Chapter 1

General introduction
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GENERAL INTRODUCTION

Over the last decades, changes in the demographic structure of populations in Europe have put considerable pressure on health care systems. Life expectancy has risen dramatically since the 1950’s, while societal changes and new possibilities of family planning have restrained the number of children being born [1] resulting in an aging population [1, 2]. Although recent studies indicate that older individuals retain a reasonably good health condition for a longer period of time [2, 3], the proportion of individuals (young and old) who suffer from chronic medical conditions, such as diabetes mellitus type 2 (DM2) and coronary heart disease (CHD) is rising [4]. This is partly due to the fact that chronic medical conditions are more prevalent in older individuals. Better medical knowledge, health care and sanitation are also keeping patients alive longer and turn once lethal illnesses into chronic medical or long-term conditions [4]. In short, more patients require more complex health care, which can result in problems regarding health care capacity and funding [1, 2, 4]. Additionally, as somatic diseases became less life threatening, the management of mental symptoms and disorders such as depression and anxiety have become more important, in their turn causing a large burden of disease and increasing demands on health care systems dramatically [5, 6].

Depression

Within these overarching societal health care developments, depression - which is increasingly conceptualized as a long-term condition itself - is a major health problem. It is currently ranked second in a list of conditions with the highest burden of disease worldwide [5]. According to the Diagnostic and Statistical Manual of mental disorders – fifth edition (DSM-5) a major depressive episode is present when a person and a qualified health care professional agree that someone has problems in daily functioning and suffers from at least one of the core symptoms: depressed mood and loss of interest or pleasure. Additionally, other symptoms can be present, such as significant weight loss or weight gain without dieting; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate or indecisiveness; recurrent thoughts of death or suicidal ideation. One must have a total of five or more depression symptoms to be diagnosed with a major depressive disorder. Additionally, the symptoms must have been present for at least two weeks, nearly every day during most of the day and be disruptive of daily functioning. When someone experiences depressive symptoms such as a lack of interest without fulfilling the diagnostic criteria for major depressive disorder, this can be defined as subthreshold depression [7].
Depression in the aging population: a chronic and disruptive health problem

Amongst adults aged 55 years and older, depression is common. Its prevalence is estimated to be 11 - 25% [8] and it is estimated that depression is chronic in 30% - 80% of patients [9-12]. This is considerably higher than in depressed individuals from the general population, in whom chronicity rates are estimated to be 5 -25% [13, 14]. Depressed older adults have lower health related quality of life [15], higher prevalence of chronic physical illnesses [16, 17], increased health care use and health care costs [18] and higher mortality rates as compared to non-depressed older adults [19]. Given its high prevalence, chronicity and negative consequences, depression is a disruptive health problem in this population.

Evidence suggests that the course of depressive symptoms over time among older adults varies greatly. Some patients recover within a relatively short period of time, while others have more severe depressive symptoms leading to adverse health outcomes and more health care utilization [8, 20]. It is unclear which different depression trajectories can be distinguished in older patients who already experience depressive symptoms [21, 22]. Also, it is not yet clear which patient characteristics can predict depression trajectories in this population and how depression trajectories are related to quality of life and health care costs. This information can be used to identify depressed older patients at risk of a chronic course of depression and adverse health outcomes in clinical practice. This way, depression care can be more targeted at patients who can benefit most, thereby using the resources available as efficiently as possible.

Depression, diabetes type 2 and coronary heart disease

DM2 and/or CHD often co-occur with depression. It is estimated that on a yearly basis about one-fifth to one-third of all patients suffer from major depression [23-25], while in the general population these estimates range from 5- 9% [23, 26]. DM2 is a chronic health condition which is characterized by high blood glucose levels that are the result of the incapability of the body to metabolize glucose. Coronary heart disease is typically also considered a long-term health condition, comprising multiple different illnesses, in which the coronary arteries are narrowed or (temporarily) blocked. Patients who have DM2 are more at risk to develop CHD and vice versa [27]. People who smoke, have low activity levels and have overweight are associated with high comorbidity rates of both DM2 and CHD [27, 28]. Also, the prevalence of both DM2 and CHD is increased in older adults, which may explain why older patients are more vulnerable to become depressed and more at risk for adverse depression outcomes compared to younger adults.

In our Western society and increasingly worldwide, the burden of DM2 and CHD is high [29, 30]. The combination of having depression and DM2 and/or CHD adds substantially to the burden of disease patients are already experiencing. It is
associated with poor medication adherence [31, 32], deteriorating health related quality of life, adverse health outcomes [33-35] and increased health care use and health care costs [36-39]. The combined burden of disease is even greater than the sum of the burden associated with any of the separate conditions [35, 38, 40, 41]. Thus, having major depression adds substantially to the burden of disease patients with DM2 and/or CHD are already experiencing.

Diagnosing and evaluating depression in patients with DM2 and/or CHD

Acknowledging, discussing, diagnosing and evaluating mood and depression in patients with DM2 and or CHD presents a big challenge in care. Patients with DM2 and/or CHD may have different perspectives on their symptoms and their mental and physical health and could be less likely to talk about their depressive symptoms [42, 43]. Instead, depressive symptoms such as fatigue and problems concentrating may be interpreted differently and can overlap with symptoms of the physical illness [44]. This may result in challenges when diagnosing depression in patients with DM2 and/or CHD [44]. Nonetheless, to be able to treat depression in this patient group, it is important to supply professionals and patients with tools to diagnose depression accurately and precisely evaluate the course of depressive symptoms over time [42, 44, 45]. A systematic review of diagnostic accuracy of screening tools used to identify depression in patients with chronic medical illnesses shows that screening tools can be both sensitive and specific [42]. Especially two-item screening tools assessing the two core symptoms of depression [46], the 9- item Patient Health Questionnaire (PHQ-9) [47], the Zung’s Self-Rating Depression Scale [48] and the 28-item General Health Questionnaire (GHQ-28) [49] perform well in this population when employed to detect patients at risk of depression [42]. Regarding the PHQ-9, these findings are in agreement with a previous systematic review [50]. However, these instruments cannot be used as single diagnostic instrument. A clinical interview and dialogue with an adequately trained health care professional is always needed [42]. Also, there is discussion about the practical use of screening tools to detect depression in medically ill patients [45] and a review comparing screening tools used for primary care patients with DM2 and/or CHD is missing. Furthermore, there is considerable heterogeneity between studies in the advised cut-off scores of the same questionnaires. Consequently, it is uncertain which case finding strategy works best in these patients with DM2 and/or CHD.

For evaluative purposes - thus comparing scores of the same patient on different time points to monitor the course of depression over time - comprehensive information about the most suitable instrument in DM2 and CHD patients is still lacking [44]. This makes it difficult to evaluate the benefit of depression care and to assess the severity
of depressive symptoms in this patient group.

**Preventing major depression in patients with subthreshold depression**

Unfortunately, even when depression is properly diagnosed, treatment does not always have the intended effect. Even when treatment is provided according to current standards, this would only avert about 30% of the total disease burden of depression [51, 52] and only about 50% of all patients would reach remission [51]. Therefore, an alternative pathway could be to try to prevent major depression, especially in high risk groups such as patients with DM2 and/or CHD.

A potentially efficient strategy is to focus on those who have ‘subthreshold’ depression (i.e. having clinically relevant depressive symptoms without fulfilling all criteria for major depression). Subthreshold depression is a strong predictor for the development of a subsequent episode of major depression [53, 54]. It is also common in older adults and in patients with DM2 and/or CHD (12-month prevalence: 10% - 18%) [55, 56]. Consequently, aiming to prevent major depression in DM2 and/or CHD patients with subthreshold depression seems a promising strategy to reduce the burden of depression.

Several care programs aiming to prevent major depression in patients with subthreshold depression have been developed. Evaluations of these care programs suggest that preventing major depression is possible, with a relative risk reduction of 21%, although the reported number needed to treat of 20 seems to be fairly high [57].

One of the most successful preventive depression care programs was published by Van ‘t Veer-Tazelaar et al. in 2009 [58]. They described a flexible, nurse-led stepped care program aimed at treating subthreshold depression in older patients in primary care[58]. The stepped care program comprised four treatment steps based on evidence-based interventions for depression. The treatment steps were of increasing intensity and tailored to the patient’s preferences to maximize effectiveness while making best use of available resources. The program was adapted from IMPACT, in which nurses, general practitioners and psychiatrists collaborate to provide mental health care in the primary care setting [59, 60]. This flexible, nurse-led stepped care program proved to be effective and cost-effective as compared to usual care in the US, with a relative risk reduction of depression of 51% [58, 61]. Stepped care, thus, seems a possible solution to prevent depression in primary care patients with long term health conditions and subthreshold depression. However, not all studied stepped care programs resulted in conclusive positive evidence for their effectiveness, leaving considerable uncertainty surrounding their success factors and usefulness in daily practice [62-66].
Preventing major depression in patients with a chronic medical illness

In recent years, there has been more attention for preventing depression in high risk groups, such as patients with a chronic medical illness like DM2 and CHD. The care programs that are implemented in these patient groups resemble the programs that are used in the general population. For example, van der Aa et al. evaluated a stepped care program to treat subthreshold depression in patients with visual impairment [67]. Stoop et al. did the same for a small sample of patients with diabetes, COPD or asthma [68]. Overall preventing major depression by treating subthreshold depression using stepped care seems to be a promising strategy in several high risk populations and may also work well in patients with DM2 and/or CHD [69, 70]. However, conclusive evidence is lacking for this specific population.

Moreover, considering the scarce resources available for health care, decision makers need to have insight into the relation between the costs and effects of new health care interventions as compared to usual care, before they can decide about their widespread implementation. It is to be expected that stepped care programs for depression are more expensive than usual care which mainly consists of prescription of antidepressants (the mean costs of 3 months of amitriptyline – the most frequently used antidepressant in 2016 by registered users in the Netherlands [71] – are €1.83) [72]. However, if stepped care is more effective than usual care, the costs of utilization of additional health care resources may be reduced both in the short and long term. Additionally, morbidity and mortality may also be reduced leading to long-term cost savings. Previous research suggests preventive depression care can indeed be cost-effective in older primary care patients [73], and chronically ill primary care patients [74]. However, conclusive evidence is still lacking for the specific group of DM2 and CHD patients. Also, it is still unclear in which format preventive depression care is most cost-effective in this population.

Barriers for and facilitators to preventive depression care in patients with a chronic medical illness

To successfully deliver preventive depression care to patients with DM2 and/or CHD, there are some barriers that have to be dealt with first. For example, patients receive care for multiple conditions and are interacting with multiple caregivers from multiple care organisations which are organized differently, resulting in potentially complex health care for these patients [75]. However, at present in the Netherlands care for chronically ill patients is predominantly provided in primary care. All in all, the potential complexity of care makes it difficult to synchronize the preventive depression care with other health care services a patient is already
receiving [76, 77]. When designing a care program to prevent major depression in patients with DM2 and/ or CHD and subthreshold depression, it is very important to take this into account. In 2011, the Trimbos institute issued a report in which barriers and facilitators for better integrated health care for patients with long term health conditions are identified for the Dutch health care situation [76].

Barriers and facilitators were identified on four different organisational levels:

a) **Organisation of the health care system.** Traditionally, health care is often offered based on standard procedures for separate health conditions. This might not work for patients with multiple conditions who may be better served by individually tailored treatment that is not by default disease-specific. Also, in the Netherlands, there is a separate reimbursement system for mental health care and somatic health care, making it difficult to integrate a program for depression care into the daily care patients are already receiving. Also, possible facilitators are described to help overcome barriers at this level in the future: to base indication for care options on burden of disease instead of specific diagnosis, and to incorporate mental health care in the existing financial structures;

b) **Organisation of health care facilities.** Mental health care is often provided in different health care facilities than somatic health care, making it difficult to work together and integrate care. However, there are possibilities to integrate different facilities, for example by combining mental health care and somatic health care in the same locations. When the management of big care facilities embrace this change, this could serve as possible facilitator to overcome this barrier;

c) **Knowledge, resources and attitude of health care providers.** Health care providers in somatic settings may not be resourced or equipped to appropriately recognize and act upon mental health issues in their patients. Adequate tools to share information are sometimes lacking, as well as the expertise to recognize the need for mental health care and the knowledge of treatment possibilities. Also, due to pressure on the health care system, care givers often do not have time to discuss the mental health of their patients. Promising facilitators to overcome barriers at this level are: employing a nurse or other caregiver who is specialized in mental health care in a somatic (primary) health care center, and specific education for care givers in somatic settings;

d) **Barriers in the knowledge, attitude and perceived need for specific mental health care of patients.** Patients with chronic medical illnesses report feeling stigmatized when referred to mental health care. Additionally, these patients
may not talk so much about their mental health issues, because they assume the caregiver may not be able to help or do something about it. Furthermore, patients often do not recognize their symptoms as a mental health issue and perceive them as being part of the chronic medical illness. Finally, some patients perceive financial barriers to seeking help for mental health issues. Possible facilitators to overcome barriers at this level are: using different terminology to talk about mental health problems; providing mental health care within the somatic setting and incorporating this care into the existing financial reimbursement system.

The Step-Dep program
To overcome the challenges in preventive depression care for patients with DM2 and/or CHD, we designed a tailored stepped care program: Step-Dep. Step-Dep is modeled after the intervention of Van ‘t Veer-Tazelaar [58] and in its development the facilitators and barriers described above were taken into account. Where necessary, Step-Dep was adjusted to optimize the chances of successfully implementing preventive depression care for patients with DM2 and/or CHD. Step-Dep is designed to be implemented in primary care, with an important role for trained practice nurses, who treat and monitor patients in collaboration with the general practitioner. It consists of four sequential evidence-based treatment steps of ascending intensity, lasting 3 months each. Based on the level of depressive symptoms, as measured using the PHQ-9, patients who still experience relevant depressive symptoms after concluding a treatment step are offered the next step in the program. When depressive symptoms are in remission, a period of watchful waiting starts until an elevated PHQ-9 score indicates the need for the next step of the intervention. Patients who meet the criteria for a major depressive disorder at any time in the Step-Dep program are referred to their general practitioner by the practice nurse for further assessment. By using this stepped care model, more intensive treatment is only offered to patients who continue to have elevated depressive symptom scores. Therefore, it is expected that treatment will be tailored to the patients need, while efficiently using resources. The four treatment steps are described below:

**Step 1: Watchful waiting.** The first step consists of watchful waiting without any therapeutic intervention, because subthreshold depression often reaches remission within the first three months after detection [78].

**Step 2: Guided self-help treatment.** In the second step, patients are offered a guided self-help course that is specially designed for patients with a chronic physical illness and subthreshold depression [79]. The course is supported by the practice nurse.
**Step 3: Problem-solving treatment.** In this third step, patients receive Problem Solving Treatment (PST), which is delivered by the practice nurse. PST focuses on practical skill building and is derived from cognitive behavioral therapy [80, 81].

**Step 4: Referral to the general practitioner.** Patients who still experience subthreshold depression after completing the first three treatment steps are referred to their general practitioner for further assessment of their depressive symptoms.

We wanted to integrate the Step-Dep program into the existing primary care structure as much as possible. Advantages of this pragmatic approach are:

a) Incorporation of the program into existing financial reimbursement structures, lowering barriers to offer the program and to participate in it;

b) The possibility to more easily integrate Step-Dep with the care for long-term health conditions that is already provided by the general practitioner and nursing team;

c) The reduction of perceived barriers for the patient. The patient does not have to go to a specialist mental health care provider, avoiding perceived stigma. Patients who are already treated by their general practitioner for their DM2 and/or CHD can receive care close to their home in a well-known and trusted setting. Finally, all patients in the Netherlands are insured against primary health care costs and will therefore not receive a bill for participating in the Step-Dep program.

In the Step-Dep program, a primary care nurse, who is already working at the general practice, has a coordinating role. This offers several advantages that could facilitate the implementation of Step-Dep:

a) The practice nurse can act as a care manager who communicates with the general practitioner who treats patients for their DM2 and/or CHD and is also available for consultation about treatment within the Step-Dep program. This way structural collaboration between the different caregivers is more easily reached and more time is available to discuss depressive complaints.

b) The primary care nurse is a familiar face in the general practice and can facilitate potentially lower perceived barriers for the patient to be treated in the Step-Dep program.

The use of a stepped care format will make sure treatment is minimally intrusive for the DM2 and/or CHD patient and tailored to the specific needs of patients. Three important advantages of this strategy could facilitate implementation of Step-Dep:

a) The program is offered based on disease burden, rather than on diagnosis, making it more suitable for patients with multiple health conditions;

b) By saving high intensity treatment options for those patients who actually need this care, available resources of health care providers can be allocated.
efficiently, which maximizes the feasibility of Step-Dep in primary care.

c) Starting with low intensity treatment can result in lower perceived barriers for patients to accept treatment.

Furthermore, within Step-Dep, all procedures and materials were intended to make minimal use of words and framing concepts or illness perceptions that are related to major depressive disorder and to mental health care. This possibly reduces perceived stigma in patients with DM2 and/or CHD and will be more in line with an interpretation of depressive symptoms that is common in this patient group.

Aims of this thesis

This thesis is aimed to answer the following three central questions:

1) Which different trajectories can depression take within an older population with a high rate of medical illnesses?

2) How can depression and depressive symptoms be measured in patients with DM2 and/or CHD?

3) Is the Step-Dep program (cost-)effective as compared to usual care in preventing the onset of depression in patients with DM2 and/or CHD?

Outline of this thesis

Part 1: Characteristics of depression trajectories in an older primary care population

In Chapter 2 multiple distinct trajectories of depression in an elderly population are described. Furthermore, potential predictors of adverse depression trajectories are identified and the trajectories are associated with health care costs and quality of life.

Part 2: Measurement of depression in patients with DM2 and/or CHD

Chapter 3 presents a systematic review of the literature on the measurement properties of depression questionnaires to evaluate depressive symptoms in patients with diabetes.
Chapter 4 describes original data on the diagnostic accuracy of the PHQ-9 to establish subthreshold depression and major depressive disorder in primary care patients with DM2 and/or CHD.

**Part 3: effectiveness and cost-effectiveness of the Step-Dep study**

In Chapter 5 the design of a cluster-randomized controlled trial to assess cost-effectiveness of the Step-Dep program is presented. This chapter also includes a detailed description of the Step-Dep program itself.

Chapter 6 and Chapter 7 describe the results of the cluster-randomized controlled trial evaluating the effectiveness (Chapter 6) and cost-effectiveness (Chapter 7) of the Step-Dep program.

**Reflections on the presented work**

In Chapter 8, a general discussion of this thesis is provided that will elaborate on the answers to the three central questions of this thesis. Furthermore, implications for practice and future research will be discussed.
REFERENCES


