CHAPTER 1

GENERAL INTRODUCTION
In the light of our aging society, late-life depression represents one of the major therapeutic challenges. Despite the fact that psychotherapy, pharmacological interventions, as well as ECT are effective treatment options, late-life depression often has a recurrent or chronic course. An important challenge in the management of this disorder is to determine which patients could benefit from lifestyle advice (only), which patients could derive sufficient benefit from monodisciplinary psychiatric treatments such as pharmacotherapy or psychotherapy, and lastly, which patients require specialized mental health care with a multidisciplinary approach, consisting of the combination of multiple treatment strategies with psychosocial support to ensure full remission and functional recovery. Specialized mental health nurses play an important role in the management in all echelons of health care systems by providing lifestyle interventions, different types of psychosocial support, and even case management for complex cases.

The unique function of nurses in caring for individuals, is ‘to assess patients responses to their health status and to assist them in the performance of those activities contributing to health or recovery that they would perform unaided if they had the necessary strength, will, or knowledge and to do this in such a way as to help them gain full of partial independence as rapidly as possible’. In line with this definition, mental health nurses generally focus on aspects of functional recovery rather than symptomatic remission, as their interventions are usually directed at the practical level of daily care, i.e. functioning according to the International Classification of Functioning Disability and Health (ICF).

Life-style factors, which include physical activity, are possible modifiable factors for improving general health and functioning. They could also play an important role in medical conditions and in reducing depressive symptoms in late life. Increasing physical activity is therefore one of the first steps in the guidelines for maintaining health and function, and in guidelines for treating depression.

Despite the well-known health benefits of an active lifestyle, most professionals in mental health care recognize that the most important preconditions for successful implementation of life-style interventions - participating and maintaining an active lifestyle - are difficult to achieve. This is especially the case for patients with late-life depression. Firstly, because lack of motivation is one of the key features of depressive disorder, and secondly because aging itself is characterized by a decline in function. Lifestyle interventions may nevertheless be particularly relevant for late-life depression, since it is increasingly recognized that increasing severity of depressive symptoms is a predictor of functional decline and vice-versa, that physical disability improves with successful treatment of late-life depression. Unfortunately, studies on the efficacy of physical exercise are limited to depressive disorder in younger adults or to samples with elevated depressive symptoms in the absence of a psychiatric disorder.

Knowledge of the determining factors of low physical activity in depressed older patients
is relevant in order to achieve an improved lifestyle, especially with an increased level of physical activity. Moreover, to improve functional outcomes, we must also understand the interaction between physical activity, daily functioning and late-life depression over time. Functional outcome is especially relevant from the perspective of the patient because symptomatic remission is only a surrogate outcome when patients remain functionally impaired. Moreover, the ultimate goal of nursing is to improve daily functioning of patients, so an understanding of the interrelationship between physical activity, functional recovery and depressive disorder, is important for the development of more targeted nurse-led interventions. This thesis therefore explores these relationships.

The concepts of late-life depression, physical activity and functional limitations

The challenge of late-life depression

Depression is common in later life. The World Health Organization estimates that among those over 60 years old, the prevalence of unipolar depressive disorder is approximately 7% in the general population and accounts for 5.7% of Years Lived with Disability (YLDs). Furthermore, in absolute terms, these figures will only increase in the near future due to the aging of society, while in relative terms, epidemiological evidence points to an increase of the prevalence of depressive disorder in the most recent generations of older adults.

The core symptom of depressive disorders is the presence of a sad, empty or irritable mood. Depending on the number, severity and duration of symptoms, depressive episodes can be categorized as major, minor or dysthymic/chronic episodes. The Diagnostic and Statistical Manual for mental disorders (DSM) has specified the criteria to classify symptoms as a diagnosis of major depression. The individual must be experiencing five or more symptoms during the same 2-week period and at least one of these symptoms should be either (1) depressed mood or (2) loss of interest or pleasure. To receive a diagnosis of a depressive disorder, these symptoms must cause significant distress or impairment in social, occupational, or other important areas of functioning.

Minor depressive disorder is the presence of two or more concurrent symptoms of depressive disorder, one of which is depressed mood, present most or all of the time for at least 2 weeks. The symptoms must also cause dysfunction and negatively impact the individual’s life and may never have met the criteria for major depression or dysthymia. Dysthymia is a state of chronic depressed mood, when the symptoms do not present the severity of a major depressive episode but persist for a long period (at least 2 years). The DSM-5 was published in 2013 and describes the diagnostic distinctions of MDD like the DSM-IV-TR. However, in this latest version, dysthymia and chronic MDD have been renamed together as persistent Depressive Disorder.
In this thesis, late-life depression refers to both older adults whose depressive disorders presented themselves either earlier in life as well as to older adults in whom depressive disorders present themselves for the first time in later life. In general, a cut-off of 60 years has been chosen to distinguish between early-onset and late-onset depression in later life.\textsuperscript{19,20}

The diagnostic criteria for major depression are identical for both older and younger patients. However, late-life depression as compared to depression in younger persons is associated with cognitive impairment, chronic medical illnesses, a higher level of medication use, and neurodegenerative diseases,\textsuperscript{21} all characteristics that could have an impact on the phenomenology as well as the prognosis of the depressive disorder. Several studies have found a prolonged course and negative treatment effects in the presence of co-morbid executive dysfunction and co-morbid vascular disease in late-life depression.\textsuperscript{22,23} This increasing heterogeneity in the etiology and symptomatic presentation with age, only increases the challenge of specifying which patients require a multidisciplinary approach with additional treatment strategies (other than pure psychiatric treatment), to ensure full remission and functional recovery.

**Physical activity**

Physical activity is defined as “any bodily movement produced by skeletal muscles that requires energy expenditure”. Exercise is a subcategory of physical activity that is planned, structured, and repetitive, the objective of which is to improve or maintain one or more components of physical fitness. Physical activity includes exercise as well as other activities that involve bodily movement and are carried out as part of playing, working, active transportation, housework and recreational activities.

The opposite, physical inactivity is one of the five major risk factors for global mortality (6% of deaths globally), after smoking, obesity, high blood pressure and diabetes.\textsuperscript{24} The
level of physical activity can therefore be regarded as a key factor with respect to modifiable behavior for improving physical health conditions and functioning, as well as for reducing depressive symptoms in later life.5,25

The amount of physical activity can be expressed as a metabolic equivalent, or MET. The MET is a useful unit for describing the energy expenditure of a specific activity. An MET is the ratio of the rate of energy expenditure during an activity compared with the rate of energy expenditure at rest. For example, 120 MET-minutes (or 2.0 MET-hours) can be achieved by doing 4 MET activities for 30 minutes during a week as well as 8 MET activities for 15 minutes a week.

The health benefits of physical activity depend mainly on the total weekly energy expenditure due to physical activity. In scientific terms, the amount of physical activity should range between 500 and 1,000 MET-minutes per week. However, the exact number of MET-minutes a person needs to remain healthy depends on personal characteristics such as age, but also gender, obesity status, functional impairment and disease status.26 The World Health Organization has therefore given global recommendations on physical activity for Health for people of 65 years and above (see Box 2).

Sedentary behavior is not the complete lack of physical activity, but rather a low energy expenditure (1.0–1.5 METS), characterized by prolonged sitting and the absence of whole-body movement.27 Sedentary behavior is inversely associated with premature mortality, type 2 diabetes, cardiovascular disease, and cardiometabolic biomarkers and an increased risk of depressive symptoms.28,29 Little is known about the determinants of sedentary behavior.30

Several direct and indirect methods are available to measure physical activity, sedentary behavior, and their related energy expenditures. Indirect measures such as physical activity questionnaires are sufficient to assess the general level of free-living physical activity. These methods are the least expensive and least burdensome,31 and are therefore often used in large-scale studies such as the Netherlands Study of Depression in Older persons (described in this thesis).
Functional limitations

The WHO International Classification of Functioning (ICF) comprises six domains: disorders or diseases; body functioning, related to different organ structures; activities in daily life; participation; environmental factors; and personal factors. The DSM-5 guidelines recommend that psychiatrists systematically assess global functioning and impairment, preferably using the WHO Disability Assessment Schedule 2.0 (WHODAS2.0) based on the activity and participation parts of the ICF model. In the DSM-5 classification system, the WHODAS 2.0 has replaced the less valid and reliable Global Assessment of Functioning (GAF) scale used in earlier versions of the DSM. While the WHODAS 2.0 is being used increasingly used in psychiatric studies, the collection of data on older adults is still in the early stages.

The relationship between physical activity, functional limitations and (late-life) depression

At the population level, physical activity and psychopathology are related, although there is a lack of consistent epidemiological evidence linking lifestyle as either a risk factor or consequence of mental disorders. Nonetheless, in specialized mental health care, lifestyle medicine is in its early stages. Lifestyle medicine seems particularly relevant in the treatment of late-life depression, in light of its association with chronic somatic diseases and prolonged fluctuating courses, generally requiring a multidisciplinary approach to ensure increased remission rates and optimal functional recovery. Because of the overlap of risk factors for somatic disease and depression in older people, lifestyle interventions could generate benefits for both depression and somatic conditions and thus improve overall functioning. But what is already known about physical activity and functional limitations in regard to late-life depression?

Physical activity and late-life depression

As pointed out above, the relationship between physical activity and depression has been studied before. Randomized control trials in the adult population have shown a modest effect of exercise on depression outcomes. However, the evidence is weak because most studies are conducted on the general population, recruiting persons with self-reported, elevated depressive symptom scores rather than depressive disorders, and only report short term effects. Generalization to depressed older patients is further limited because older persons are barely included in these studies.

Nonetheless, cohort studies have provided strong evidence for the association between (in)activity and (risk for) depressive disorder in older people. In addition, older people
with emerging depression are more likely to concurrently adopt a sedentary lifestyle.\textsuperscript{40} Until now, the effectiveness of increasing physical activity or specific exercises for the treatment late-life depression has been weak and addresses only the short term.\textsuperscript{41,42} While exercise therapy is also advocated for frail-depressed older patients with multiple medical comorbidities, the evidence remains limited.\textsuperscript{1}

Taken together, for the development of targeted lifestyle interventions, the longitudinal relation between physical activity and late-life depression is less clear than the guidelines suggest and more importantly, distinguishing features in a clinically depressed older population remain unexplored. This knowledge is also of interest for somatic health care, because studies on the impact of physical activity on health often neglect depression,\textsuperscript{43} or even exclude depressed individuals from participating.\textsuperscript{44-46} This is particularly relevant, as in the case of the Cardiovascular Health Study, because it has been shown that physical inactivity accounts for a significant proportion of the risk of cardiovascular mortality due to depression.\textsuperscript{47}

**Functional limitations and late-life depression**

Both depression and increasing age are associated with functional decline.\textsuperscript{48-52} Studies in old-age are increasingly recognizing functional decline as an important outcome measured in studies on depression.\textsuperscript{53,54} Empirical evidence has already shown that increasing severity of depressive symptoms is a predictor of functional decline,\textsuperscript{11-13} and that physical disability improves with treatment for depression.\textsuperscript{14} However, studies to date have been limited to younger adults or to depressive symptoms counts in population-based studies in older people.\textsuperscript{55}

More knowledge regarding the longitudinal relation of functioning in late-life depression and more insight into the determinants of functional recovery over time may provide new insights into what is needed in the treatment and care for older persons with depression.

In summary, we have concluded that increased knowledge of the interrelations between physical activity and functional limitations in late-life depression could be important for the future development of (nurse-led) interventions targeted at functional recovery in these patient groups. Since the knowledge gained thus far is fragmented and limited, this thesis examines the relation between physical activity, functional limitations and late-life depression, from a biopsychosocial approach.\textsuperscript{56} Demographic characteristics, psychopathology, comorbid chronic diseases, cognitive and somatic functioning, psychosocial characteristics, environmental and lifestyle factors will be taken into account when examining these interrelations, as shown in figure 1.
Figure 1: The main associations studied in this thesis

This thesis

This thesis aims to explore the natural longitudinal relation between level of physical activity, as well the relation between (the course of) functional limitations in late-life depression, both with an emphasis on contributing factors from a biopsychosocial approach.

Aims and outlines of this thesis

The main aim of this thesis is to explore the relation between physical activity and functional limitations in late-life depression. To do this, the thesis incorporates data from a large-scale patient cohort sample: the Netherland Study of Depression in Older Persons (NESDO), in chapter 4, supplemented by data from the Netherlands Study of Depression and Anxiety (NESDA). A more comprehensive description of these two large cohort studies is provided in section 1.3.2 below.

The thesis is divided into two parts. Part one focuses on physical activity and its specific features in relation to late-life depression. Chapter 2 examines the cross-sectional relation between physical activity and depression in older people and the distinctive features of the most inactive older subjects. Chapter 3 provides a longitudinal analysis, testing the hypothesis that depressed subjects who are least physically active at baseline will show the worst depression outcomes at the two-year follow-up. Chapter 4 describes the role of age in the relation of depression and physical activity by comparing younger and older adults.
The second part of this thesis focuses on the relation between daily functioning and late-life depression. Chapter 5 describes the impact of late-life depression on functional limitations over time, in a longitudinal follow-up study, while Chapter 6 analyzes the course and determinants of functional limitations in late-life depression, also in a 2-year follow-up of older subjects who were depressed at baseline. Chapter 7 presents a review on the evidence on the impact of interventions in late-life depression on functional limitations.

The general discussion (Chapter 8), summarizes and discusses the results of these studies, placing them within the context of other research on the subject of physical activity and daily functioning in late-life depression.

Cohort studies used in this thesis

Data from two longitudinal cohort studies was used in this thesis. Chapters 2-6 are based on data from the NEtherlands Study of Depression in Older Persons (NESDO; age range 60-93 years),57 and for chapter 4, in combination with data from the NEtherlands Study Depression and Anxiety (NESDA; age range 18-65 years).58 Since largely similar measures were used for these multi-site naturalistic prospective cohort studies, data can be pooled thus creating a large longitudinal database of clinically depressed persons and a large set of biopsychosocial variables from both younger and older depressed persons.

The NESDO studied depressive disorders in older persons over a period of six years. From 2007 until 2010, the NESDO consortium recruited 510 depressed and non-depressed older persons (≥ 60 years) in 5 locations throughout the Netherlands. Depressed persons were recruited from both mental health care institutes and general practices in order to include persons with late-life depression in various stages of developmental and severity. Non-depressed persons were recruited from general practices. The baseline assessment included written questionnaires, interviews, a medical examination, cognitive tests and collection of blood and saliva samples. Information was gathered about mental health outcomes and demographic, psychosocial, biological, cognitive and genetic determinants. The baseline NESDO sample consisted of 378 depressed (according to DSM-IV criteria) and 132 non-depressed persons 60 to 93 years of age. Follow-up assessments were done with 6 monthly written questionnaires and face-to-face interviews after 2 and 6 years. Approval of the study protocol was granted by the Ethical Review Boards of all of the participating centers, and all participants gave informed consent in writing.

The NESDA is a longitudinal cohort study, consisting of 2,981 persons (aged 18–65 years), including those with anxiety and/or depressive disorders (78%) as well as healthy controls (22%). The aim of the study was to describe the long-term course and consequences of depression and anxiety disorders. Participants were recruited from the community (19%), in primary care (54%), and in specialized mental health settings (27%).
The exclusion criteria used were (1) a primary clinical diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder, or severe addiction disorder and (2) not being fluent in Dutch. Approval of the study protocol was granted by the Ethical Review Boards of all of the participating centers, and all participants gave informed consent in writing.
PART I:
The impact of physical activity in late-life depression