Chapter I

General introduction

Due to the baby boom after World War II and an (still) increasing life expectancy, around 25% of the Dutch population is 65 years of older, of which more than 30% is older than 80 years in 2050 (www.cbs.nl). One of the most challenging aspects of an ageing population is to preserve or improve a good physical and mental health of older adults (WHO, 2015). From a medical perspective, interventions should be focused on those people with the highest risk of adverse health outcomes (Fried et al., 2001; Collard et al., 2012; WHO, 2015). To this end, frailty has been introduced as a core concept in geriatric medicine as frail older persons have the highest risks of adverse health outcomes and are high users of community resources, hospitalization, and nursing homes (Morley et al., 2013). While the relevance of frailty is increasingly recognized in geriatric as well as general medicine, this concept is largely ignored in geriatric psychiatry. This is remarkable, as several psychiatric disorders, in particular depression, negatively interfere with life-expectancy (Cuijpers et al., 2014; Brandao et al., 2019). This thesis focusses on the validity and clinical relevance of frailty in late-life depression.

Depression - a disorder of accelerated aging

Globally, depression contributes significantly to the burden of disease (Lépine & Briley, 2011) and is identified as an independent predictor for the onset of many chronic somatic diseases (Penninx et al., 2013). Current predictions indicate that by 2020, depression will be the second leading cause of disease burden, and by 2030 it probably will be the leading cause worldwide (www.who.int). In later life, depression has higher recurrence rates, a more chronic course, and a higher level of co-morbidity with cognitive impairment and somatic diseases (Comijs et al., 2011; Schaakxs et al., 2018). The prevalence of depressive disorder according to the diagnostic criteria of the DSM or ICD classification systems is estimated at 1.8% among community-dwelling people aged 55 years and older (Beekman et al, 1999) and 7.2% among older adults aged 75 years and over (independent of the living

arrangement) (Luppa et al, 2012). Furthermore, in older populations, subthreshold depression is more prevalent than a major depressive disorder (Hasin et al., 2005; Fiske et al., 2009), with prevalence rates estimated between 13.5% and 17.5% (Beekman et al., 1999; Luppa et al., 2012). As these latter estimates are often based on self-report symptom scales, confounding by underlying and/or subthreshold somatic diseases cannot be excluded (Thombs et al., 2010). Thus far, studies on the impact of depression on the onset of somatic diseases have not included physical frailty as a confounding and/or mediating variable (Collard et al., 2015).

The hypothesis that depression itself is a clinical condition of accelerated aging (Verhoeven et al., 2014) has originated from findings that depression is prospectively associated with the onset of chronic somatic diseases and an increased mortality rate independent of lifestyle characteristics (Cuijpers et al., 2013; Penninx et al., 2013). This hypothesis is further fed by associations between ageing-related biomarkers and depressive disorder (e.g. Howren et al., 2009; Dowlati et al., 2010; Wolkowitz et al., 2011; Pan et al., 2012; Verhoeven et al., 2014; Morrison et al., 2019). Most studies on the association between ageing biomarkers and depression did not take frailty into account. This might be relevant, as frailty and depression share partly overlapping diagnostic criteria as well as assumed underlying pathophysiological mechanisms (Mezuk et al., 2012), see below for more detailed discussion. Therefore, in this thesis, we examined the association between frailty and ageing-related biomarkers of ageing among depressed older patients. We examined specifically low graded inflammation (chapter 2), shortened telomere length (chapter 3), and lowered vitamin D levels (chapter 4).

Low graded inflammation - This process of accelerated aging is thought to occur as a result of dysregulations in immune responses that may contribute to changes of the affective and cognitive neural systems associated with the development of late-

life depression (Alexopoulos & Morimoto, 2011). The aging process creates a condition of chronic low-grade inflammation, also called "inflamm-ageing" (Grolleau-Julius et al., 2010) that leads to the production of several pro-inflammatory cytokines (Alexopoulos & Morimoto, 2011). Many studies focused on the association of cytokines and depression, and found that C-reactive protein as well as pro-inflammatory cytokine levels were increased in older adults with depressive symptoms (Dentino et al., 1999; Penninx et al., 2003; Tiemeier et al., 2003; Bremmer et al., 2008; Milaneschi et al., 2009; Zalli et al., 2016), albeit negative studies have also been reported (Stewart et al., 2009; Matsushima et al., 2015).

Shortened telomere length - Telomere length is widely considered as a marker of cellular aging, as shortened telomeres in white blood cells are associated with increased mortality rates (Cawthon et al., 2003; Honig et al., 2006) and the onset of various age-related diseases (Collado et al., 2007; Willeit et al., 2010). Associations between shortened leucocyte telomere length and depression in young- and middle-aged patients have been found (e.g. Epel et al., 2004; Damjanovic et al., 2007; Kananen et al., 2010; Tyrka et al., 2010; Garcia-Rizo et al., 2013; Verhoeven et al., 2014; Lin et al., 2016). However, these findings could not be replicated in the Netherlands Study of Depression in Older persons (NESDO) (see appendix) (Schaakxs et al., 2015). This has amongst others been explained by the fact that late-life depression has a more heterogeneous nature as compared to depression earlier in life, which may mask (small) effects pertaining to specific subgroups. Whether this subgroup is characterised by the presence of physical frailty has not been examined yet.

Vitamin D deficiency - Vitamin D is involved in various cellular ageing processes, including proliferation, cellular differentiation, and apoptosis (Pusceddu et al., 2015; Berridge, 2017). In human studies, an inverse association between vitamin D and

ageing-related diseases and mortality has been reported (Pusceddu et al., 2015). A growing body of evidence relates lower vitamin D levels to physical frailty (Shardell et al., 2009; Chang et al., 2010; Wilhelm-Leen et al., 2010; Ensrud et al, 2011; Smit et al., 2012; Hirani et al., 2013; Pabst et al., 2015; Ju et al., 2018). Low vitamin D levels may to some extent predict frailty and could represent a biomarker for identifying older adults at risk for frailty (Buta et al., 2017). Underlying mechanisms of this relationship may be the involvement of vitamin D in sarcopenia, which is closely related to frailty, as vitamin D stimulates of Ca^{2+} and phosphorus transport, muscle contraction, and muscle differentiation (Garcia et al., 2011; Ju et al., 2018). The association between vitamin D deficiency and depression has been widely debated (Kerr et al., 2015). While low levels of vitamin D are consistently associated with depression (Anglin et al., 2013; Spedding, 2014), meta-analyses of treatment studies have reported no significant effects on depression after vitamin D supplementation (Li et al., 2013; Shaffer et al., 2014).

Frailty - a concept of biological aging

Frailty is a vulnerability state characterized by poor resolution of homeostasis after a stressor, placing persons at risk of iatrogenic damage, dependency and death (Morley et al., 2013). A consensus group, consisting of frailty-experts and delegates from six major international societies, defined *physical* frailty as an important medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function (Morley et al., 2013). This concept of physical frailty was considered relevant to target geriatric care to the most vulnerable patients. Promising prevention and treatment strategies for physical frailty included reduction or prevention of polypharmacy, more physical exercise, protein-calorie supplementation, and regular monitoring of vitamin D status to provide tailored care (Morley et al., 2013). Among community-dwelling

persons aged 65 years and over, the mean prevalence rate of physical frailty was 9.9% (range 4.0 – 17.0%) (Collard et al., 2012).

Two dominant operationalisations are 1) the deficit accumulation model (Frailty Index), stating that the proportion of ageing-related deficits reflects biological age on top of chronological age, and 2) the Fried Frailty Phenotype, which mark an underlying physiological state of multisystem and energy dysregulation (Fried et al., 2001; Mitnitski et al, 2001; Cesari et al., 2014). According to Cesari et al (2014), the Fried Frailty Phenotype and the Frailty Index should not be considered substitutable with each other, but as complementary constructs.

The Frailty Index has been developed in the Canadian Study of Health and Aging (CSHA), a five-year prospective cohort study which included 10.263 older adults aged 65 years and older (Rockwood et al., 2005). The Frailty Index was originally calculated by measuring the absence or presence of 92 clinical deficits (Mitnitski et al., 2001; Mitnitski et al., 2002; Rockwood et al., 2005). Ongoing research has shown that the Frailty Index is not dependent on the number of deficits taken into account, as long as at least 30 deficits from several health domains have been included. However, the Frailty Index may substantially overlap with psychiatric conditions, as several measures of mental and cognitive capacity are included.

The Fried Frailty Phenotype is defined as the presence of at least three out of five criteria, i.e. weight loss, exhaustion, weakness, slowness, and reduced physical activity. This definition has been validated in the Cardiovascular Health Study (CHS), showing predictive value for incident falls, worsening mobility, hospitalization, and death during follow-up independent of multimorbidity or disability (Fried et al., 2001). Although the Fried Frailty Phenotype has been used by many researchers, the operationalisation of the specific components slightly differs between studies. Some

studies have shown that self-report indices of the five components also provide a reliable proxy of the Fried Frailty Phenotype (Lee et al., 2017; Papachristou et al., 2017). In this thesis, frailty has been defined according to the Fried Frailty Phenotype (Fried et al., 2001). We assumed that this model would be most appropriate for application in a psychiatric setting in order to prevent symptom overlap and confounding with psychiatric disorders. It allows us to study frailty in relation to psychiatric disorders without including psychopathology in the broad definition of frailty (Fried et al., 2001; Collard et al., 2012). Hereby, we would be able to disentangle the relationship between psychopathology, frailty, and underlying ageing mechanisms as well as the clinical impact of frailty in geriatric psychiatry (Collard et al., 2012).

Frailty and depression - approaching concepts with increasing age?

Depression is, analogously to frailty, associated with negative health outcomes, including somatic diseases and increased mortality rates (Penninx et al, 2013; Cuijpers et al, 2014). Nonetheless, in the hallmark study of Fried and colleagues (2001) on the Fried Frailty Phenotype, depressed patients or persons on antidepressants were a priori excluded to prevent being classified as physically frailty due to the presence of only one (psychiatric) disorder (Fried et al, 2001). This might unnecessarily have contributed to the neglect of the concept of frailty in geriatric psychiatry.

A narrative review on the association between depression and frailty points not only to overlap between both conditions, but also to similarities in the determinants and consequences of both concepts (Mezuk et al., 2012). The overlap between both constructs has been confirmed in empirical studies. Using latent class analyses among adults aged 41 – 96 years, depression and physical frailty appeared to be distinct concepts, although 100% of the severely depressed persons were classified

as physically frail (Mezuk et al., 2013). Moreover, factor analyses on the criteria for depression and frailty in the Health and Retirement Study, showed that depression and frailty represent two distinct, but highly associated dimensions (Lohman et al, 2016). These findings suggest that frailty and depression in later life are difficult to disentangle. A recent meta-analysis on the association between depression and frailty among older adults estimated that across cross-sectional studies, 40.4% of depressed persons were frail and that 38.6% of frail persons were depressed (Soysal et al., 2017). A limited number of longitudinal studies confirmed these findings (Soysal et al., 2017). Therefore, frailty and late-life depression may partly share some of their etiological pathways as well as their phenotypic expression (Ni Mhaolain et al., 2012). Nonetheless, only three studies included in the above mentioned meta-analysis have assessed depression according to the diagnostic criteria of the DSM, among which a study from the Netherlands Study of Depression in Older persons (NESDO). In NESDO, only 27.2% of the patients suffering from a DSM-IV defined depressive disorder were classified physically frail, which could not be explained by overlapping criteria for frailty and depression (Collard et al., 2014). These prevalence rates are comparable to the prevalence of frailty among populations with chronic somatic conditions in which the clinical relevance of frailty becomes more and more evident (Denfeld et al., 2017).

Thus far, frailty has neither been examined as a determinant of the course of depression nor of an increased mortality rate in late life depression, as done in chapter 7 and chapter 8.

Frailty and common (neuro)psychiatric symptoms in later life

While studies on the association between psychopathology and frailty primarily focusses on depression, frailty is probably as relevant for other (neuro)psychiatric disorders (Andrew & Rockwood, 2007). Therefore, in this thesis we also investigate the association between physical frailty and neuropsychiatric disorders in later life.

We will focus on “cognitive impairment” and “medically unexplained symptoms” (MUS).

Cognitive impairment - The association between physical frailty and cognitive performance is complex (Malmstrom et al., 2013; Panza et al., 2014). A systematic review has identified eleven longitudinal studies that show the predictive value of physical frailty for subsequent cognitive decline or dementia (Robertson et al., 2013). Although less often studied, cognitive impairment conversely may be a risk factor of physical frailty (Robertson et al., 2013; Nishiguchi et al., 2015). Some researchers have included cognitive deficits as a component of physical frailty for two reasons. Firstly, adding cognitive performance to a frailty index adds to its predictive validity for adverse health outcomes (Ávila-Funes et al., 2009). Secondly, significant overlap exists in the mechanisms underlying physical frailty and cognitive impairment (Halil et al., 2015). In 2013, the concept “cognitive frailty” has been introduced by a consensus panel to emphasize the important role of brain aging (Kelaiditi et al., 2013). Cognitive frailty was defined as a subtype of physical frailty and characterized by the concurrence of cognitive deficits in physically frail older persons in the absence of an accompanying neurological disorder (Kelaiditi et al., 2013). Cognitive frailty may represent a prodromal phase for neurodegenerative diseases (Kelaiditi et al., 2013), but its potential for reversibility makes it an ultimate target for early intervention (Kelaiditi et al., 2013). Late-life depression can also have a detrimental effect on cognitive performance (Panza et al., 2009; Wilkins et al., 2009; Korten et al., 2014; Panza et al., 2014). Nonetheless, the association between physical frailty and cognitive performance has been hardly studied among clinically depressed older persons (as will be done in chapter 5).

Medically unexplained symptoms - Medically unexplained symptoms (MUS) are defined as physical symptoms that, after appropriate medical assessment, cannot

be explained in terms of a conventionally defined medical disease (Wessely, 1999; Beck, 2008). Patients with medically unexplained symptoms (MUS) often describe a low quality of life and frequently suffer from co-morbid anxiety and depressive disorders (De Waal et al., 2004). This gives rise to high levels of health care consumption in the search for an organic origin of complaints and places especially older persons at risk for iatrogenesis (Smith et al., 2005). Besides a small pilot study (Benraad et al., 2013), no studies have been conducted on the physical performance of older patients with MUS. This pilot study suggests that MUS in later life might be related to the presence of frailty. Therefore, in this thesis we want to examine the association between frailty and somatic comorbidity among older patients with MUS and older patients with Medically Explained Symptoms (MES) who have participated in the "Older Persons with medically Unexplained Symptoms" (OPUS) study (see appendix). We will particularly explore the association between the severity of MUS and frailty (chapter 6).

Aims and outlines of this thesis

The main aim of this thesis is to study physical frailty in an older population of depressed older adults. This thesis consists of three parts.

Part I:

Ageing-related biomarkers of physical frailty in late-life depression.

The huge variability in biological ageing among individuals who live in a population characterised by an increasing life expectancy has stimulated the search for biomarkers of biological ageing. Ageing-related biomarkers should be associated with physical frailty as a clinical phenotype of ageing, but also with conditions of accelerated ageing like depression. This first part of the thesis focuses on the relationship between physical frailty and age-related biomarkers in a population of depressed older adults. As physical frailty and late-life depression partly overlap and the association between depression and ageing-related biomarkers decreases with age, we examined whether associations between ageing-related biomarkers and physical frailty were moderated by the presence of a late-life depression within the Netherlands Study of Depression in Older persons (NESDO). The specific research questions that have to be answered are (numbers corresponding with chapters):

- Chapter 2: Is physical frailty associated with low-grade inflammation in a cohort of depressed older patients?
- Chapter 3: Is physical frailty associated with telomere length in a cohort of depressed older patients?
- Chapter 4: Is physical frailty associated with vitamin D levels in a cohort of depressed older patients?

Part II:

Association between physical frailty and common (neuro)psychiatric symptoms.

The operationalisation of the concept of (physical) frailty is still debated and psychiatric disorders beyond depression have also been associated with increased mortality rates. Therefore, the idea underlying this second part is the question whether the physical frailty phenotype should be broadened with neuropsychiatric symptoms beyond depression. Firstly, we set up a study to explore whether physical frailty is associated with poorer cognitive functioning in a sample of depressed older adults. Secondly, we examined the level of physical frailty and somatic comorbidity in older patients with medically unexplained symptoms (MUS) and compared this to patients with medically explained symptoms (MES). The following research questions have to be answered:

- Chapter 5: Is cognitive impairment in late-life depression associated with physical frailty?
- Chapter 6: Are medically unexplained symptoms in later life associated with physical frailty?

Part III:

Adverse health outcomes of physical frailty in late-life depression.

The third part of the thesis is more clinically oriented by focusing on the predictive value of physical frailty in late-life depression. First, we investigated the prognostic impact of frailty on the outcome and course of late-life depression. Secondly, we examined whether physical frailty predicts mortality among clinically depressed older persons. The corresponding research questions are:

- Chapter 7: Does physical frailty negatively impacts the course of depression in later life?
- Chapter 8: Does physical frailty increase mortality risk in late-life depression?

Appendix

Netherlands Study of Depression in Older persons (NESDO)

The NESDO study was set up to study neurobiological, physical, and psychosocial determinants and the course of late-life depression. NESDO is a multisite, naturalistic cohort study (Comijs et al., 2011) and included 378 older (>= 60 years) participants with a 6-months diagnosis of major or minor depression or dysthymia, as well as a comparison group of 132 never depressed participants (>= 60 years). Depressed participants were recruited in primary care as well as secondary and tertiary mental health care institutes. Non-depressed controls were recruited from general practices only. Exclusion criteria were a suspected or established diagnosis of dementia or a Mini Mental State Examination-score <18 (Folstein et al., 1975) and insufficient command of the Dutch language. Participants were followed-up for six years including self-report symptom severity scales every six months by post and full re-examinations at two- and six-year follow-up (site visits). A more detailed description of the NESDO study can be found elsewhere (Comijs et al., 2011; Comijs et al., 2015; Jeuring et al., 2018).

Older Persons with medically Unexplained Symptoms (OPUS) Study

The OPUS study was set up to explore the biopsychosocial determinants and course of medically unexplained symptoms (MUS) in later life. A mixed method design has been adopted by including both quantitative and qualitative data collection. In this thesis, only the quantitative baseline assessment will used, which consists of a case-control study of 118 older MUS-patients (>60 years) with chronic MUS (>3 months) to 154 older patients with chronic (>3 months) medically explained symptoms (MES), such as diabetes or COPD. To compose a sample of patients representing the whole severity range of MUS, participants with MUS and MES were recruited in the community (advertisements in local newspapers), in primary care, and in secondary health care (outpatient mental health clinic as well as outpatient geriatric

department of a University Medical Center). Exclusion criteria were the presence of a primary psychotic disorder, cognitive impairment, terminal illness, severe auditory and/or visual limitations, and insufficient command of the Dutch language.

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Part I

Ageing-related biomarkers of physical frailty in late-life depression

Chapter 2

The relation between physical frailty and low-grade inflammation in late-life depression

MHL Arts, RM Collard, HC Comijs, PJW Naudé, R Risselada, P Naarding, RC Oude Voshaar

J Am Geriatr Soc 2015;63(8):1652-1657

Chapter 3

Telomere length and physical frailty in late-life depression

MHL Arts, RM Collard, HC Comijs, L de Jonge, P Naarding, B Penninx, Kok RM, RC Oude Voshaar

Exp Gerontol 2018;111:229-234

Chapter 4

Vitamin D deficiency and course of frailty in a depressed older population

KS vd Berg, MHL Arts, RM Collard, RHS van den Brink, HC Comijs, RM Marijnissen, RC Oude Voshaar

Aging Ment Health 2018;15:1-7