition on continuous prescription of antidepressant therapy (Table 5, last two columns). Sensitivity analyses using a more (90%) or a less (70%) stringent CMA cut-off score to define being prescribed continuous treatment revealed basically the same results as using the conventional threshold of 80%. Only patients with thyroid disease were found to be significantly less likely than patients without chronic somatic morbidity to have been prescribed continuous antidepressant therapy when using a threshold of 70% (p = .022).

Table 4
Characteristics of patients newly diagnosed with depression by their general practitioner and who are being prescribed antidepressant therapy according to presence or absence of chronic somatic morbidity

Characteristic	Patients with chronic somatic morbidity (*n* = 437) *n* (%)	Patients without chronic somatic morbidity (*n* = 230) *n* (%)
Gender		
Male	154 (35.2)	75 (32.6)
Female	283 (64.8)	155 (67.4)
Age (years): mean (SD)	53.2 (17.5)	44.9 (14.1)
Age groups		
18-24	16 (3.7)	12 (5.2)
25-44	149 (34.1)	119 (51.7)
45-64	145 (33.2)	73 (31.7)
65-74	65 (14.9)	19 (8.3)
≥ 75	62 (14.2)	7 (10.1)
Educational level		
Low	103 (23.6)	26 (11.3)
Middle	190 (43.5)	112 (48.7)
High	48 (11.0)	30 (13.0)
Unknown	96 (22.0)	62 (27.0)
Previous depressive episode	104 (23.8)	39 (17.0)
Psychiatric comorbidity variables		
Comorbid anxiety	56 (12.8)	15 (6.5)
Other comorbidity	74 (16.9)	33 (14.3)
Type of chronic somatic condition[a]		
Hypertension	83 (19.0)	
Skin	58 (13.3)	
Chronic lung	53 (12.1)	
Stomach/duodenal	44 (10.1)	
Diabetes mellitus	38 (8.7)	
Colon	36 (8.2)	
Osteoarthritis/rheumatoid arthritis	34 (7.8)	
Neurological	31 (7.1)	
Thyroid	30 (6.9)	
Ischemic heart	25 (5.7)	
Cancer	21 (4.8)	
Migraine	14 (3.2)	
Cardiac arrhythmia	12 (2.7)	
Any other	320 (73.2)	

[a] Not mutually exclusive.

Table 5
Results regarding prescription of continuous antidepressant therapy for 180 days after being newly diagnosed with depression. Shown are the unadjusted rates of patients being prescribed continuous antidepressant treatment by their general practitioner. The last two columns present the results of multi-level logistic regression for continuous antidepressant prescription. Values shown in bold indicate significant effects

Characteristic	Unadjusted rate of continuous prescription (%)	B	95% CI
Without chronic somatic condition	39.1		
With chronic somatic condition	37.1		
Type of chronic somatic condition[a]			
Cardiac arrhythmia	50.0	0.80	-0.47 to 2.06
Migraine	42.9	-0.11	-1.36 to 1.12
Diabetes mellitus	42.1	0.35	-0.40 to 1.11
Neurological	41.9	0.29	-0.54 to 1.13
Hypertension	39.8	0.18	-0.40 to 0.76
Skin	37.9	-0.055	-0.70 to 0.59
Chronic lung	32.1	-0.22	-0.90 to 0.45
Stomach/duodenal	31.8	-0.025	-0.77 to 0.72
Colon	30.6	-0.29	-1.08 to 0.51
Osteoarthritis/rheumatoid arthritis	26.5	-0.72	-1.64 to 0.19
Ischemic heart	24.0	-0.61	-1.62 to 0.40
Cancer	23.8	-0.45	-1.59 to 0.68
Thyroid	23.3	-0.83	-1.84 to 0.17
Any other	40.0	0.26	-0.17 to 0.58
Previous depressive episode			
No	35.5	reference	
Yes	46.2	**0.73**	**0.26 to 1.20**[c]
Psychiatric comorbidity variables			
Comorbid anxiety			
No	37.8	reference	
Yes	38.0	0.17	-0.41 to 0.75
Other psychiatric comorbidity			
No	37.9	reference	
Yes	37.4	-0.034	-0.54 to 0.47
Socio-demographic variables			
Gender			
Male	30.6	reference	
Female	41.6	**0.58**	**0.19 to 0.97**[c]
Age groups			
18-24	17.9	**-1.25**	**-2.32 to -0.19**[b]
25-44	39.6	reference	
45-64	43.1	0.22	-0.21 to 0.65
65-74	33.3	-0.23	-0.89 to 0.43
≥ 75	27.5	-0.49	-1.26 to 0.28
Educational level			
Low	34.9	reference	
Middle	43.4	0.32	-0.22 to 0.85
High	43.6	0.33	-0.35 to 1.02
Unknown	26.6	-0.48	-1.10 to 0.14

B, regression coefficient; CI, confidence interval. [a] Not mutually exclusive.
[b] $p < .05$; [c] $p < .005$ (determined by Wald chi-square tests)

6.4 Discussion

Principal findings The present study indicated that general practice patients with pre-existing ischemic heart disease or cardiac arrhythmia were less likely than patients without chronic somatic disease to have any depression care being initiated after being newly diagnosed with depression by their GP. No other specific chronic somatic condition impacted significantly on GP initiation of any depression care. Furthermore, among the patients being prescribed antidepressants by their GP, no specific chronic somatic condition was found to have a significant influence on prescription of continuous antidepressant treatment for 180 days.

Strengths and weaknesses of the study

Our study is the first effort to examine the relationship between specific chronic somatic conditions and depression management in general practice using a nationally representative sample of general practice patients. Unlike previous primary care based studies [18; 20], this study considered a wide range of specific chronic somatic conditions, both initiation of depression care as well as prescription of continuous antidepressant treatment, and used a study population that was not confined to older patients. Furthermore, besides controlling for several potential confounders at the level of individual patients, including history of depression, psychiatric comorbidity, and socio-demographic characteristics, we adjusted for variation at the practice level by using multilevel modelling.

A number of potential limitations of our study must be considered. First, we relied on data from medical record systems, which may be incomplete. However, it is likely that the completeness of registration of antidepressant drug prescriptions is high because the study was carried out in computerized practices where prescriptions are facilitated by the computer software. Furthermore, to identify patients with chronic somatic morbidity, in addition to diagnoses recorded during patient contacts, also diagnoses recorded on problem lists were used, making it unlikely that a substantial number of patients were misclassified as having no (specific) chronic somatic morbidity. Secondly, the data did not allow us to take into account the severity of specific chronic somatic conditions. Thirdly, the number of patients with a specific chronic condition was sometimes low, which may have limited statistical power

to obtain significant results for smaller effects. Fourthly, our data did not include direct information on whether a psychological intervention or watchful waiting approach was initiated by the GP after having diagnosed depression. Finally, the operationalization of being prescribed continuous antidepressant therapy may be criticized. The time period a drug prescription was intended to cover was estimated by using the DDD. The DDD assigned to a drug is nearly always a compromise based on systematic review of the available literature and does not necessarily equal the dose actually prescribed. Our results regarding continuous prescription should not be biased if the difference between the DDD and actual prescribed dose did not differ substantially depending on presence or absence of (a specific) chronic somatic illness. Lastly, although a CMA threshold value of 80% is used commonly there exists no clear clinical or pharmacological rationale for the appropriateness of this cut-off score [28]. However, results using different thresholds did not differ substantially from those using the conventional 80% cut-off score, aside from the finding that patients with thyroid disease were less likely than patients without chronic somatic morbidity to have been prescribed continuous antidepressant treatment for 180 days when using the less stringent threshold of 70%.

Clinical implications and suggestions for future research

Our finding that general practice patients with ischemic heart disease or cardiac arrhythmia are less likely to have any care being initiated for newly diagnosed depression is clinically important because the presence of comorbid depression in patients with heart disease has been found to adversely impact various domains of functioning, quality of life, symptom burden, health-care utilization, self-care and adherence to medical regimens [3-4]. Furthermore, there is substantial evidence that depression increases the risk of subsequent cardiovascular events and mortality in patients with coronary heart disease or post myocardial infarction (MI) patients [5; 35]. Given the adverse effects of comorbid depression, an active approach to the management of depression in patients with heart disease is supported, all the more because a growing body of research indicates that concomitant depression with ischemic heart disease can be effectively and safely treated with selective serotonin reuptake inhibitors (SSRIs) [36]. Use of SSRIs may even reduce the risk for cardiovascular morbidity and mortality in post MI patients [37-38]. The beneficial influence of

antidepressant treatment is further substantiated by a recent naturalistic study demonstrating that primary care patients with ischemic heart disease and comorbid depression showed significant improvement in mood, social and emotional functioning, and disability following initiation of antidepressant treatment [10]. Besides pharmacological treatment, current preliminary evidence suggests that psychological interventions also lead to a reduction in depression, although they appear to have no effect on mortality and non-fatal infarction [39-40]. Our data did not permit us to identify the mechanism(s) underlying the observed negative effect of having ischemic heart disease or cardiac arrhythmia on initiation of any depression care. It is possible that particularly heart disease exerts a strong competing effect on GPs' limited attention and time, that especially co-existent depression in heart conditions is being viewed as a "natural" reaction not needing active treatment or monitoring, and/or that particularly in heart disease potential adverse side effects or drug interactions have a strong negative effect on initiating antidepressant therapy. One may wonder whether the well-documented unfavourable cardiovascular profile of tricyclic antidepressants (TCAs) largely explains our findings [36]. Indeed, in our study, GPs, when initiating antidepressant therapy, not often prescribed TCAs to their patients with ischemic heart disease (8.0%) or cardiac arrhythmia (8.3%). However, the relative contraindication for the use of TCAs in patients with heart disease does not seem to be the reason for the observed low rates of initiation of any depression care, since TCAs were also infrequently prescribed for non-chronically ill patients with newly diagnosed depression. Furthermore, we found not only relatively low rates of initiation of any antidepressant drug therapy among the patients with ischemic heart disease or cardiac arrhythmia, but also relatively low rates of referral and having at least one follow-up face-to-face contact for depression in the four weeks following diagnosis (see table 2). This could suggest that GPs have a relative general "reservation" about initiating any form of depression care in patients with heart conditions, including watchful waiting. Further research is required to understand the mechanism(s) underlying the relationship between having ischemic heart disease or cardiac arrhythmia and a lower likelihood of receiving any care for comorbid depression in general practice.

A number of other suggestions for future research are offered by our study results. Apart from the negative influence of having ischemic heart disease or cardiac arrhythmia on initiation of any depression care, we observed no other

significant impact of specific chronic somatic morbidity on GP management of depression. However, as already stated above, the lack of other findings may have been due to insufficient statistical power. Further research using even larger samples of general practice patients is required to settle this issue. Our finding that initiation of any depression care as well as prescription of continuous antidepressant therapy varied considerably across the various conditions at least indicate that future studies using a composite measure of chronic somatic morbidity need to be aware of the possibility of obscuring meaningful differential effects of specific chronic conditions on depression management.

In our study, we examined depression care routinely provided by GPs, and thus relied on their clinical diagnoses of depression and not on diagnoses based on DSM-IV criteria. Accordingly, the observed rates of depression management were determined by the probability that the GPs diagnosed depression and their decision to initiate some type of depression care. Not addressing diagnosis of depression may give an incomplete picture of the relationship between primary care depression management and specific chronic somatic conditions, because of the possibility that underdiagnosis of depression by GPs may vary by type of condition [41]. Ideally, future research on this relationship should include a validated measure of depression to be able to take into consideration accuracy of GPs' diagnosis of depression. Also, including an objective measure of depression severity will allow a detailed investigation of the adequacy of GP management of comorbid depression. For instance, given the inconclusive evidence for the effectiveness of antidepressants for minor depression [42], it is interesting to know how many chronically ill patients with milder forms of depression are being prescribed antidepressants by their GP and how such treatment practice influences continuity of antidepressant treatment.

Although not the primary focus of this study, it is noteworthy that 15.8% of the total variance in initiation of depression care and 21.5% of that in prescription of continuous antidepressant therapy was due to difference between practices, which indicates that general practice characteristics are important determinants of management of depression. Further study is needed to identify and understand GP variation.

6.5 Conclusion

This study indicates that patients with ischemic heart disease or cardiac arrhythmia and who are newly diagnosed with comorbid depression by their GP have a lower likelihood of having any care for depression being initiated by their GP compared with non-chronically ill patients newly diagnosed with depression. This finding points to the importance of developing interventions targeted at supporting GPs in the adequate management of comorbid depression in patients with heart disease to reduce the negative impacts of comorbid depression and possibly improve outcomes from heart disease. To this end, first the mechanisms have to be ascertained that underlie the decreased likelihood of GP initiation of any depression care in heart disease patients.

Appendix

ICPC diagnoses included in the categories of specific chronic somatic morbidity

Chronic somatic condition	ICPC diagnoses
Colon	Diverticular disease, irritable bowel syndrome, or chronic enteritis/ ulcerative colitis
Stomach/duodenal	Duodenal or other peptic ulcer, or disorder of the stomach function
Hypertension	Uncomplicated hypertension or hypertension with involvement of target organs
Cardiac arrhythmia	Atrial fibrillation/ flutter, paroxysmal tachycardia, or ectopic beats
Ischemic heart	Angina pectoris, acute myocardial infarction, other chronic ischemic heart disease, or heart failure
Osteoarthritis/ rheumatoid arthritis	Osteoarthritis of spine/ hip/ knee, other osteoarthritis, or rheumatoid arthritis/ allied condition
Migraine	Migraine
Neurological conditions	Multiple sclerosis, Parkinson's disease/ parkinsonism, epilepsy, dementia, or stroke/ transient ischemic accident
Chronic lung	Chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or asthma
Skin	Eczema or psoriasis
Diabetes mellitus	Diabetes mellitus
Thyroid	Hyperthyroidism, hypothyroidism, or goiter
Cancer	Any malignant neoplasm[a]

ICPC, International Classification of Primary Care [24].
[a] skin cancer was excluded because of supposed lack of chronicity.

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7 Impact of pre-existing depression on length of stay and discharge destination among patients hospitalized for acute stroke: linked register-based study

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Abstract

Background and purpose: There exists limited knowledge regarding the relationship between depression and healthcare utilization in stroke patients. The objective of this register-based study was to examine the impact of having pre-existing depression at the time of hospital admission for acute stroke on length of hospital stay (LOS) and discharge destination (DD).

Methods: Data from a general practice database were linked to those of a hospital database to identify patients hospitalized for stroke and used to categorize these patients into three groups based on pre-existing mental health (MH) status at admission, i.e. those with pre-existing depression, those with another pre-existing MH condition and those without any pre-existing MH condition. Multilevel analyses controlling for several potentially important covariates were performed to estimate the associations under study.

Results: Both patients with pre-existing depression (*n* = 41) and those with another pre-existing MH condition (*n* = 62) did not differ significantly from patients without any pre-existing MH condition (*n* = 211) regarding LOS for acute stroke. Among patients who survived hospitalization, those with pre-existing depression had significantly higher odds of being discharged to an institution instead of their home than patients without any pre-existing MH condition. Having another pre-existing MH condition had no significant effect on DD.

Conclusions: Having pre-existing depression at admission seems to be a relevant factor in determining discharge to institutional care after acute stroke hospitalization. Further research is needed to determine the mechanism(s) through which pre-existing depression decreases the chances of being discharged to home.

7.1 Introduction

Poststroke depression (PSD) is common, occurring in about one third of all stroke survivors at some time following stroke onset [1], and has been associated with slower recovery [2], cognitive dysfunction [3] and lower quality of life [4]. Given these poorer outcomes, one may expect that stroke survivors who develop depression have higher healthcare utilization than their nondepressed counterparts. However, limited information is available on this issue. Most studies have examined the impact of PSD on length of stay in a rehabilitation setting and their findings are equivocal. Some studies found an association between PSD and increased length of stay [e.g. 5], whereas other studies did not demonstrate such a relationship [e.g. 6]. Recently, PSD among veterans has been found to be associated with more outpatient visits and an increase in the total length of re-hospitalization in the 1-year [7] as well as the 3-year [8] period after initial stroke hospitalization.

Whereas the relationship of PSD with healthcare utilization has received some attention, no study to date has examined, to our knowledge, whether there exists a link between pre-existing depression at the time of stroke and higher use of healthcare services. Such a link may be expected since, considering the high prevalence of depression in the elderly general population [9], a substantial number of patients is likely to suffer from or have a recent history of depression at the time of stroke, and considering the observation that, in general, depression in older persons is associated with adverse health outcomes and increased healthcare utilization [10].

The objective of this register-based study was to extend the knowledge regarding the relationship between depression among stroke patients and healthcare use by focusing on the impact of having pre-existing depression at hospital admission for first-ever or recurrent stroke on (1) the length of acute hospital stay (LOS) and (2) discharge destination (DD). Given that significant depressive symptomatology at admission has been associated with increased healthcare utilization at follow-up in the general population of older hospitalized patients [11], it was hypothesized that having pre-existing depression would prolong LOS for patients admitted for stroke and would increase the likelihood of being discharged to an institution (i.e. nursing home or rehabilitation centre) instead of their home among those who survived

acute care hospitalization.

7.2 Methods

Data sources

For this study, data from a general practice database, i.e. the National Network of General Practice (LINH) [12], were linked to data from a hospital database, i.e. the National Medical Register (LMR) [13]. Information from the LINH database was used to identify patients' pre-existing mental health (MH) status at hospital admission for stroke as well as to assess potential confounding variables (see below). LMR data were used to identify patients who were hospitalized for stroke and to measure LOS and DD (see below).

The LINH database holds longitudinal data extracted from electronic medical records of general practitioners (GPs) on all patient contacts, including diagnoses and drug prescriptions. Data from a subset of 74 practices were used, because these practices provided additional information on morbidity, i.e. diagnoses recorded by GPs on so-called "problem lists" of relevant health problems of patients, including those developed in the past. These additional data were collected within the framework of the second Dutch National Survey of General Practice [14]. Diagnoses are coded by GPs according to the International Classification of Primary Care (ICPC) [15] based on the criteria of the International Classification of Health Problems in Primary Care [16]. Prescribed drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [17]. Furthermore, the indication (i.e. ICPC-coded diagnosis) for a prescription is recorded.

The longitudinal LMR database has an almost complete coverage (99%) of all hospital admissions in the Netherlands. Recorded data include date of admission, date of discharge, diagnosis at discharge, and DD. Diagnosis at discharge is considered the reason for hospital admission and is coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Patient records from the LINH database were linked to those from the LMR database by using three patient identifiers that were present in both databases, i.e. gender, date of birth and 4-digit postal code. A pilot study has shown the feasibility of this linkage procedure [18].

Study population

First, persons 50 years of age or older registered with the 74 general practices on January 1, 2001 were selected (*n* = 68,152). Since almost all non-institutionalized Dutch inhabitants are registered with a GP, this can be regarded as a general population sample of individuals aged 50 years or older. Persons were excluded when they had a missing value on any of the three linkage variables or a non-unique combination of these variables (*n* = 2,190). Next, records of the remaining 65,962 persons from the LINH database were linked to those from the LMR database to identify those who were admitted to hospital for stroke between January 1, 2001 and December 31, 2003. Stroke comprised hemorrhagic stroke (ICD-9-CM code 430 or 431), acute ischemic stroke (code 434 or 436) and transient ischemic attack (TIA; code 435). The linkage procedure resulted in the identification of 847 patients who were hospitalized for stroke, corresponding approximately to an admission rate of 4 per 1000 persons aged 50 years or older per year. This rate compares well to the expected yearly hospital admission rate for stroke in the general Dutch population aged 50 years and older [19-20].

Of the 847 identified patients, 236 were excluded because general practice data were not available throughout the six months preceding hospital admission (either because a practice ended participating in LINH or because a patient was no longer registered with the practice). Additionally, eight patients diagnosed with dementia (ICPC code P70) were excluded to minimize the influence of having dementia on the associations under study. These exclusions left 603 patients for study.

Dependent variables

LOS was calculated by subtracting the date of admission from the date of discharge and expressed in days. DD was treated as a dichotomous variable: discharge to an institutional setting (i.e. rehabilitation centre or nursing home) versus discharge to home (including homes for the elderly, i.e. homes specially designed for the elderly and their needs [21]).

Independent variables

The 603 patients were divided into three nonoverlapping groups by pre-existing MH status at admission: (1) those with pre-existing depression, (2) those with a

pre-existing MH condition other than depression and (3) a reference group without any pre-existing MH condition. The heterogeneous group of patients with another pre-existing MH condition was formed to ensure that the reference group consisted of patients who had no pre-existing MH problems.
Pre-existing depression was defined as having been diagnosed at least once with depression (ICPC code P76) or depressive feelings (code P03) and/or having received at least one prescription for any antidepressant (ATC code N06A) in the six months preceding admission. The ICHPPC-2-Defined criteria for depression correspond largely to those of the DSM-IV for major depression [22]. The P03 code is used for patients with depressive feelings who do not fulfil criteria for depression.
Patients were considered to have another pre-existing MH condition when they had been diagnosed at least once with a MH condition other than depression (i.e. a "P"-diagnosis other than P76 or P03) and/or had been prescribed at least once an antidepressant for a MH condition other than depression or another psychotropic medication (i.e. ATC codes N05, N06B, N06C or N07B) in the six months preceding admission. The remaining patients were defined as having no pre-existing MH condition. Patients identified as having both pre-existing depression and another MH condition were classified into the group of patients with pre-existing depression.
Applying these definitions, resulted in the identification of 41 (6.8%) patients with pre-existing depression, 132 (21.9%) patients with another pre-existing MH condition and 430 (71.3%) patients without any pre-existing MH condition. The 41 patients with pre-existing depression were registered with 26 general practices.

Covariates

Other variables were taken into account that could potentially influence the relationship of pre-existing depression with LOS and DD, including age, gender, education, living situation before stroke (alone or living with others), year of hospitalization, stroke type, history of prior stroke or TIA, presence of other stroke risk factors and somatic comorbidity [23-25]. Educational level was categorized into low (no education or elementary school), middle/high (high school, college or university) and missing. This last category was created because attained educational level was unknown for a substantial number of patients (17%). History of prior stroke or TIA at admission was defined as

having been diagnosed with stroke or TIA (ICPC code K90 or K89) in the six months preceding admission. Presence of other stroke risk factors (hypertension: code K86 or K87; diabetes mellitus: code T90; atrial fibrillation: code K78; any cardiovascular condition: code K74 to K77, or K92) and other somatic conditions was established in a similar fashion. Somatic comorbidity was operationalized as a count of the number of somatic conditions [26] other than the stroke risk factors examined (0, 1, 2, and ≥3 conditions). Year of hospitalization was included to allow for the potential influence of changes in the organization of hospital care of stroke patients during the study period.
Furthermore, both death during hospitalization and DD have consistently been shown to significantly influence LOS [23,27]. In general, the period of hospitalization is shortest for patients who die in hospital, intermediate for patients discharged to home and longest for patients discharged to an institution. Therefore, death during hospitalization and DD were included as covariates in the analysis concerning LOS.
Finally, since severity of stroke has been found to be an important factor influencing LOS [24-25], LOS was included as a proxy for stroke severity in the analysis concerning DD.

Statistical analysis

Two steps were taken to reduce the potential confounding influence of variation between practices on the associations under study: (1) analyses included only patients with a pre-existing MH condition other than depression (*n* = 62) and those without any pre-existing MH condition (*n* = 211) who were registered with the 26 practices with whom the 41 patients with pre-existing depression were registered and (2) multilevel modeling was employed to further statistical control for potential variation between these 26 practices. Hospitals could not be included as higher-level units because hospital identifiers are not disclosed for analyses by third parties. Though, allowing for variation at the practice level was considered an adequate proxy for taking into account variation at the hospital level (e.g. variation in care for stroke patients, availability of a stroke unit, discharge planning) based on the assumption that most stroke patients who were registered with the same practice were admitted to the same hospital.
The distribution of LOS was skewed. However, logarithmic transformation resulted in an approximately normal distribution. A two-level random-

intercept linear regression model was used to analyze the influence of having pre-existing depression on the log-transformed LOS. A two-level random-intercept logistic regression model was used to assess the relationship between having pre-existing depression and discharge to an institution among the stroke patients who survived hospitalization. The reference category was being discharged to home. Multilevel analyses were performed using MLwiN version 2.0 and statistical significance was tested using the Wald statistic ($P < 0.05$).

7.3 Results

Patients with pre-existing depression and their general practices

The majority of the 41 patients with pre-existing depression (80.5%) were diagnosed at least once with depression (*n* = 31) or depressive feelings (*n* = 2) in the six months preceding hospital admission. The eight remaining patients defined as having pre-existing depression had been prescribed at least once an antidepressant in this period. The vast majority of the 41 patients (90.2%) were prescribed antidepressant drug therapy, most frequently selective serotonin reuptake inhibitors (59.5%).

The studied 26 practices were widely geographically distributed. Though, with regard to urbanization level of the practice location, practices located in rural areas were relatively over-represented.

Length of acute hospital stay (LOS)

Table 1 presents baseline characteristics as well as LOS and DD (including death during hospitalization) for the three groups classified by pre-existing MH status. The three groups did not differ significantly with regard to LOS in bivariate analysis. The distribution of gender, history of prior stroke/TIA and diabetes mellitus differed overall significantly between the groups. Post hoc tests showed that relative to patients without a pre-existing MH condition, a higher number of patients with another pre-existing MH condition were female (*p* = .020), had a history of prior stroke/TIA (*p* = .010) and had diabetes mellitus (*p* = .057). Also, more patients with another pre-existing MH condition than those with pre-existing depression had diabetes mellitus (*p* = .033).

Table 1

Characteristics at admission as well as length of stay (LOS) and discharge destination (DD) of hospitalized stroke patients grouped by pre-existing mental health (MH) status

	Pre-existing depression (*n* = 41)	Pre-existing other MH condition (*n* = 62)	No pre-existing MH condition (*n* = 211)	*p*
Age (years):				
mean(SD), range	71.1(10.1);51.6-89.5	74.1(8.2);52.8-87.1	72.9(9.3);51.3-92.5	.28[a]
50-59	7(17.1)	4(6.5)	23(10.9)	.56[b]
60-69	12(29.3)	15(24.2)	50(23.7)	
70-79	13(31.7)	26(41.9)	92(43.6)	
≥80	9(22.0)	17(23.6)	46(21.8)	
Female gender	25(61.0)	41(66.1)	103(48.8)	.034[b]
Educational level				
Low	12(29.3)	33(53.2)	91(43.1)	.11[b]
Middle/High	21(51.2)	23(37.1)	80(37.9)	
Unknown	8(19.5)	6(9.7)	40(19.0)	
Living alone	10(24.4)	15(24.2)	46(21.8)	.89[b]
Year of hospitalization				
2001	7(17.1)	16(25.8)	31(14.7)	.15[b]
2002	17(41.5)	18(29.0)	95(45.0)	
2003	17(41.5)	28(45.2)	85(40.3)	
Stroke type				
Acute ischemic stroke	27(65.9)	39(62.9)	145(68.7)	.13[b]
Hemorrhagic stroke	4(9.8)	16(25.8)	37(17.5)	
TIA	10(24.4)	7(11.3)	29(13.7)	
History of prior stroke/TIA	8(19.5)	15(24.2)	22(10.4)	.015[b]
Hypertension	15(36.6)	27(43.5)	80(37.9)	.69[b]
Diabetes mellitus	5(12.2)	20(32.3)	42(19.9)	.035[b]
Atrial fibrillation	3(7.3)	7(11.3)	15(7.1)	…[c]
Cardiovascular disease	7(17.1)	11(20.4)	36(17.1)	.99[b]
Somatic diseases				
0	16(39.0)	21(33.9)	82(38.9)	.39[b]
1	12(29.3)	15(24.2)	73(34.6)	
2	7(17.1)	13(21.0)	25(11.8)	
≥ 3	6(14.6)	13(21.0)	31(14.7)	
DD (including death)				
Home	21(51.2)	30(48.4)	132(62.6)	.45[b]
Institution	12(29.3)	14(22.6)	43(20.4)	
Death	8(19.5)	18(29.0)	36(17.1)	
LOS (days):				
median; IQR	13.0;5.5-23.5	10.5;5.8-20.5	10.0;6.0-22.0	.92[d]

Data presented are n(%) unless stated otherwise.

TIA, transient ischemic attack; IQR, interquartile range.

[a] ANOVA; [b] chi-square test; [c] requirements for chi-square test were not met; [d] Kruskal-Wallis test.

Table 2
Two-level linear regression model for log-transformed length of stay (LOS) among hospitalized stroke patients (*n* = 314)

	B	95% CI	*p*
Pre-existing MH status			
No pre-existing MH condition	reference		
Pre-existing depression	0.149	-0.12–0.42	.27
Pre-existing other MH condition	0.103	-0.13– -0.33	.38
DD (including death)			
Home	reference		
Institution	0.847	0.62–1.08	< .001
Death	-0.923	-1.18– -0.67	< .001
Stroke type			
Acute ischemic stroke	reference		
Hemorrhagic stroke	-0.067	-0.33–0.19	.62
TIA	-0.726	-0.99– -0.47	< .001
History of prior stroke/TIA	0.068	0.19–0.32	.60
Hypertension	0.145	-0.034–0.33	.11
Diabetes mellitus	-0.049	-0.27–0.17	.66
Atrial fibrillation	-0.053	-0.39–0.28	.76
Cardiovascular disease	0.005	-0.23–0.24	.97
Somatic diseases			
0	reference		
1	-0.028	-0.24–0.18	.79
2	-0.118	-0.40–0.17	.42
≥ 3	-0.119	-0.39–0.15	.39
Age groups			
50–59	reference		
60–69	0.153	-0.18–0.48	.36
70–79	0.389	0.075–0.70	.015
≥ 80	0.501	0.15–0.85	.0055
Female gender	-0.142	-0.33–0.050	.15
Educational level			
Low	reference		
Middle/High	-0.186	-0.39–0.017	.072
Unknown	-0.105	-0.35–0.14	.41
Living with others	-0.090	0.31–0.13	.42
Year of hospitalization			
2001	reference		
2002	-0.075	-0.33–0.18	.56
2003	-0.100	-0.35–0.15	.43

MH, mental health; TIA, transient ischemic attack.

The results of the two-level regression analysis for log-transformed LOS are shown in Table 2. Compared to having no pre-existing MH condition at admission, neither having pre-existing depression nor having another pre-existing MH condition did significantly influence duration of hospitalization, after controlling for the measured covariates as well as inter-practice variation. As expected, being admitted to a hospital because of a TIA (compared to being admitted because of an ischemic stroke) and dying during hospitalization (compared with being discharged to home) were associated with shorter LOS, while being sent to an institution (compared to being discharged to home) was related to prolonged LOS. Furthermore, patients aged 70 years or older at admission were more likely to stay longer in hospital than patients aged between 50-59 years.

Discharge destination (DD)

Sixty-two (19.7%) of the stroke patients died in hospital (see Table 1). Two-level logistic regression analysis showed that neither having pre-existing depression nor having another pre-existing MH condition significantly influenced risk of dying (data not shown). Two hundred fifty-two patients survived acute hospitalization for stroke. Bivariate analysis showed that the proportion of patients discharged to institutional care did not differ significantly by pre-existing MH status (pre-existing depression: 36.4%; pre-existing other MH condition: 31.8%; no pre-existing MH condition: 24.6%; p = .29). Further bivariate analyses revealed similar between-group differences when using the total study sample (see above), with the exception that the difference in gender distribution was no longer significant.

Table 3 shows the results of the two-level logistic regression analysis for DD. Patients with pre-existing depression had a significantly higher odds of being discharged to an institution than patients without any pre-existing MH condition, after adjusting for the measured covariates and variation between practices. Having another pre-existing MH condition did not exert a significant effect. Patients with a cardiovascular condition were significantly more likely to be sent to an institution compared to those without cardiovascular disease. Unsurprisingly, having been admitted to hospital because of TIA was associated with decreased odds of being discharged to institutional care, while increased LOS was related to higher odds of discharge to an institution. Finally, patients aged 80 years or older were more likely to be sent to institutional care than

patients aged between 50-59 years.

Table 3
Two-level logistic regression model for discharge to institution (vs. discharge to home) among stroke patients who survived initial hospitalization (*n* = 252)

	OR	95% CI	*p*
Pre-existing MH status			
No pre-existing MH condition	reference		
Pre-existing depression	4.86	1.69-14.02	.0034
Pre-existing other MH condition	1.61	0.53-4.89	.40
Length of hospital stay (LOS)	1.12	1.08-1.15	< .0001
Stroke type			
Acute ischemic stroke	reference		
Hemorrhagic stroke	1.08	0.35-3.32	.89
TIA	0.063	0.010-0.41	< .005
History of prior stroke/TIA	0.69	0.24-2.02	.50
Hypertension	0.58	0.28-1.22	.15
Diabetes mellitus	2.02	0.83-4.90	.12
Atrial fibrillation	0.27	0.048-1.52	.14
Cardiovascular disease	2.57	1.00-6.64	.051
Somatic diseases			
0	reference		
1	0.43	0.18-1.03	.060
2	0.88	0.27-2.82	.82
≥ 3	0.98	0.31-3.07	.98
Age groups			
50-59	reference		
60-69	2.74	0.61-12.30	.18
70-79	2.41	0.55-10.49	.24
≥ 80	6.19	1.34-28.62	< .05
Female gender	0.85	0.40-1.77	.66
Educational level			
Low	reference		
Middle/High	0.89	0.39-2.03	.79
Unknown	0.67	0.23-1.95	.46
Living with others	1.14	0.45-2.93	.78
Year of hospitalization			
2001	reference		
2002	1.12	0.40-3.13	.83
2003	1.48	0.55-3.93	.44

MH, mental health; TIA, transient ischemic attack; OR, odds ratio.

7.4 Discussion

The present register-based study indicated that having pre-existing depression at the time of hospital admission for a new or recurrent stroke did not influence LOS. Though, among patients who survived hospitalization for acute stroke, we found that patients who were already depressed at admission were more likely to be discharged to an institution instead of their home than those without any pre-existing MH condition, after controlling for the influence of several potentially confounding factors including socio-demographic variables, living alone or not, stroke type, history of prior stroke or TIA and somatic comorbidity. This is an important finding because it indicates that having pre-existing depression may be a relevant factor in determining discharge to institutional care rather than to home after acute stroke hospitalization. As far as we are aware no previous studies have examined the impact of pre-existing MH status at hospital admission for stroke on use of healthcare services.

Some potential limitations of our study should be acknowledged. First, the generalizability of our findings to the general population of patients hospitalized for stroke may be limited due to the exclusion of 28% of eligible patients. However, these patients did not differ from those that were included regarding gender, age, and educational level. Moreover, it is highly unlikely that the reason for excluding these patients, namely unavailability of general practice medical records, would have been associated with having pre-existing depression at admission. Another feature that may have limited the generalizability is that the final study population, and especially the group of patients with pre-existing depression, was rather small. Nevertheless, the studied patients were registered with 26 different practices that were geographically located throughout the Netherlands. Though, practices located in rural areas were somewhat over-represented. Second, using medical records of GPs to identify patients who were depressed at the time of admission for stroke has some drawbacks. Research has shown substantial underdiagnosis of depression in Dutch general practice [28]. In comparison, the rate of overdiagnosis seems to be considerably lower [29]. Importantly however, misclassification of cases due to overdiagnosis or underdiagnosis of depression would most likely have attenuated a true relationship between pre-existing depression and a higher likelihood of being discharged to institutional care

after stroke hospitalization rather than have produced a spurious one. In addition, by using GP records no standardized assessment of severity of depression was available, nor was information concerning possible initiated psychological treatments for depression. A third limitation is that the influence of potentially important unmeasured factors could not be taken into account. Our study lacks a detailed assessment of stroke severity, which is an important factor in determining both LOS and DD [23,25]. Though, LOS was included as a proxy for stroke severity in the analysis concerning discharge destination. Other unmeasured factors including subtype of ischemic stroke, functional status, cognitive functioning and availability of social support may have had modifying or confounding effects on the associations under study. In particular, poorer social support networks, functional and cognitive impairment are linked with depression in the elderly, probably in a complex and reciprocal manner [10], and each of these factors has been found to reduce the chances of discharge to home after acute stroke hospitalization [23, 30-31].

Bearing these limitations in mind, an obvious question that comes up is how the observed association between having pre-existing depression at hospital admission for stroke and increased likelihood of institutionalization can be explained. Possibly, this finding reflects a heightened level of dependency at discharge among patients with pre-existing depression. Their depressive symptoms, such as having pessimistic expectations, being demotivated, having less energy and diminished concentration, could reduce their ability to adapt to the impairments caused by stroke and thereby lead to slowed recovery during hospitalization [32]. The possibility of a relationship between antecedent depression and increased stroke severity could offer another explanation. The emerging body of evidence that suggests a role of depressive symptoms in the development of stroke does leave open the possibility of such a relationship [33]. Finally, having pre-existing depression at admission may contribute to a higher level of dependency at discharge through its potential associations with unmeasured factors such as functional disability, cognitive dysfunction and poor social support.

Evidently, further studies are needed to confirm our results and to better understand the mechanism(s) through which having pre-existing depression increases the likelihood of discharge to institutional care among patients hospitalized for acute stroke. Identification of the underlying mechanism(s) is essential to determine whether there exist opportunities to improve outcomes

for stroke patients with pre-existing depression and to reduce their frequency of discharge to an institution. Possible targets for intervention may include the routine assessment of pre-existing levels of depression at hospital admission for acute stroke and the optimization of depression management during hospitalization for stroke when necessary. GPs regularly miss depression in older persons, and when they do, often provide inadequate treatment [10]. A further potential intervention strategy might be to intensify the level of care and support provided in the home situation for stroke patients with pre-existing depression, for instance, by supporting informal caregivers and/or increasing the degree of home healthcare. Our study complements findings of two prior studies using administrative databases indicating a relationship between PSD and long-term healthcare utilization after acute hospitalization [1-2]. Altogether, these findings indicate the need for further studies specifically designed to disentangle the relationships between a past history of depression, pre-existing depression at the time of stroke, PSD and acute as well as long-term healthcare utilization.

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8 General discussion

This thesis addressed some identified gaps in the knowledge about the occurrence of comorbidity involving depression and its health care consequences. In this closing section first the main findings of the thesis will be presented, followed by reflections on the merits and disadvantages of using data from general practice records, while finishing with a discussion of the relevance and implications of the findings for future research and clinical practice.

8.1 Principal findings

Part A. Studies on occurrence

Part A started with a cross-sectional study that addressed the following research question (chapter 2):

> *What are the patterns of somatic and psychiatric cluster comorbidity in depression, stroke, multiple sclerosis, Parkinson's disease/ parkinsonism, dementia, migraine and epilepsy?*

Of the 30 categories of somatic illness studied, a broad and diverse set of 21 categories were identified as possible or highly probable instances of somatic cluster comorbidity in a large group of general practice patients with a lifetime GP diagnosis of depression.* This finding indicates that patients who have (had) depression are generally more likely to have a somatic illness than those who never had a depression. Noteworthy, when analyses were restricted to the subgroup of patients with a current GP diagnosis of depression, 12 of the 21 somatic disease categories were no longer identified as (possible or highly probable) cluster comorbidity. This was interpreted to reflect reduced statistical power due to the smaller size of this subgroup.

* Being of most interest to this thesis, summary of findings is limited to those concerning somatic cluster comorbidity in depression.

Part A continued with a case-control study that attempted to answer the following research question (chapter 3):

> *Is there a relationship between cerebrovascular risk factors (CVRFs) and the subsequent development of depression in older general practice patients?*

In this study, CVRFs included diagnoses of hypertension, diabetes mellitus, and cardiovascular disease. None of the CVRF variables examined (i.e. any CVRF, individual CVRF, number of CVRFs, and exposure duration to CVRFs) was found to be significantly associated with the subsequent onset of depression in a sample of older general practice patients. However, several of the CVRF variables under study were associated with a significantly increased odds of developing depression with onset between ages 50 and 69 years. It was suggested that these findings could indicate that CVRFs play a relevant role in the development of depression with onset between ages 50 and 69 years, but that no evidence was found that CVRFs contribute to the occurrence of depression with onset at age 70 years or later. These results should be considered preliminary given the possibility of bias inherent in using morbidity data recorded by GPs.

Part A finished with a systematic review in which the following research question was examined (chapter 4):

> *Is there a relationship between severity of Alzheimer's disease (AD) and prevalence of comorbid depressive symptoms and depression?*

A search strategy identified twenty-four studies that fulfilled pre-defined inclusion criteria. Of these, 19 reported findings on the relationship between severity of AD and prevalence of depressive symptoms and seven on the association of AD severity with frequency of diagnosed depression. Four of the 19 studies on the former association were rated as being of high quality, and three of these found no significant association. Three of the seven studies on the latter relationship were rated as being of high quality, and none of these reported a significant result. It was concluded that no evidence exists for a relationship between severity of AD and prevalence of comorbid depressive symptoms or depression.

Part B. Studies on health care consequences

Consequences for quality of care

The first study presented in Part B set out to answer the following research question (chapter 5):

> *Is there an interaction effect between psychiatric and chronic somatic comorbidity on GPs' diagnosis of depression?*

It was shown that approximately half of a group of patients with major depression and/or dysthymic disorder established according to a structured diagnostic interview, the Composite International Diagnostic Interview (CIDI) [1], had either comorbid psychiatric (as indicated by the CIDI) or comorbid chronic somatic disease (as indicated by GP records). Almost a quarter of them had both types of comorbidity. About 65% of the patients with psychiatric comorbidity were not diagnosed as being depressed by their GP, as reflected by having no GP record of a diagnosis of depression or depressive feelings. The rate of underdiagnosis of depression was somewhat higher among those with comorbid chronic somatic illness (74%). Multivariate analysis demonstrated an interaction effect between somatic and psychiatric comorbidity on GPs' diagnosis of depression. Further analysis showed that - among the patients without chronic somatic comorbidity - a lower educational level, less severe depression, and fewer GP contacts all were independently associated with a decreased likelihood of being diagnosed as depressed. Among the chronic somatically ill patients only having no comorbid psychiatric disorder was associated with a decreased likelihood of receiving a depression diagnosis. It was concluded that the factors associated with underdiagnosis of depression by GPs differ depending on whether or not depressed patients have a chronic somatic illness.

Next a prospective study was described in which two research questions were examined (chapter 6):

> *What is the influence of specific chronic somatic conditions on the initiation of any depression care in patients newly diagnosed with depression by their GP?; and*
>
> *Among those being prescribed antidepressants by their GP, what is the influence of these conditions on prescription of continuous antidepressant treatment?*

Any depression care was initiated in 86% of the patients with chronic somatic illness. A comparable percentage was observed among the non-chronically ill patients (88%). Rate of initiation of any depression care varied by type of condition, ranging from 59% in patients with cardiac arrhythmia to 93% among those with a thyroid condition. Multivariate analysis showed that, compared to patients without chronic somatic illness, patients with pre-existing ischaemic heart disease or cardiac arrhythmia had a significantly lower likelihood of having any depression care being initiated after being newly diagnosed with depression by their GP. None of the other 12 chronic somatic conditions under study was found to significantly impact the initiation of any depression care. The proportion of patients with continuous prescription after initiating antidepressant therapy was comparable among the groups with and without chronic somatic illness (resp. 37% and 39%). The rate of continuous prescription differed according to the type of the comorbid condition. Patients with cardiac arrhythmia showed the highest rate (50%), while the lowest rate was observed among those with a thyroid condition (23%). Multivariate analysis demonstrated that none of the chronic somatic conditions significantly influenced the prescription of continuous antidepressant treatment. These findings were interpreted as pointing to the relevance of supporting GPs in the management of comorbid depression in patients with heart disease to reduce its negative impact.

Consequences for health care utilization

Part B finished with a prospective study that investigated the following research question (chapter 7):

> *What is the impact of having pre-existing depression at hospital admission for stroke on the length of acute hospital stay and discharge destination?*

It was found that having pre-existing depression at the time of hospital admission for a new or recurrent stroke did not significantly affect length of acute hospital stay. It was further shown that among the survivors of hospitalization for acute stroke, the patients who were already depressed at admission had a significantly greater likelihood of being discharged to an institution instead of their home than those without any pre-existing mental health condition. Having a pre-existing mental health condition other than depression did neither influence length of acute hospital stay nor discharge

destination. These findings were interpreted as indicating that having pre-existing depression is a possibly important factor in determining discharge to institutional care after hospitalization for acute stroke.

8.2 Strengths and limitations of using general practice records

As has been discussed to some extent in the preceding chapters, using data from general practice records for studying occurrence of comorbidity involving depression and its health care consequences has its strengths and limitations. These will be considered below.

Strengths

Morbidity data that are continuously collected within a large, representative network of general practices, such as the National Information Network of General Practice (LINH) (www.linh.nl), have a combination of characteristics that makes them, in principle, very useful for research into the *occurrence* of comorbidity involving depression. Firstly, at least in countries such as the Netherlands, in which virtually all inhabitants are listed in a general practice and where GPs fulfil a gatekeeper's role towards the access to medically specialized care, the data represent the morbidity of a largely unselected population. It is essential to study associations between depression and other health conditions in an unselected population sample to preclude the identification of spurious cluster comorbidity due to selection bias [2]. Secondly, data on a large number of persons are available. This is important because the study of the occurrence of comorbidity involving depression may require very large samples, especially when the focus lies on specific associations between depression and other, less common health conditions. For instance, the large sample examined in the study presented in *chapter 2* allowed the investigation of the association of lifetime depression with disorders with a relatively low prevalence in the general population, such as multiple sclerosis and Parkinson's disease. Thirdly, the morbidity data reflect GP-defined health problems rather than being based on self-report. Fourthly, morbidity information from general practice is relatively comprehensive. GPs, as generalists, see a broad spectrum of somatic and mental health problems. They record diagnoses made by themselves, complemented with records of

diagnoses made by other health care professionals after referral. By comparison, large-scale population health surveys usually focus on (selected) somatic and/or psychiatric morbidity and rely fully on self-report. The resulting datasets may therefore have limited value for the study of comorbidity between depression and somatic illnesses. For instance, psychiatric morbidity surveys obviously collect extensive data about mental disorders, but usually only basic, self-reported information on (a restricted set of) chronic somatic conditions. A fifth strong point is that morbidity data that are continuously collected within a general practice network allows prospective or retrospective research to be conducted that spans long periods of time (of which the case-control study described in *chapter 3* is an example) [3]. Such research is vital to enhance our knowledge of the (time of) occurrence and the longitudinal pattern of depression during the course of another health condition, and vice versa. Other datasets usually cover a restricted time window.

The value of data collected in the primary setting for the study of the *health care consequences* of comorbidity involving depression is obvious. GPs in various countries play a key role in the diagnosis and management of persons with depression and in their referral to other health care professionals. Therefore, an important part of the research on the impact of comorbidity on the quality of depression care must be undertaken within the primary care setting. The same holds true for research on the relationship between comorbidity involving depression and health service utilization. Moreover, because opportunities exist to link datasets from general practice networks with data from patient based registers from other care settings, research on the health care use of general practice patients in relation to comorbidity involving depression can be extended to cover use of services in these settings (of which the study described in *chapter 7* is an example).

Limitations

There are a number of limitations inherent to using data from general practice records that hamper research into the *occurrence* of comorbidity involving depression. A first limitation is the reliance on GP-diagnosed depression. Several studies, including our own presented in *chapter 5*, have consistently shown that a considerable number of persons with major depression according to DSM-IV criteria are not diagnosed as being depressed by their GP [4-6].

Overdiagnosis of depression appears to occur less often in Dutch general practice [7-8]. Misclassification of depressed individuals as nondepressed and vice versa due to missed and incorrect diagnosis may lead to a biased estimation of the rates of comorbidity involving depression (i.e. concurrent comorbidity). Regarding research into cluster comorbidity, of which the studies presented in *chapters 2* and *3* are examples, such misclassification will probably lead to an underestimation of the comorbid associations under study. However, the possibility of differential misclassification cannot be ruled out, which could result in overestimated effects and thereby increase the chance of finding instances of spurious cluster comorbidity. With regard to the findings of chapters 2 and 3, which concentrated on associations between depression and somatic conditions, it is to some extent reassuring that research, including our own, has indicated that the rate of underdiagnosis of depression by GPs generally tends to be higher among chronically ill patients [5; 9-10].

A second limitation is that not all diagnoses made by GPs and other health care professionals after referral will be completely and fully correctly recorded in the patient's electronic medical record. This may lead to misclassification of depression and thereby bias both rates of comorbidity and strength of comorbid associations. Again, differential misclassification cannot be excluded. It may be possible that the quality of recording of depression diagnosis depends on whether persons have other (specific) health conditions problems. It is difficult to assess the quality of diagnosis recording because "gold" standards to determine completeness and accuracy are lacking [11-12]. Anyhow, within the LINH network measures are being taken to facilitate coding of diagnosis. Moreover, the extent of agreement regarding diagnostic coding between GPs participating in the second Dutch National Survey of General Practice and GPs highly experienced in coding was found to be reasonably high [13]. Research into the occurrence of comorbidity involving depression may also be hampered by deficiencies in the recording of other data types. For instance, the study described in *chapter 3* could only use a subset of patients' health history data because in a considerable number of participating practices electronic medical records included incomplete information about dates of diagnosis. Recently, an instrument was developed in the Netherlands that gives an indication of the quality of data included in electronic medical records [14]. Implementation of such an instrument may improve quality of recording.

A third limitation is that the accuracy of diagnoses of health problems and the

quality with which this information and other relevant data are recorded in an electronic patient record system may differ between participating GPs and practices [15]. However, there are analytical techniques available to control for this variation among GPs and practices, such as multilevel analysis.

Fourthly, a general practice database usually provides relatively crude measures of morbidity. The GPs participating in the LINH network use the ICPC-1 [16] to record health problems. This classification system offers no measure of the type and severity of depression according to standard psychiatric criteria. This is relevant because the occurrence of comorbidity involving depression may differ depending on these characteristics. The ICPC-1 provides diagnostic criteria from the International Classification of Health Problems in Primary Care (ICHPPC-2-Defined [17]). Given that the ICHPPC-2-Defined criteria for depressive disorder (ICPC code P76) are less strict than the DSM-IV criteria for major depression (e.g. a lower number of symptoms is required; no clinical significance criterion), it is likely that a proportion of the persons who are diagnosed as being depressed by their GP suffer from a dysthymic disorder or subthreshold depression [8]. Furthermore, it is unclear how the symptom diagnosis depressive feelings (ICPC code P03) relates to a diagnosis of subthreshold depression as defined by psychiatric criteria. Coding morbidity according to the ICPC does also provide relatively crude measures of other health conditions. A limited number of classes for diagnoses is offered by the classification system and assessment of the severity of a particular health condition is not included [18-19]. These characteristics preclude more in-depth research into the occurrence of comorbidity involving depression that considers the influence of specific types and severities of health conditions. Noteworthy, the second edition of the ICPC includes an extension to assess severity of a health condition and it appears to be feasible for GPs to routinely code this information [19].

A final limitation is that within a general practice database generally no or restricted information is available about other characteristics that could confound or modify associations between depression and other health conditions. For instance, research on the relationship between somatic illness and the subsequent development of depression, of which the study described in *chapter 4* is an example, would ideally take into account the influence of psychological and social risk factors for depression, such as personality disorder, stressful life events, and poor social support [20-21].

All above-mentioned limitations regarding the value of general practice records for research on the occurrence of comorbidity involving depression are also broadly relevant to studies on its *health care consequences*. In some cases, though, reliance on GP diagnosis of depression is not a shortcoming but a prerequisite in this research area. For instance, if the focus lies on the influence of the presence of other health conditions on the care for depression in general practice, as in the study described in *chapter 6*, patients who are diagnosed as depressed by their GPs are the study population of interest, irrespective of whether or not they meet standard psychiatric criteria for depression. Moreover, inter-practice or inter-GP variation needs not necessarily be treated as a factor whose influence has to be controlled for in analysis, but may also be a variable of interest. For instance, it is possible that GPs with certain characteristics have particular difficulties with diagnosing or managing depression in the context of (a specific) somatic illness.

8.3 Directions for future research

Implications of the studies on occurrence

Although addressing different research topics, all three studies presented in Part A point to the need for well-designed longitudinal research to better describe the occurrence of comorbidity between depression and other health conditions and to better understand its underlying mechanisms. Based on the study findings some (interrelated) research objectives for future longitudinal research could be formulated specifically regarding comorbidity of depression and somatic illness.

Gain more insight into the specificity of cluster comorbidity between depression and somatic illness

The finding of the study presented in *chapter 2* that lifetime and (to a lesser extent) current depression are cross-sectionally associated with a wide and diverse range of chronic somatic conditions in a largely unselected population corroborates the findings of two recent large-scale population-based studies [22-23]. The consistent finding of extensive cross-sectional cluster comorbidity stresses the relevance of gaining a better understanding of the comorbid relationships between depression and chronic somatic illnesses. In particular,

it does raise the question of how specific these associations are. Is depression largely non-specifically associated with a wide and diverse set of chronic somatic conditions or are specific chronic somatic conditions uniquely linked to depression? Such knowledge is important as an indicator for the pathways that may underlie links between depression and somatic illnesses [24-27]. To shed more light on this issue longitudinal research using unselected populations is needed that evaluates whether any association between depression and a specific chronic somatic illness is maintained after taking the influence of other coexisting somatic disorders into account. A longitudinal design is required to disentangle the bidirectional relationship that is likely to exist between depression and various chronic somatic illnesses [28]. Recently, a population-based longitudinal study examined the risk of depression in the 8-year period after the onset of cancer, diabetes, hypertension, heart disease, arthritis, chronic lung disease, or stroke [29]. Unlike most prior research, this study took into account the co-occurrence between the specific chronic conditions. It was found that the risk of depression over time varied by chronic condition, which suggests that there does not merely exist a general association between any chronic somatic condition (no matter which one) and risk of depression. Though, to clarify the specificity of comorbidity between depression and chronic somatic illness future longitudinal research also needs to consider the influence of mental disorders that are known to co-occur commonly with depression [23]. In particular, depression and anxiety disorders are closely related to each other, and anxiety disorders have also been shown to be associated with a range of chronic somatic conditions [30-31]. Given that most research performed to date has not taken the comorbidity of depression with anxiety and other mental disorders into account, it remains unclear whether depression's association with chronic somatic conditions is independent of other co-existing mental disorders.

Gain more insight into the interplay between having a chronic health condition and other risk factors in the onset of depression

The case-control study presented in *chapter 3* provided some support for a role of cerebrovascular risk factors (CVRFs) in the development of depression with onset between ages 50 and 69 years, but, paradoxically from the viewpoint of the vascular depression theory, not in the onset of depression at a later age. This adds to the inconsistency in findings across studies performed to date on

the association between CVRFs and depression in later life [32]. Well-designed, prospective research over a long follow-up period is required before more definite conclusions can be drawn regarding this relationship. Such research should take into account the various other biological, psychological, and social risk factors for later-life depression that have been reported in the literature [20-21] and determine their possible interplay with CVRFs in the onset of depression in older people. It has been proposed, for instance, that the presence of non-biological factors might be conditional to trigger depression in patients predisposed to it by cerebrovascular disturbance [33-35]. The question regarding the interaction with other risk factors for depression is generally relevant to any research into the role of a chronic health condition in the development of depression [36]. Yet, risk factors for depression are not often studied simultaneously [37]. Future longitudinal studies on the association between a chronic health condition and onset of depression should be designed taking a broad range of risk factors into account to allow investigation of interaction with possible other biological, psychological and social determinants of depression.

Gain more insight into the course of depression in the context of a chronic health condition and its determinants

The systematic review described in *chapter 4* suggests that, on the basis of published cross-sectional data, severity of dementia is not an important correlate of depression or depressive symptoms in Alzheimer's disease (AD). Evidently, though, prospective longitudinal studies with follow-up of patients who are in the early stages of AD can determine more definitely how the occurrence of depression and depressive symptoms relates to the various stages of severity of AD. To date, however, such studies have scarcely been performed [38]. The need for prospective research that examines the long-term course of comorbid depression and its determinants pertains not specifically to patients with AD, but generally to patients with any long-term health condition [28]. Given the heterogeneous nature of depression [39], it is important that such research determines if relevant subtypes of depression can be distinguished in the context of a particular chronic health condition. Recent studies of subtypes of depression following myocardial infarction (MI) offer potential insights in this respect. Firstly, incident post-MI depression, i.e. depression that develops for the very first time after MI, and non-incident post-MI

depression, i.e. depression that is preceded by or is a continuation of previous episodes of depression present before the occurrence of MI, appear to constitute meaningful subtypes of post-MI depression. Specifically, this subtyping describes subgroups of patients with post-MI depression that differ in pre-MI characteristics, severity of the MI, cardiovascular prognosis and response to psychiatric treatment [40-42]. Secondly, other studies indicate that distinct courses of depressive symptoms can be distinguished in post-MI patients [43-44].

Implications of the studies on health care consequences

Gain more insight into the mechanisms underlying suboptimal diagnosis and management of depression in the context of somatic illness

The study presented in *chapter 5* found a low rate of depression diagnosis by Dutch GPs among depressed patients with chronic somatic illness, which is especially noteworthy in view of the fact that the vast majority of these patients had regular contact with their GP. This is a worrisome finding given the evidence that depression negatively affects the course and outcome of somatic illnesses [45; 28], and vice versa [46]. Further research is needed to uncover the mechanisms that underlie underdiagnosis of depression in chronically ill patients. In our study different factors were found to affect diagnosis of depression by Dutch GPs in depressed patients with and without chronic somatic illness. However, a limited set of variables was considered and much of the variance was left unexplained. Future research should take into account the various other patient-related, GP-related, and health system-related factors that have been reported to hinder depression diagnosis in the general population of depressed general practice patients [47-49], and determine whether or not they apply to the subpopulation of depressed patients with a chronic somatic condition. Moreover, such future studies should ideally be large enough to allow investigation of the influence of characteristics of chronic somatic disorders (e.g. type and severity of somatic illness), characteristics of depression (e.g. depression subtypes), and common co-existent mental disorders (e.g. anxiety, somatisation) on the likelihood of depression diagnosis by GPs.

The study described in *chapter 6* indicates that patients newly diagnosed with depression are generally not managed differently by their GP depending on

whether or not they have a chronic somatic condition. Though, patients with pre-existing ischaemic heart disease or cardiac arrhythmia appear to be an exception: they were found to have a lower likelihood of any care for depression being initiated than those without chronic somatic illness. Further research is needed to replicate and elaborate on these findings. Given the adverse effects of comorbid depression in patients with ischaemic heart disease and available effective treatment strategies [50-51], it is important to understand the reasons why Dutch GPs are less likely to initiate depression care in patients with heart disease. Apart from pointing to the potential special case of patients with heart disease, the findings of our study also suggest that, once initiated, management of comorbid depression is less-than-optimal in the total group of patients with chronic somatic illness. For instance, a high rate of initiation of antidepressant treatment was observed among chronically ill patients with newly diagnosed depression (79%), while the rate of prescription of continuous therapy was found to be low (37%). To date, only a small number of studies in primary care settings have addressed the quality of depression treatment in patients with chronic somatic illness, and they used rather crude indicators for adequate depression treatment, i.e. treatment according to clinical guidelines [52-54]. Future research should more thoroughly examine the adequacy of pharmacological and psychological treatment initiated for depression in the context of specific chronic somatic illnesses and identify the mechanisms that underlie the occurrence of suboptimal depression treatment.

In this thesis the focus was laid on the influence of comorbidity on the care for depression in general practice, as Dutch GPs play a central role both in the diagnosis and management of depression [55]. Though, underdiagnosis and undertreatment of depression have also been found to be widespread among patients hospitalized for somatic illness [e.g. 56-57]. Future research should also focus on identifying the barriers to diagnosis and treatment of comorbid depression in the general hospital setting, and determine how these barriers relate to those in the primary care setting.

Gain more insight into the mechanisms underlying the association between comorbid depression and increased health care utilization among persons with somatic illness

The study presented in *chapter 7* found evidence suggesting that depression

already present at the time of stroke plays a relevant role in determining discharge to institutional care after acute stroke hospitalization. Coupled with earlier findings of a relationship between post-stroke depression (PSD) and increased health care utilization among stroke survivors in the years following hospitalization [58-59], this finding highlights the necessity that future longitudinal research uncovers the mechanisms by which depression exerts its effects on health care utilization after stroke, with a specific focus on the role of time of onset of depression.

This research issue is also relevant for patients with other somatic illnesses leading to hospital admission. Studies have found associations between comorbid depression and increased health care use in both the general population and various subpopulations of hospitalized patients, but the specific reason(s) for these links remain largely unclear [60-62]. Moreover, most previous research did not differentiate between patients for whom depression represented a first-ever depressive episode, those for whom depression was a continuation of a depression already present at the time of admission, and those for whom depression represented a recurrence of depression [63]. As mentioned before, such subtyping allows to identify subgroups of patients with depression after myocardial infarction (MI) that differ in pre-MI characteristics, severity of the MI, cardiovascular prognosis, and response to psychiatric treatment [40-42]. Further longitudinal research is needed to determine whether these, and other possibly relevant subtypes of depression differ in their effects of increasing use of health care services among patients hospitalized for somatic illness and whether the mechanisms through which they exert their influence are different. Such research should also clarify whether the association between comorbid depression and increased health care use and its underlying mechanisms are generalizable to any somatic illness leading to hospital admission or only to specific somatic illnesses requiring hospitalization.

Finally, these research questions need to be answered in the outpatient population as well. For instance, research in the primary care setting has consistently demonstrated that comorbid depression is associated with increased use of health services in patients with chronic somatic illness [64-67; 45].

Gain more insight into the (cost-)effectiveness of interventions for depression comorbid with somatic illness

Given the findings of suboptimal diagnosis and management of depression

comorbid with chronic somatic illness in Dutch general practice, future research needs to develop and evaluate strategies to improve quality of care for comorbid depression in chronically ill patients. An appealing strategy to improve the diagnosis of comorbid depression is to routinely screen for depression in patients with chronic somatic illness. Although routine screening for depression in chronically ill patients has been recommended in a number of guidelines [e.g. 68-69], its effectiveness in improving diagnosis, management and outcomes of depression has scarcely been investigated [70]. Research is needed in this area. Studies in depressed patients in the primary care setting indicate that screening works best when embedded within multifaceted disease management programs for depression, thereby helping to ensure that adequate treatment and follow-up is provided [71-72]. These multifaceted organisational interventions, also termed "collaborative care" interventions, have been shown to be effective in improving short- and long-term outcomes in depression in the primary care setting, at least in the US and UK [73-75]. Trials in primary care in the US indicate that collaborative care may also be effective in improving depression care and outcomes in depressed patients with diabetes mellitus [76-77], those with arthritis [78], and those with multiple chronic somatic conditions [79]. However, effects on outcomes related to the somatic illnesses under study were inconsistent or not investigated. Recently, evidence was found that collaborative care for patients with diabetes mellitus and comorbid depression significantly reduces outpatient health services costs [80]. Further research is needed to evaluate whether collaborative care is (cost-)effective in patients with (multiple) chronic somatic illness(es) in general practice in the Dutch health care setting [81], which intervention components are essential, and how such interventions can be further elaborated to also lead to improved outcomes of chronic somatic illnesses. Furthermore, such research needs to determine how disease management for depression can best be incorporated into the present-day care for chronic somatic illness in Dutch general practice, including integration within existing disease management programs for chronic somatic disorders.

The questions regarding the (cost-)effectiveness of complex organisational interventions to improve care for comorbid depression in the primary care setting are also relevant to the general hospital setting. As mentioned previously, there appears to be substantial room for improvement in the diagnosis and management of comorbid depression among patients hospitalized

for somatic illness [e.g. 56-57]. Interestingly, however, most studies performed to date have not demonstrated clear beneficial effects of enhanced depression care programs in the general hospital setting [82-86].
Finally, besides research that evaluates organisational strategies to improve quality of care for comorbid depression, more studies are needed that examine the effectiveness of pharmacologic and psychological treatments for depression in the context of chronic somatic illness. Although a growing body of evidence indicates that depression comorbid with chronic somatic illness can be effectively treated [28; 46; 87] more research is needed in this area, also to determine whether outcomes of somatic illnesses can be positively influenced.

8.4 Relevance and implications for Dutch general practice

Findings of this thesis point to less-than-optimal diagnosis and management of comorbid depression in patients with chronic somatic illness in general practice in the Netherlands. This underscores the need for educational initiatives to increase the awareness of GPs and other health professionals working in Dutch general practice about the commonness of comorbid depression in chronically ill patients, its negative impact on the course and outcomes of chronic somatic illnesses, and the options for its diagnosis and management. In this respect, clinical guidelines on somatic illnesses need to be amended to include existing knowledge about comorbidity with depression. Current practice guidelines of the Dutch College of General Practitioners as well as current Dutch multidisciplinary guidelines concerning somatic illnesses generally devote little or no attention to psychiatric comorbidity [88].
It is unlikely, however, that educational efforts and introducing adjusted clinical guidelines will be sufficient to lead to better care for comorbid depression in chronically ill patients. Reviews of strategies to enhance quality of depression care in the primary care population have indicated that organizational restructuring is an essential component for improving care and outcomes [48; 73]. As mentioned before, the collaborative care model has been demonstrated to be effective in the primary care setting in the US and UK [74-75], and recent US studies have suggested that this multifaceted organisational intervention may also result in better outcomes in the subpopulation of chronic somatically ill patients [76-79]. Collaborative care introduces several changes in

the way care for depression is organized and delivered in primary care, among which are the use of a care manager to coordinate and monitor care, the availability of a mental health specialist who provides supervision and consultation, screening for depression, the formulation of a personalized treatment plan, a stepped-care model of treatment, and systematic follow-up [89]. These redesigns can be considered starting-points to improve present-day care of chronically ill patients with comorbid depression in the primary care setting.

In the Dutch health care setting there are a number of potential candidates who may take on the role of care manager, including primary care psychologists, social workers, community psychiatric nurses, and mental health care practice nurses (a new function which was introduced just recently in Dutch general practice) [90]. These persons have a mental health background, which appears to be conducive to the effectiveness of collaborative care [91]. However, with regard to chronically ill patients, practice nurses or specialized nurses could be involved as well. They usually have already regular contacts with chronically ill patients. Moreover, they play an important role in existing disease management programs for chronic somatic illnesses (e.g. www.diabeteszorgbeter.nl), and could therefore provide together with GPs the necessary link between disease management programs that are currently focused on a single somatic or mental disorder. The consultant psychiatrist would be a likely candidate to fulfil the role of supervising mental health specialist. Adequate medical and pharmacological knowledge and experience is a prerequisite to ascertain the diagnosis of depression in chronically ill patients and to formulate a treatment and management plan [92]. An important element of collaborative care is a close liaison between the patient, the care manager, the GP, and the supervising mental health specialist. Continued efforts are therefore needed to strengthen existing multidisciplinary relationships and to develop new ones in practices where they are not present yet. Collaboration between the different health care providers may be fostered by using technology, such as, for instance, a computerized tracking system which enables them to monitor patient progress and communicate with each other [93]. Routine screening for depression in a person with a chronic somatic condition can be performed during the regular contacts with his or her GP, practice nurse or specialized nurse. Short screening instruments exist that have shown there value in detecting depression in the context of medical

illness [94]. A positive screening result needs to be followed up by diagnostic assessment and, when necessary, by evidence-based, stepped-care treatment for depression in the context of somatic illness. Both a screening instrument and evidence-based treatment algorithms for comorbid depression could be incorporated into the electronic medical record systems used in Dutch general practice.

Evidently, whether the above-mentioned suggested reorganizations will actually improve quality of care and outcomes for patients with chronic somatic illness and comorbid depression needs to be evaluated in practice.

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Summary

Depression and comorbidity. General practice-based studies on occurrence and health care consequences.

Introduction (chapter 1)

Depression often co-occurs with other mental and somatic disorders in one patient. This comorbidity is associated with increased personal and societal burden. Depression comorbid with another mental disorder is more severe and has a poorer prognosis than depression alone. The course of depression also tends to be more protracted in the context of somatic illness. The other way around, there is ample evidence that depression negatively affects the course and outcome of chronic somatic disorders. From a societal viewpoint, comorbidity involving depression is important given its association with increased use of health care services and increased absence from work.
Although its relevance is clear, substantial knowledge gaps about comorbidity involving depression remain. In this thesis two sets of research questions were examined to extend knowledge about: (a) the occurrence of comorbidity involving depression; and (b) the health care consequences of comorbidity involving depression, specifically consequences for quality of care and health care utilization. The studies are mainly based on general practice data collected within the framework of the second Dutch National Survey of General Practice (DNSGP-2) and the National Information Network of General Practice (LINH).

Part A. Studies on occurrence

Knowledge on somatic *cluster* comorbidity, i.e. somatic illness that occurs at a higher rate than expected by chance, among depressive patients in the general population is limited. Dutch general practice provides a good opportunity to study the pattern of somatic cluster comorbidity in a largely unselected sample of depressed persons. *Chapter 2* reports on a cross-sectional study that

used medical records of general practitioners (GPs) to address the following research question:

What are the patterns of somatic and psychiatric cluster comorbidity in depression, stroke, multiple sclerosis, Parkinson's disease/ parkinsonism, dementia, migraine and epilepsy?

Of the 30 categories of somatic illness studied, a broad and diverse set of 21 categories were identified as possible or highly probable instances of somatic cluster comorbidity in a large group of general practice patients with a lifetime GP diagnosis of depression.* This finding indicates that patients who have (had) depression are generally more likely to have a somatic illness than those who never had a depression. Noteworthy, when analyses were restricted to the subgroup of patients with a current GP diagnosis of depression, 12 of the 21 somatic disease categories were no longer identified as (possible or highly probable) cluster comorbidity. This was interpreted to reflect reduced statistical power due to the smaller size of this subgroup.

Part A continued with a case-control study that examined the association between cerebrovascular risk factors (CVRFs) and the subsequent development of depression in later life. There is little research on this relationship. Demonstrating the existence of such a link would lend support for the vascular depression hypothesis of late-life depression, which postulates that cerebrovascular disease may cause or exacerbate depression with late onset in life. The following research question was addressed in *chapter 3*:

Is there a relationship between CVRFs and the subsequent development of depression in older general practice patients?

In this study, CVRFs included diagnoses of hypertension, diabetes mellitus, and cardiovascular disease. None of the CVRF variables examined (i.e. any CVRF, individual CVRF, number of CVRFs, and exposure duration to CVRFs) was found to be significantly associated with the subsequent onset of depression in a sample of older general practice patients. However, several of the CVRF variables under study were associated with a significantly increased odds of developing depression with onset between ages 50 and 69 years. It was suggested that these findings could indicate that CVRFs play a relevant role in the development of depression with onset between ages 50 and 69 years, but

* Being of most interest to this thesis, summary of findings is limited to those concerning somatic cluster comorbidity in depression.

that no evidence was found that CVRFs contribute to the occurrence of depression with onset at age 70 years or later. These results should be considered preliminary given the possibility of bias inherent in using morbidity data recorded by GPs.

Part A finished with a systematic review. The various cross-sectional studies performed to date that have examined the relationship between severity of Alzheimer's disease (AD) and prevalence of comorbid depressive symptoms or depression have yielded inconsistent results. *Chapter 4* describes a systematic review of these cross-sectional studies to address the following research question:

Is there a relationship between severity of AD and prevalence of comorbid depressive symptoms and depression?

A search strategy identified twenty-four studies that fulfilled pre-defined inclusion criteria. Of these, 19 reported findings on the relationship between severity of AD and prevalence of depressive symptoms and seven on the association of AD severity with frequency of diagnosed depression. Four of the 19 studies on the former association were rated as being of high quality, and three of these found no significant association. Three of the seven studies on the latter relationship were rated as being of high quality, and none of these reported a significant result. It was concluded that no evidence exists for a relationship between severity of AD and prevalence of comorbid depressive symptoms or depression.

Part B. Studies on health care consequences

Consequences for quality of care

The focus was laid on the influence of comorbidity on the care for depression in general practice in the Netherlands, as Dutch GPs play a central role both in the diagnosis and management of depression.

Given that previous studies have suggested opposite effects of psychiatric and somatic comorbidity on underdiagnosis of depression by GPs, the study described in *chapter 5* set out to answer the following research question:

Is there an interaction effect between psychiatric and chronic somatic

comorbidity on GPs' diagnosis of depression?

It was shown that approximately half of a group of patients with major depression and/or dysthymic disorder established according to a structured diagnostic interview had either comorbid psychiatric (as indicated by the interview) or comorbid chronic somatic disease (as indicated by GP records). Almost a quarter of them had both types of comorbidity. About 65% of the patients with psychiatric comorbidity were not diagnosed as being depressed by their GP, as reflected by having no GP record of a diagnosis of depression or depressive feelings. The rate of underdiagnosis of depression was somewhat higher among those with comorbid chronic somatic illness (74%). Multivariate analysis demonstrated an interaction effect between somatic and psychiatric comorbidity on GPs' diagnosis of depression. Further analysis showed that - among the patients without chronic somatic comorbidity - a lower educational level, less severe depression, and fewer GP contacts all were independently associated with a decreased likelihood of being diagnosed as depressed. Among the chronic somatically ill patients only having no comorbid psychiatric disorder was associated with a decreased likelihood of receiving a depression diagnosis. It was concluded that the factors associated with underdiagnosis of depression by GPs differ depending on whether or not depressed patients have a chronic somatic illness.

There is limited information on whether having a specific chronic somatic condition influences the care for depression in general practice. *Chapter 6* presents a prospective study in which two research questions were addressed:

What is the influence of specific chronic somatic conditions on the initiation of any depression care in patients newly diagnosed with depression by their GP?; and

Among those being prescribed antidepressants by their GP, what is the influence of these conditions on prescription of continuous antidepressant treatment?

Any depression care was initiated in 86% of the patients with chronic somatic illness. A comparable percentage was observed among the non-chronically ill patients (88%). Rate of initiation of any depression care varied by type of condition, ranging from 59% in patients with cardiac arrhythmia to 93% among those with a thyroid condition. Multivariate analysis showed that patients with pre-existing ischaemic heart disease or cardiac arrhythmia had a significantly

lower likelihood of having any depression care being initiated after being newly diagnosed with depression by their GP than patients without chronic somatic illness. None of the other 12 chronic somatic conditions under study was found to significantly impact the initiation of any depression care. The proportion of patients with continuous prescription after initiating antidepressant therapy was comparable among the groups with and without chronic somatic illness (resp. 37% and 39%). The rate of continuous prescription differed according to the type of the comorbid condition. Patients with cardiac arrhythmia showed the highest rate (50%), while the lowest rate was observed among those with a thyroid condition (23%). Multivariate analysis demonstrated that none of the chronic somatic conditions significantly influenced the prescription of continuous antidepressant treatment. These findings were interpreted as pointing to the relevance of supporting GPs in the management of comorbid depression in patients with heart disease to reduce its negative impact.

Consequences for health care utilization

Although a number of studies have addressed the impact of depression on use of health care services by patients who suffered a stroke, none of them has specifically focussed on the influence of already existing depression. Part B finished with a prospective study that attempted to answer the following research question (*chapter 7*):

> *What is the impact of having pre-existing depression at hospital admission for stroke on the length of acute hospital stay and discharge destination?*

It was found that having pre-existing depression at the time of hospital admission for a new or recurrent stroke did not significantly affect length of acute hospital stay. It was further shown that among the survivors of hospitalization for acute stroke, the patients who were already depressed at admission had a significantly greater likelihood of being discharged to an institution instead of their home than those without any pre-existing mental health condition. Having a pre-existing mental health condition other than depression did neither influence length of acute hospital stay nor discharge destination. These findings were interpreted as indicating that having pre-existing depression is a possibly important factor in determining discharge to institutional care after hospitalization for acute stroke.

General discussion (chapter 8)

Strengths and limitations of using general practice records

The studies showed that using data from general practice records for studying the occurrence of comorbidity involving depression and its health care consequences has its strengths and limitations.

Strengths include:

- Data represent a largely unselected population, at least in countries where GPs act as a gatekeeper to other health care facilities;
- Data on a large number of persons are available;
- Morbidity data reflect doctor-defined health problems rather than being based on self-report;
- Morbidity information is relatively comprehensive given that GPs come across a broad spectrum of somatic and mental health problems;
- Data are continuously collected, which allows prospective or retrospective research to be conducted that spans long periods of time;
- Opportunities exist to link datasets from general practice networks with data from patient based registers from other care settings;
- In various countries GPs play a important role in the diagnosis and management of persons with depression and in their referral to other health care professionals.

Potential limitations include:

- Reliance on GP-diagnosed depression including its inherent variability;
- Suboptimal recording of morbidity in terms of completeness and accuracy;
- Variation between GPs and practices regarding quality of recording;
- Low specificity of diagnoses recorded, by which no information is available on the type and severity of depression and other health problems;
- No or restricted information is available about important potential confounders or effect modifiers, such as psychological and social risk factors for depression.

Directions for future research

Research on occurrence

Based on the findings in Part A, it was concluded that there exists a need for well-designed longitudinal research to better describe the occurrence of comorbidity between depression and other health conditions and to better understand its underlying mechanisms. Three more specific research objectives were suggested regarding comorbidity between depression and somatic illness:

- Gain more insight into the specificity of cluster comorbidity between depression and somatic illness;
- Gain more insight into the interplay between having a chronic health condition and other risk factors in the onset of depression;
- Gain more insight into the course of depression in the context of a chronic health condition and its determinants.

Research on health care consequences

Three objectives for future research were proposed based on the findings in Part B:

- Gain more insight into the mechanisms that underlie suboptimal diagnosis and management of depression in the context of somatic illness;
- Gain more insight into the mechanisms underlying the association between comorbid depression and increased health care utilization among persons with somatic illness;
- Gain more insight into the (cost-)effectiveness of interventions for depression comorbid with somatic illness.

Relevance and implications for Dutch general practice

Study findings indicate that the diagnosis and management of comorbid depression in patients with chronic somatic illness is less-than-optimal in general practice in the Netherlands. This finding is of concern given the commonness of comorbidity between depression and chronic somatic illness and the evidence that depression negatively affects the course and outcome of somatic illnesses, and vice versa. Some suggestions are given to improve care for chronic somatically ill patients with comorbid depression in general

practice, such as regular screening for depression, stepped-care treatment, the availability of a care manager and supervision by a mental health specialist.

Samenvatting

Depressie en comorbiditeit. Studies in de huisartsenpraktijk naar voorkomen en gevolgen voor de zorg.

Inleiding (hoofdstuk 1)

Een depressie komt vaak tegelijkertijd voor met een chronische lichamelijke ziekte of een andere psychische stoornis. Deze comorbiditeit bij depressie heeft belangrijke gevolgen voor zowel de individuele patiënt als voor de samenleving als geheel. Een depressie die samengaat met een andere psychische stoornis is over het algemeen ernstiger en heeft een minder goed beloop. Een slechtere prognose van depressie wordt ook gezien wanneer er sprake is van een chronische lichamelijke aandoening. Andersom bekeken zijn er sterke aanwijzingen dat depressie het beloop van chronische lichamelijke ziekten ongunstig beïnvloedt. Maatschappelijk gezien is comorbiditeit bij depressie van belang gezien de samenhang met meer gebruik van zorgvoorzieningen en meer werkverzuim.
Hoewel de relevantie van comorbiditeit bij depressie duidelijk is, bestaan er nog tal van leemtes in de kennis op dit gebied. In dit proefschrift worden twee sets van onderzoeksvragen beantwoord om meer kennis te verkrijgen over: (a) het voorkomen van comorbiditeit bij depressie; en (b) de gevolgen van comorbiditeit bij depressie voor de kwaliteit van zorg en het zorggebruik. Voor de studies is gebruik gemaakt van gegevens uit huisartsenpraktijken die verzameld zijn in het kader van de Tweede Nationale Studie naar ziekten en verrichtingen in de huisartsenpraktijk (NS2) en het Landelijk Informatie Netwerk Huisartsenzorg (LINH).

Deel A. Studies naar voorkomen

De kennis over het voorkomen van lichamelijke *cluster* comorbiditeit, oftewel lichamelijke ziekten die vaker voorkomen dan op basis van toeval verwacht wordt bij personen met een depressie in de algemene bevolking is beperkt. In

Nederland biedt de huisartsenpraktijk een goede mogelijkheid om het patroon van lichamelijke cluster comorbiditeit in een goeddeels ongeselecteerde groep van personen met een depressie te onderzoeken. In *hoofdstuk 2* wordt een cross-sectionele studie beschreven waarin gebruik gemaakt is van door huisartsen geregistreerde morbiditeitgegevens om de volgende onderzoeksvraag te beantwoorden:

> *Wat zijn de patronen van lichamelijke en psychische cluster comorbiditeit bij depressie, beroerte, multiple sclerose, ziekte van Parkinson/ Parkinsonisme, dementie, migraine en epilepsie?*

Uit de analyses van een grote groep van personen die depressief zijn of zijn geweest volgens hun huisarts, bleken 21 van de 30 onderzochte lichamelijke ziektecategorieën naar voren te komen als mogelijke of zeer waarschijnlijke lichamelijke cluster comorbiditeit.[*] Deze bevinding geeft aan dat personen die een depressie hebben of ooit gehad hebben over het algemeen vaker een lichamelijke aandoening hebben dan degenen die nooit depressief zijn geweest. Wanneer de analyses beperkt werden tot de subgroep van personen met een huidige depressie, bleken 12 van de 21 ziektecategorieën niet meer als lichamelijke cluster comorbiditeit naar voren komen. Dit is mogelijk te verklaren door een lagere statistische power vanwege de kleinere omvang van deze subgroep.

Deel A vervolgt met een patiënt-controle-onderzoek waarin het verband onderzocht is tussen het hebben van risicofactoren voor cerebrovasculaire ziekte (CVRF's) en het ontwikkelen van een depressie later in het leven. Hier is tot dusverre weinig onderzoek naar gedaan. Indien dit verband zou bestaan, ondersteunt dit de "vasculaire depressie" hypothese. Deze hypothese veronderstelt dat cerebrovasculaire ziekte depressie op oudere leeftijd kan veroorzaken of verergeren. In *hoofdstuk 3* is gepoogd de volgende onderzoeksvraag te beantwoorden:

> *Bestaat er een relatie tussen het hebben van CVRF's en het ontwikkelen van een depressie bij oudere patiënten in de huisartsenpraktijk?*

CVRF's omvatten in deze studie de diagnoses hypertensie, diabetes mellitus en cardiovasculaire ziekte. Het bleek dat in de onderzochte groep van oudere huisartspatiënten (≥50 jaar) het hebben van een CVRF (ongeacht welke) niet

[*] Gezien de focus van het proefschrift worden hier alleen de resultaten met betrekking tot lichamelijke cluster comorbiditeit bij depressie besproken .

samenhing met het ontstaan van een depressie op latere leeftijd. Ook het hebben van een specifieke CVRF, het aantal CVRF's en de duur van de aanwezigheid van CVRF's bleken niet van invloed. Wel werd gevonden dat een aantal van de bestudeerde CVRF-variabelen samenhing met een verhoogde kans op het krijgen van een depressie op de leeftijd tussen 50 en 69 jaar. Dit suggereert dat CVRF's een rol spelen bij het ontwikkelen van een depressie in deze leeftijdsperiode, maar dat er geen aanwijzingen zijn dat CVRF's bijdragen aan het ontstaan van een depressie op 70-jarige leeftijd of later. Deze bevindingen moeten echter als voorlopig beschouwd worden omdat het mogelijk is dat de resultaten vertekend zijn door gebruik te maken door huisarts geregistreerde morbiditeitgegevens.

Deel A eindigt met een systematische review. In de loop der tijd zijn er verscheidene cross-sectionele studies gepubliceerd die de relatie tussen de ernst van de ziekte van Alzheimer (AD) en het voorkomen van comorbide depressie of depressieve symptomen hebben onderzocht. Deze studies laten echter inconsistente resultaten zien. *Hoofdstuk 4* presenteert een systematische review van de studies om de volgende onderzoeksvraag te beantwoorden:

> *Bestaat er een relatie tussen de ernst van AD en de prevalentie van comorbide depressie en depressieve symptomen?*

Een zoekstrategie vond 24 studies die voldeden aan vooraf gestelde inclusiecriteria. Negentien studies beschreven bevindingen omtrent de relatie tussen de ernst van AD en de prevalentie van comorbide depressieve symptomen. Slechts vier van de 19 studies werden als kwalitatief goed beoordeeld, en van deze vier studies vonden drie geen verband. De relatie tussen de ernst van AD en het voorkomen van depressie werd door zeven studies onderzocht. Drie werden als kwalitatief goed beoordeeld, maar in geen van deze studies werd een verband gevonden. Op basis hiervan is geconcludeerd dat er geen bewijs bestaat voor een relatie tussen de ernst van AD en de prevalentie van comorbide depressie en depressieve symptomen.

Deel B. Studies naar gevolgen voor de zorg

Gevolgen voor de kwaliteit van zorg

Nederlandse huisartsen spelen een centrale rol in de diagnose en behandeling van depressie. Om deze reden is in dit proefschrift de focus gelegd bij de invloed van comorbiditeit op de huisartsgeneeskundige zorg voor depressie.

Bevindingen uit eerdere studies geven aan dat psychische en lichamelijke comorbiditeit tegengestelde effecten hebben op de kans dat een depressie niet gediagnosticeerd wordt door een huisarts. Daarom stond in *hoofdstuk 5* de volgende onderzoeksvraag centraal:

> *Bestaat er een interactie-effect tussen psychische en lichamelijke comorbiditeit op de kans dat een depressie gediagnosticeerd wordt door een huisarts?*

Ongeveer de helft van een groep personen met een depressieve en/of dysthyme stoornis zoals vastgesteld via een gestructureerd psychiatrisch diagnostisch interview bleek ofwel een comorbide psychische stoornis (bepaald middels het psychiatrisch interview) ofwel een comorbide chronische lichamelijke aandoening (bepaald aan de hand van door huisartsen geregistreerde morbiditeitgegevens) te hebben. Bijna een kwart had beide typen comorbiditeit. Ongeveer 65% van de depressieve personen met psychische comorbiditeit waren niet als depressief gediagnosticeerd door hun huisarts, blijkend uit het ontbreken van een geregistreerde diagnose depressie of depressieve gevoelens. De mate van onderdiagnostiek van depressie was hoger onder degenen met een comorbide chronische lichamelijke aandoening (74%). Multivariate analyse toonde een interactie-effect aan tussen psychische en lichamelijke comorbiditeit op de kans dat een depressie gediagnosticeerd werd door de huisartsen. Verdere analyses gaven aan dat – onder de personen zonder chronische lichamelijke comorbiditeit – een lager opleidingsniveau, een minder ernstige depressie, en minder contact met de huisarts, onafhankelijk samenhingen met een kleinere kans op het krijgen van de diagnose depressie. Onder de chronisch lichamelijk zieke, depressieve personen was alleen het niet hebben van een comorbide psychische stoornis gerelateerd aan een minder grote kans op de diagnose depressie. Op basis van deze bevindingen is geconcludeerd dat de factoren die samenhangen met de onderdiagnostiek van depressie in de huisartsenpraktijk verschillen, afhankelijk van of depressieve personen wel of niet chronisch lichamelijk ziek zijn.

Er is weinig informatie over de invloed van specifieke chronische lichamelijke aandoeningen op de zorg voor depressie in de huisartsenpraktijk. *Hoofdstuk 6* presenteert een prospectieve studie die ingaat op twee onderzoeksvragen:

Wat is de invloed van specifieke chronische lichamelijke aandoeningen op het beginnen van enige vorm van depressiebehandeling bij personen die door hun huisarts nieuw gediagnosticeerd zijn met depressie?; en

Wat is – onder degenen die antidepressiva voorgeschreven kregen door hun huisarts – de invloed van deze aandoeningen op het voorschrijven van een continue behandeling met antidepressiva gedurende zes maanden?

Bij 86% van de personen met een chronische lichamelijke aandoening werd begonnen met enige vorm van behandeling voor de nieuw gediagnosticeerde depressie. Dit gebeurde bij een vergelijkbaar percentage van de niet-chronisch zieke personen (88%). Het percentage personen bij wie een vorm van depressiezorg gestart werd verschilde per type aandoening, variërend van 59% van de personen met een hartritmestoornis tot 93% van degenen met een schildklieraandoening. Multivariate analyse liet zien dat personen met een ischemische hartaandoening of hartritmestoornis een kleinere kans hadden dan niet-chronisch zieke personen dat er enige vorm van depressiebehandeling geïnitieerd werd na nieuw gediagnosticeerd te zijn met depressie. Geen van de andere 12 bestudeerde chronische lichamelijke aandoeningen had invloed op de kans dat depressiebehandeling gestart werd. Het percentage personen dat gedurende zes maanden op continue basis antidepressiva kreeg voorgeschreven was vergelijkbaar in de groep chronisch lichamelijk zieke personen en de groep niet-chronisch zieken (resp. 37% en 39%). De mate van continu voorschrijven varieerde per type chronische aandoening. Bij personen met een hartritmestoornis werd het hoogste percentage (50%) gevonden, terwijl het laagste percentage (23%) gevonden werd onder degenen met een schildklieraandoening. Multivariate analyse toonde aan dat geen van de specifieke chronische lichamelijke aandoeningen de kans op het continu voorschrijven van antidepressiva beïnvloedde. De bevindingen van deze studie wijzen op het belang om huisartsen te ondersteunen in het adequaat behandelen van comorbide depressie bij personen met een hartaandoening om de negatieve gevolgen van de depressie te verminderen.

Gevolgen voor het zorggebruik

Een aantal eerdere studies heeft de invloed onderzocht van depressie op het gebruik van zorgvoorzieningen door personen die een beroerte hebben doorgemaakt. Echter, dit onderzoek heeft zich niet specifiek gericht op het effect van een al bestaande depressie op zorggebruik. Deel B (*hoofdstuk 7*) van dit proefschrift eindigt met een prospectieve studie waarin getracht is de volgende onderzoeksvraag te beantwoorden:

> *Wat is de invloed van het reeds hebben van een depressie ten tijde van een ziekenhuisopname vanwege een beroerte op de duur van de opname en de ontslagbestemming?*

Een reeds bestaande depressie bleek geen effect te hebben op de duur van de ziekenhuisopname vanwege een eerste of recidief beroerte. Verder werd er gevonden dat – onder de personen die de beroerte overleefden – degenen die al depressief waren een grotere kans hadden om opgenomen te worden in een verpleeghuis of revalidatiecentrum dan degenen die niet reeds depressief waren. Het hebben van een ander psychisch probleem dan depressie ten tijde van de ziekenhuisopname had geen invloed op zowel opnameduur als ontslagbestemming. De bevindingen suggereren dat een reeds bestaande depressie een mogelijk belangrijke factor is bij het bepalen of een patiënt wel of niet naar huis kan na een ziekenhuisopname vanwege een beroerte.

Algemene discussie (hoofdstuk 8)

Voor- en nadelen van gegevens uit de huisartsenpraktijk

De studies in dit proefschrift laten zien dat het gebruiken van door huisarts geregistreerde gegevens voor het bestuderen van het voorkomen en de gevolgen van comorbiditeit bij depressie voor- en nadelen heeft.

Voordelen van gegevens uit huisartsenpraktijken zijn onder andere:

- Gegevens hebben betrekking op een grotendeels ongeselecteerde populatie, althans in landen zoals Nederland waarin de huisarts fungeert als poortwachter van de gezondheidszorg;
- Gegevens hebben betrekking op een groot aantal personen;
- Morbiditeitgegevens zijn niet gebaseerd op zelfrapportage, maar hebben betrekking op gezondheidsproblemen die gediagnosticeerd zijn door artsen;

- Morbiditeitgegevens zijn omvangrijk in die zin dat de huisarts als generalist te maken heeft met een breed spectrum van lichamelijke en psychische gezondheidsproblemen;
- Gegevens worden op continue basis geregistreerd wat retro- en prospectief onderzoek over lange tijdsperioden mogelijk maakt;
- Er bestaan mogelijkheden om door huisarts geregistreerde gegevens te koppelen aan geregistreerde gegevens uit andere zorgsettingen;
- In diverse landen, waaronder Nederland, speelt de huisarts een belangrijke rol in de diagnose, behandeling en verwijzing van personen met een depressie.

Nadelen van gegevens uit huisartsenpraktijken zijn onder andere:

- Het baseren van onderzoek op depressie zoals gediagnosticeerd door de huisarts en de daarmee samenhangende variabiliteit;
- Het niet optimaal registreren van morbiditeitgegevens in termen van compleetheid en accuraatheid;
- Variatie tussen huisartsen en huisartsenpraktijken wat betreft de kwaliteit van registratie;
- Het globale karakter van de geregistreerde diagnoses, waardoor er geen informatie aanwezig is over het type en de ernst van een depressie en van andere gezondheidsproblemen;
- Het niet of beperkt beschikbaar zijn van gegevens over mogelijk belangrijke vertekenende factoren variabelen of effect-modificatoren zoals psychologische en sociale risicofactoren voor het ontwikkelen van depressie.

Aanbevelingen voor toekomstig onderzoek

Onderzoek naar voorkomen

Op basis van de bevindingen van Deel A van dit proefschrift wordt algemeen gesteld dat er behoefte is aan goed opgezet longitudinaal onderzoek zodat een beter inzicht verkregen wordt in het voorkomen en de onderliggende mechanismen van comorbiditeit van depressie en andere gezondheidsproblemen. Er worden drie meer specifieke doelen voor toekomstig onderzoek geformuleerd met betrekking tot comorbiditeit van

depressie en lichamelijke ziekte:

- Het verkrijgen van meer inzicht in de specificiteit van *cluster* comorbiditeit tussen depressie en lichamelijke ziekte;
- Het verkrijgen van meer inzicht in de wisselwerking tussen het hebben van een chronische lichamelijke aandoening en andere risicofactoren voor het ontstaan van een depressie;
- Het verkrijgen van meer inzicht in het beloop van depressie bij personen met een chronische lichamelijke aandoening en de determinanten hiervan.

Onderzoek naar gevolgen voor de kwaliteit van zorg en het zorggebruik
Er wordt een drietal aanbevelingen voor toekomstig onderzoek gedaan op basis van de bevindingen in deel B van dit proefschrift:

- Het verkrijgen van meer inzicht in de mechanismen die ten grondslag liggen aan de suboptimale diagnostiek en behandeling van depressie bij personen met een chronische lichamelijke aandoening;
- Het verkrijgen van meer inzicht in de onderliggende mechanismen van de relatie tussen comorbide depressie en meer zorggebruik bij lichamelijk zieke personen;
- Het verkrijgen van meer inzicht in de (kosten-)effectiviteit van interventies voor comorbide depressie bij lichamelijke aandoeningen.

Relevantie en aanbevelingen voor de huisartsgeneeskundige zorg
De bevindingen in dit proefschrift geven aan dat de diagnostiek en behandeling van comorbide depressie bij chronisch lichamelijk zieke personen niet altijd optimaal verloopt in de huisartsenpraktijk in Nederland. Dit is een zorgelijke constatering omdat deze vorm van comorbiditeit vaak voorkomt. Verder zijn er sterke aanwijzingen dat depressie het beloop van een chronisch lichamelijke aandoening ongunstig beïnvloedt en vice versa. Er worden een aantal suggesties gedaan die de diagnostiek en behandeling van comorbide depressie bij chronisch zieken in de huisartsenpraktijk kunnen verbeteren, zoals onder andere het geregeld screenen op depressie, het opstellen van een persoonlijk behandelplan, een getrapte zorg benadering voor depressie, het aanstellen van een “care manager” en het consulteren van specialisten op het gebied van diagnostiek en behandeling van (comorbide) depressie.

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Curriculum Vitae

After finishing primary and secondary school in Emmen, his place of birth, Jasper Nuijen went to study psychology at Utrecht University, specializing in neuropsychology. Following his graduation, he started working part time as a junior researcher at the Department of Neuroscience of the University Medical Center Utrecht. Meanwhile, he had already begun to study fine art at the Utrecht School of the Arts, which he finished in 2001. In 2002 he began working on his PhD thesis at NIVEL, Netherlands Institute for Health Services Research. A master's degree in epidemiology was obtained in 2007 at the VU University Amsterdam. Since September 2006, he is working as a research associate at the program on Diagnosis and Treatment of the Trimbos Institute, which is Netherlands Institute of Mental Health and Addiction.

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