Frailty & late-life depression: a delicate balance

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door
Rose Milou Collard
geboren op 29 augustus 1978
te Nijmegen

Professor Dan Blazer looking back at the research progress in the field of old age psychiatry:

…"In this editorial, I will review the findings of seven studies published here (Aging & Mental Health, ed.) and compare these studies with the state of the field in terms of empirical research when I wrote my 1982 book."…"Collard et al. (2014) explored late- life depression and vulnerability to frailty. The authors found that the frequency of this vulnerability was 27% among a depressed sample of persons 60+ years of age compared to non-depressed. Many, if not most, investigators will include depression in their list of symptoms of frailty, yet this study turns the tables, namely examining the association of the vulnerability for frailty among the depressed. Frailty has been recognized for centuries as a companion of aging, yet only in the past 20 years or so has it taken a central place among the conditions to which geriatricians specifically focus, a defined phenotype with clear symptoms, signs, biomarkers, and course (Fried, Tangen, & Walston, 2001). In 1982, I could not find any empirical studies of the association of frailty with late-life depression (and to be honest, the association did not occur to me at that time)."…

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Chapter 1

General Introduction

Depression (major depressive disorder: MDD) is a multi-causal disorder that is characterized by a depressed mood and/or a loss of interest in normally enjoyable events (anhedonia).[3] For a diagnosis of depression, these symptoms have to persist for >two weeks, most of the day, almost every day, and are accompanied by at least five of the following symptoms: fatigue, or loss of energy, changes in appetite or weight, sleep disturbances, psychomotor agitation or retardation, feelings of worthlessness or excessive guilt, diminished ability to concentrate or indecisiveness, and thoughts of death or suicide.[3]

Subthreshold depression is characterized by elevated depressive symptoms that do not meet diagnostic criteria for MDD, and includes clinically relevant depressive symptoms and minor depression.[6]

Frailty is a condition of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse health outcomes, operationalized as physical frailty: weight loss, weakness, exhaustion, slowness and low activity.[17]

In old age, somatic diseases, disability, depression, cognitive impairment and frailty often appear simultaneously, all reciprocally and adversely influencing health outcomes. In research into old age phenomena, these concepts are intertwined and sometimes they are used interchangeably. In this thesis we aim to unravel two of these concepts, i.e. frailty and depression.

One striking myth about aging is that aging and depression go hand in hand or, in other words, that aging is inevitably accompanied by depression.[1, 2] For many years, this myth has been taken for granted by clinicians, researchers and older persons themselves. The result was a neglect of late-life depression in research programs and therapeutic nihilism.[4] Facing the challenge of an aging society, clinical and scientific interest in old age psychiatry has gradually grown between 1950 and 1990 and almost exploded during the past few decades.[5] As a consequence, accumulating evidence has been found for both the predictive value of depression with regard to adverse health outcomes, and the effectiveness of treating mental health problems in later life, particularly depression.[7-9]

Pioneers of old age psychiatry fought against ageism, pointing to similar treatment results in older and younger patients.[10, 11] This optimism, however, was not shared by the entire old age psychiatry community. As research into late-life depression progressed, it became apparent that these critics of effectiveness of late-life depression treatment may have had a point, because the course of late-life depression is characterized by high recurrence and relapse rates.[12-14] This indicates that the course and treatment of late-life depression are complicated.[15, 16]

A closer look at these findings puzzled me. First, most observational studies on late-life depression have used depression severity rating scales instead of psychiatric interviews to diagnose depressive disorder. The predictive value with regard to adverse health outcomes however, is not restricted to major depressive disorder. Subthreshold depression also predicts negative health outcomes. This is generally explained by a dose-response effect, pointing to the relevance of subthreshold depression in later life and/or the need for age-specific criteria.[18] The latter is specifically important in old age, since it is known that depression severity scales, especially when scores are lower, pick up signs and symptoms of physical illnesses.[19] This raises the question whether depression, and especially depressive symptoms, can be confounded by physical frailty (see below)?

Second, the growing number of randomized controlled trials on the effectiveness of antidepressants in later life, enabled meta-analyses. A thought-provoking study showed that effect-sizes for antidepressant drug therapy are smaller in older, compared to younger depressed persons.[20] Recently, meta-regression of 34 randomized controlled trials including depressed patients of 65 years and older, showed that even in an older sample, increasing age is associated with a less favorable outcome.[21] Can this age-related effect be explained by physical frailty?

Little is known about age-related mechanisms, such as frailty, underlying late-life depression. This thesis contributes to the current body of knowledge of intertwined old age phenomena, as we aim to disentangle part of the association between frailty and late-life depression.

Frailty

"I am 70 years old, but I look and feel like I am 85 years", said ms E with a gloomy voice. Glancing at ms E while she shared this with me, I could only agree with her. I wondered, where does this discrepancy between her presentation and her real age come from? Why does her neighbor that has the same age still babysits her grandchildren and has an independent life, while ms E is obviously struggling with active aging? Should we consider ms E frail?

The case of ms E demonstrates the mystery of aging. Why do some persons look older than others, despite a similar chronological age? Why do some, apparently healthy, persons react resilient to a stressor like a hip fracture, while other, also seemingly healthy persons, experience several complications that may even culminate in death?

Normal aging is inevitably associated with functional and physical changes and even damage. For some persons, these changes are emphasized and lead to decreased levels of well-being and susceptibility to diseases and disability.[17] Frailty is a concept that attempts to capture the increased vulnerability of older people to the stressors they face.[22]

During the last half of the 20th century, life expectancy rapidly increased and marked the appearance and growth of a vulnerable group of older persons. This shift in age distribution resulted in the introduction of the term frailty in 1968 by O'Brien and colleagues.[23] They outlined frailty as an excessive, disproportionate reaction of older persons to adverse events. Their concept of frailty, however, remained rather subjective and was based on retrospective case-analyses of only 48 older persons.[23] In this paper and in most papers that followed in the subsequent years, frailty was used to describe a population that nowadays would be considered "typical geriatric patients" who need more complex (medical) care than standardly delivered in traditional hospitals.

A first attempt to quantify frailty was undertaken by Winograd and colleagues in 1988,[24] by defining frailty as the presence of one or more of fifteen common geriatric clinical conditions (multi-causal health problems which are common in later life). Frailty was placed as an intermediate state on a continuum that ranges from independence to severely impaired.[25]

Considerable progress in the evolvement of the concept of frailty was made by Fried and colleagues, with their introduction of a standardized phenotypical definition of frailty in 2001.[17] This purely physical definition of frailty was based on a large sample of community-dwelling older persons participating in the Cardiovascular Health Study (CHS). In this study, a decade of research into age-associated risk factors of adverse health outcomes, such as declines in balance and lean body mass were combined in a theoretical model. Analogue to the metabolic syndrome in cardiovascular medicine, physical frailty was defined as the presence of three out of five criteria, i.e. unintended weight loss, weakness, exhaustion, slowness and low activity level. This model was tested for predictive validity with regard to negative health outcomes, such as falls, disability and mortality over three and seven years of follow-up. In the past century, frailty has often been confused with disability, comorbidity, or advanced old age.[26, 27] The predictive value of frailty regarding adverse health outcomes however, was independent of activities of daily living (ADL) functioning and somatic comorbidities.

Despite this breakthrough in frailty research, controversy remained about both

the conceptualization and the operationalization of frailty. While there is implicit agreement that frailty is a condition conferring vulnerability to poor physical health outcomes, there is little consensus about what factors, physical or otherwise, may contribute to this vulnerability. As a consequence, a range of symptoms, including biological, psychological, and sensory deficits have been incorporated into extant frailty definitions.[28] Different operationalizations emerged in medical literature, mostly supported by good predictive validity with regard to negative health outcomes.[29, 30] Since psychological and social conditions also predict negative health outcomes, some researchers included these aspects into their frailty concepts (e.g.[31-33]). Parallel to this discussion, the relevance of frailty was increasingly acknowledged by findings such as the higher usage of community resources, nursing homes and hospitalization by frail persons, whereas early intervention was shown to improve quality of life and reduce costs of care.[34] Albeit the operationalization of frailty was still subject of discussion,[35, 36] in 2012, after the start of the research described in this thesis, four major consensus points were created on physical frailty by six international societies and seven other frailty experts. They agreed that physical frailty is an *important medical syndrome* for geriatric health care that can be *prevented or treated,* for which *screening tests* are available that should be *applied to all persons aged 70 years and over, or those with significant weight loss due to chronic disease*.[37]

Although the concept of frailty has been proven relevant in different medical (somatic, e.g. cardiology, neurology) disciplines,[38, 39] to date no studies have been conducted in old age psychiatry. Broad definitions of frailty (including also psychological components)[31-33] largely overlap with the criteria of psychiatric disorders and limit its use within a psychiatric population. This may have contributed to the neglect of frailty in old age psychiatry. A requirement for research into the potential benefit of frailty for depressed older patients is to select the most appropriate operationalization of frailty (see Chapter 2 of this thesis), and prevalence rates in the community should be summarized (see Chapter 3) enabling interpretation of findings among depressed older patients.

Depression

"I am 70 years old, but I look and feel like I am 85 years", said ms E with a gloomy voice. Glancing at ms E while she shared this with me, I could only agree with her. I wondered, where does this discrepancy between her presentation and her real age come from? Why does her neighbor that has the same age still babysits her grandchildren and has an independent life, while ms E is obviously struggling with active aging? Should we consider ms E depressed?

The difficulty of diagnosing depression in later life is demonstrated in ms E's case. Does ms E suffer from depression or should we consider these symptoms part of her aging process? Depression can be classified according to formal and strict psychiatric criteria, although a dimensional approach is gaining more and more attention in modern psychiatry.[40, 41] Are we able to discern late-life depression from frailty or can we only make best guesses?

Depression is the most common psychiatric disease worldwide.[42] Globally, more than 350 million people of all ages suffer from depression (www.who.int). The World Health Organization (WHO) predicted that by 2020, depression will be second only to heart disease as a cause of disability and premature death in established market economies.[43]

Severity of depression ranges from some clinically relevant depressive symptoms to minor depression and eventually, major depression. Subthreshold depression (including clinically relevant depressive symptoms and minor depression) can be operationalized according to the research criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV-TR) for minor depression,[3] as well as based on a score above the cutoff of a (self-report) questionnaire assessing depressive symptoms.[6] Meanwhile the fifth edition of the DSM is already available. With regard to depressive disorder no major alterations were incorporated, as compared to DSM-IV.

With demographic balance shifting towards an older population, the number of older adults with a lifetime history of depression or subthreshold depression will be significant over the next decades.[44] Although direct comparisons are lacking, subthreshold depression is assumed to be more prevalent in older persons than in persons aged <65 years,[45] with prevalence rates of 9.8% for minor depression and 13.5% for clinically relevant depressive symptoms.[46] The prevalence rate of subthreshold depression in a pooled sample of community dwelling European older adults was estimated at 15.2%.[47] Meta-analysis has estimated the prevalence of major depressive disorder (MDD) among community-dwelling older persons at 1.8% (ranging from 1-5%).[46] In older persons, major depression is less prevalent than in adults.[48, 49]

Whether subthreshold or "minor" is indeed minor in old age psychiatry is debated, as the burden of minor depression and major depression have similar negative consequences for well-being and health outcomes.[50-52] Studies in later life, however, are often based on clinically relevant depressive symptoms, and not on a DSM-IV classification. Although most of these studies adjust their analyses for somatic comorbidity

and ADL-disabilities, the severity of the underlying somatic diseases and also frailty may falsely inflate the symptom scores and thus exaggerate the predictive value of so-called "clinically relevant depressive symptoms". Furthermore, high recurrence rates and a chronic course of late-life depression are widely known,[53] but again, most studies are based on self-report questionnaires.[12, 54] Whether these findings might partly be explained by physical frailty, has not been examined yet (see Chapter 7 and 8 of this thesis).

Another issue are the underlying mechanisms postulated to drive the negative health consequences of late-life depression. These mechanisms include somatic diseases, metabolic disturbances, immune-inflammatory dysregulation, autonomic dysregulation and hypothalamus-pituitary-adrenal axis dysregulation,[55] but are primarily based on cross-sectional association studies. Inflammation is of particular interest for this thesis, as this has been reported as an underlying mechanism of both frailty and depression.[56-58] Therefore, we will explore the association of physical frailty with somatic comorbidity as well as low-grade inflammation among depressed older patients (see Chapter 5 and 6 of this thesis).

Do physical frailty and depression represent distinct syndromes in old age?

Even though the physical frailty phenotype described by Fried and colleagues attempted to define frailty in biomedical terms, two out of five criteria directly overlap with the criteria for major depressive disorder (unintentional weight loss and exhaustion), while one criterion (low activity level) may be a direct consequence of depression. In their hallmark study in 2001, Fried and colleagues even excluded participants using antidepressants, in order to prevent that these persons would be classified as frail on the presence of one disorder, namely major depressive disorder.[17] Using data driven techniques (latent class analyses) in an adult sample aged >40, however, it was shown that depression and physical frailty are indeed distinct concepts, although their operational criteria identify substantially overlapping subpopulations.[59] This initial finding may suggest that physical frailty is highly prevalent in depressed older persons, but unfortunately, this has not been examined hitherto (see Chapter 4).

In summary, the only scientifically sound conclusion with respect to the relation between frailty and late-life depression is that thus far frailty has largely been ignored in old age psychiatry.

Aims and outlines of this thesis

The main aim of this thesis is to study physical frailty in late-life depression. This thesis consists of three parts.

Part I: *The concept of frailty and prevalence rates.*
This first part focuses on the conceptualization of frailty and the prevalence of frailty in the general population. A necessary first step is to justify how frailty should be operationalized when studied within a mental health care setting for older people. For this purpose, two systematic reviews (one including also a meta-analysis) were conducted. The specific research questions that need to be answered are (numbers correspond with chapters):

2. Which operationalizations of the concept of frailty are available and how do they relate to psychopathology?
3. What is the prevalence of frailty in the general population?

Part II: *Is physical frailty associated with late-life depression?*
Since frailty has not been examined within a sufficiently large and well-defined cohort of depressed older patients, we set-up some studies to examine whether physical frailty is indeed more prevalent in late-life depression than can be expected by chance. This was examined within the Netherlands Study of Depression in Older persons (NESDO). The corresponding research questions are:

4. What is the prevalence of physical frailty in depressed older patients compared to a non-depressed comparison group, taking symptomatic overlap between frailty and depression into account?
5. How do late-life depression and physical frailty relate to somatic comorbidity?
6. Is the mechanism of low-grade inflammation associated with physical frailty in depressed older patients?

Part III: *Does physical frailty affect the incidence and course of late-life depression?*
The third part of the thesis focuses on the longitudinal association between physical frailty and late-life depression, exploring frailty as a predictor of late-life depression. Frailty, as well as depression are disentangled in a community-dwelling cohort of older persons and in a sample of clinically depressed older persons. The following research questions have to be answered:

7. Does physical frailty predict a higher incidence of depressed mood, as well as a less favorable course of depressed mood?
8. Does physical frailty predict depression diagnosis after two years of follow-up and chronicity of depression respectively?

Figure 1 The Associations That Are Studied in This Thesis (numbers refer to chapters)
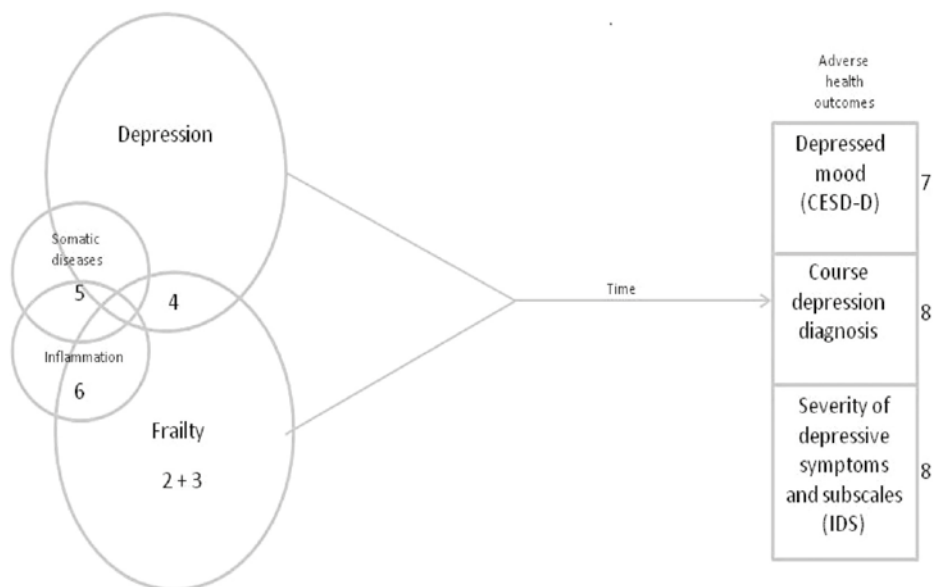
Case report

To illustrate the clinical relevance of the research questions that are addressed in this thesis, we will take a closer look at the case of ms E. In the General discussion (Chapter 9) we will address the questions that arise from this case report in the light of the findings of this thesis.

Case description

Ms E, a 70-year-old woman was admitted to the acute ward of old age psychiatry. She was diagnosed with a depressive episode and a history of recurrent depressive disorder. She had been admitted to the ward ten years before, after the death of her husband. In her adult life, she had been admitted to psychiatric wards two more times. She fully recovered after each admission.

Despite the absence of somatic comorbidities, a geriatrician was consulted as part of the multi-disciplinary procedure that was carried out when a person aged >70 was admitted. The physical examination showed no abnormalities. Her daughter however, informed the nurses about how her mother had given up her Nordic walking activities two years ago due to a diminished physical condition, and that she stayed in the house more and more ever since. She did not experience pain during walking.

Ms E's depressive disorders were usually successfully treated with a tricyclic anti-depressant, combined with cognitive behavioral therapy. After admission to the ward of old age psychiatry this treatment was started. After a few weeks ms E was feeling better. Her mood was no longer sad, however she remained wearily and exhausted. Her antidepressant level seemed adequate, and the intensive cognitive behavioral therapy did not result in complete recovery. Ms E remained admitted for almost twice as long as compared to previous depressive episodes. When she was discharged from the hospital she was visited by a mental health care nurse weekly and continued the anti-depressant medication.

Before ms E was discharged, the multi-disciplinary team deliberated about her condition. Interestingly, a trichotomy in opinions became apparent, represented by the psychiatrist who attributed the remaining symptoms to depression, the geriatrician who attributed these symptoms to frailty, and the nurse who considered ms E both depressed and frail.

Who is right? To what condition should we attribute ms E's symptoms? How do we distinguish between depression and frailty?

Appendix

Studies used in this thesis
NESDO
The Netherlands Study of Depression in Older persons (NESDO) is an ongoing cohort study aimed at examining the long-term course and consequences of depressive and anxiety disorders in older persons (aged 60 through 93 years). Baseline data of NESDO consists of 378 depressed subjects with a current DSM-IV[3] diagnosis of major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%), of which 26.5% have two depressive disorders, and 132 non-depressed subjects.[13]

Persons with a primary diagnosis of dementia, a Mini Mental State Examination score (MMSE) under 18 or an organic or psychotic disorder were excluded, since the course of these persons will be largely determined by the primary disorder. Insufficient mastery of the Dutch language was another exclusion criterion.

Depressed participants were recruited from mental health institutes (both in- and outpatients) and from primary care. The non-depressed comparison group was recruited from primary care practices. All participants were competent to consent to participation. Written informed consent was obtained from the participants. The ethical review boards of the participating institutes approved of this study.

Assessments consisted of an examination at one of the participating clinics or at the homes of the participants, including a structured diagnostic interview, physical tests (such as blood pressure and gait speed), and paper and pencil questionnaires. These examinations were conducted at baseline (n=510) as well as 2 year follow-up (overall attrition rate: 21.4%).[60]

InCHIANTI
Invecchiare nel CHIANTI (aging in the Chianti area); the InCHIANTI Study is a prospective, population-based cohort study.[61] The baseline data collection started in 1998 and was completed in 2000. It included an interview at the homes of the participants and a medical examination at the study clinic. The medical examination was conducted within 21 days after the home interview. Follow-up assessments took place at 3, 6 and 9 years after baseline. After explaining the study procedures to the participants, they were asked to sign informed consent. The ethics committee of the Italian National Institute of Research and Care on Ageing approved of the study protocol. The InCHIANTI study has included 1155 persons aged 65 years and older.

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Part I:

The concept of frailty and prevalence rates

Chapter 2

Frailty; a fragile concept

Abstract

Background- Frailty can be regarded as a condition in which the reserve capacity of various physical systems has sunk to a critical low, at which point minor disturbances can develop into serious health problems.

Aim- To review the various operationalizations of the concept of frailty and describe the relationship between frailty and psychopathology.

Method- We searched the literature up to October 2010 using PubMed, PsycINFO and CINAHL.

Results- We found 35 operationalizations of the concept of frailty; four single measurements as a proxy for frailty (e.g. muscle strength), 18 syndrome diagnoses which can be subdivided into single (n=5) and multiple syndrome diagnoses (n=13) and 13 dimensional operationalizations for which measurement instruments were used. Only six studies reported the relationship between frailty and psychopathology. The studies revealed an association between depression and psychopathology. An important finding was the association between depression and frailty, but the direction of the association is unknown.

Conclusion- No consensus has been reached regarding the operationalization of the concept of frailty. For the purpose of gerontopsychiatric research we recommend the inclusion of a syndrome diagnosis based on physical criteria (physical frailty) because this should make it possible to unravel the relationship between psychopathology and underlying aging mechanisms.

Keywords: definition, frailty, psychopathology

Introduction

Why does one person die 'of old age' at the age of 75, while another person still independently manages her (and less often, his) household at the age of 90? This discrepancy between chronological and biological age is the basis of the heterogeneity in old age health care. The concept of frailty can be seen as a measure of biological age and as an attempt to explain this heterogeneity.[1] However, frailty is not synonymous with having chronic diseases or disorders. Instead, it is an underlying vulnerability for the occurrence of health complications caused by a diminished physical reserve capacity.[2-4] A diminished reserve capacity of various physiological systems may explain why two apparently healthy older adults have a different response to a hip surgery: one older person experiences a series of complications, while the other older person has a problem-free recovery.

Definitions and criteria

Obscurity about how this reserve capacity can be measured, has led to a variety of operational frailty definitions. Despite, two findings are consistently found in research. First, frailty prevalence increases with age. In Canada frailty prevalence was 7% for 65-74 years old, 18% for 75-84 years old, and finally, 37% for persons aged 85 and over.[5] Second, frailty prevalence is higher in women than in men.[2, 5, 6]

Frailty definitions in clinical practice are based on cohort studies.[2, 5] These studies assess which characteristics predict adverse health outcomes (i.e. hospitalization, death or institutionalization). Next, the characteristics are clustered, in order to find the most predictive combination. It is assumed that these characteristics together are more predictive of negative health outcomes than the sum of these characteristics. This is analogue to the procedure used with metabolic syndrome.[7]

However, diversity in baseline, as well as outcome measures in these cohort studies, has led to a variety of frailty definitions. Moreover, the concept of frailty is increasingly defined as a broad concept, that in addition to physical components, also includes psychological and social components. A qualitative study among (inter)national experts was conducted by Gobbens and colleagues[8] and led to the following conceptual frailty definition: *Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social) that are caused by the influence of a range of variables and which increases the risk of adverse outcomes.* Since both cognitive dysfunctioning and depression are associated with higher risks of disability and death,[2, 9, 10] these variables could be included in operational definitions of frailty. However, cognitive decline and depression can be a risk factor for the onset of frailty as well as a consequence of frailty.

The concept of frailty is an important concept in old age psychiatry for several reasons. First because of the overlap between psychiatric disorders and frailty, especially the broad frailty definitions. Second, frailty enables the early detection of a group of older persons at risk of (somatic) complications and the adjustment of the treatment of this particularly vulnerable group of older persons. In somatic medicine, this distinction between frail and nonfrail older persons has led to the development of specific interventions and adjustments in treatment policies.[11-13]

In this paper, we aim to provide an overview of the existing operationalizations and various definitions of frailty, and to describe the relation between frailty and psychiatric disorders.

Method

We conducted a systematic review of the literature in three databases (PubMed, PsycINFO and CINAHL) in the period up to October 2010. Considering the strong increase in the amount of articles about the concept and definition of frailty, we included only review articles for the first part of the aim. The following search strategy was applied: *'(criteria OR definition) AND frailty AND review'*. Inclusion criteria were: a primary focus on frailty, written in English, a study population aged 60 and over and access to the full-text version of the article. All operational definitions of frailty were extracted from these articles. When the article provided insufficient information, the original source was consulted. In order to prevent missing recent frailty definitions, the search strategy was repeated for the period of 2008-October 2010 without the keyword 'review'.

For the second aim, the following search strategy was applied: *'frailty'* combined with 'psychia*' and *'psycho-pathology'*. Since anxiety and depression are the most prevalent psychiatric disorders in older adults, the search strategy was subsequently expanded with MeSh-terms *'depression'* and *'anxiety'*.

Results of frailty operationalizations

Regarding the first aim, the searches resulted in, after removing double articles, 78 articles. These articles were selected on the title and the summary, and screened for the inclusion criteria, leaving fifteen relevant articles. The references of the included articles yielded 28 additional articles. Finally, three more articles were known by the authors to be relevant for this review and were also included. These articles were not found with the previous searches.

Until the early nineties frailty measures were primarily focused on muscle strength

and loss of muscle mass (sarcopenia). During the following years, research into the various definitions of frailty was conducted. On a conceptual level, a dichotomy became apparent. One group of researchers primarily defined frailty according to physical components, the physical phenotype of frailty,[2] as oppose to another group of researchers, who also included psychosocial components and health care consumption in the definition of frailty; the broad phenotype.[14]

A total of 35 different operationalizations of frailty were extracted from the articles (Table 1). Besides the conceptual discussion about the operationalization of frailty, three different approaches exist. To begin with, some studies primarily focus on the identification of a unidimensional measure of frailty (proxy) (n=4). In the next approach, frailty is conceptualized on a syndromal level. This implies that frailty is present when for instance, three out of five criteria are met (n=18). In a final approach, frailty is placed within a continuum and quantified by a severity scale or a questionnaire (n=13).

Unidimensional measures (proxies)
All but one[15] unidimensional frailty measures are based on a physical symptom. In literature, these measures are not frequently used and are pragmatically based. Formal validation studies are lacking.

Syndromal definitions
The majority of the research groups define frailty on a syndromal level. Definitions that define frailty as present when a minimum amount of criteria is met, varying from two-five criteria, are found most frequently (multiple syndromal definitions). Only four out of eighteen studies prefer a singular syndromal definition, that defines frailty as present when only one out of multiple criteria is present (Table 1).

When determinants or consequences of frailty are studied, the frailty definition by Fried and colleagues[2] is most frequently used.[9, 16] This research group has defined frailty as the presence of three out of the following five criteria: weight loss, weakness, exhaustion, slowness and low activity level. Accordingly, this definition reflects the physical phenotype of frailty. Etiology of frailty is sought in changes in muscle mass, and hormonal and immunological changes.[17] However, comparison of studies that used these frailty criteria remains difficult due to various operationalizations of the criteria. For instance, multiple definitions and measures of weakness and exhaustion can be found.

Because the assessment of the five frailty characteristics is often regarded impractical in clinical practice, a simplified 'frailty index' was developed.[18] This simple index has

the same predictive value as the physical frailty phenotype[2] with regard to adverse health outcomes, such as falls, hospitalization and emergency room visits.[9]

Dimensional severity scales
Since 1995 a diversity of scales was developed, varying from self-report questionnaires to screening instruments for clinicians. Some scales consist of a combination of physical measures and psychosocial components,[3, 19] while other scales focus on Instrumental Activities of Daily Living (IADL).[20, 21] The scales that were validated in clinical studies had good validity with regard to the prediction of adverse health outcomes.[20, 22-25]

Relation with psychiatric disorders
After removing double articles, the searches resulted in 98 articles. Of these articles, three articles were relevant with regard to the second research aim.[26-28] References of these articles were checked and this yielded two additional articles.[2, 29] One of the articles was an editorial advocating multidisciplinary research into frailty and depression.[27]

Three studies reported a positive association between the physical frailty phenotype and depression.[2, 26, 29] Depression correlated with frailty according to Fried et al,[2] and with the frailty-index by Mitnitski et al.[30]; even when the criterion 'trouble with nerves' was deleted from the index. Hackstaff et al.[29] did not mention the frailty definition that was used in their study.

Only two studies conducted a broader evaluation of psychiatric disorders than only depression. It was found that frailty prevalence was higher and more characteristics were present among older persons with a psychiatric disorder, as compared to older persons with no psychiatric disorder.[26] In this study, the frailty-index by Jones et al.[23] was used (Table 1). Each step of one frailty characteristic on the frailty-index, increased the odds of having a psychiatric disorder with 1.23 (95% Confidence Interval: 1.19-1.26).

Table 1 Definitions and Operational Frailty Criteria

Author(s)	Definition	Criteria
Single Measures		
Vellas et al. 1997[31]		Limitation in one-leg balance skills
Syddall et al. 2003[32]		Diminished hand grip strength (women <17.5 kg; men <30 kg)
Cesari et al. 2005[33]		Slow gait speed (<1.0 m/s)
Vellas et al 2006[15]		Score between 17 and 23.5 on the MNA
Single Syndromal Diagnoses		
Winograd et al. 1991[34]	Condition in which an older person is not too independent and too disabled, placing this person at risk of adverse health outcomes	≥1 of the following criteria: diminished functioning, highly prevalent geriatric condition (i.e. falls, depression, cognitive impairment, incontinence, poly pharmacy), chronic and disabling diseases, social problems
Rockwood et al. 1999[35]	Combinations of aging, disease, and other factors (e.g. fitness, nutritional status) that make some people vulnerable	Cognitive impairment in 2 domains or limited mobility, or ADL-functioning, or incontinence
Gill et al. 2002[36]	Two physical parameters that are strongly associated with the development and progression of disability	Requiring a gait speed of >10 s for 6 m or not being able to stand up from a seated position with folded arms
Studenski et al. 2003[37]		Limited gait speed (based on SPPB), or limited balance
Nourhashémi et al. 2001[20]	Combination of deficits that is seen in aging and which makes an older person vulnerable for environmental changes and stressors	Deficits in at least 1 IADL, measured by the IADL-scale
Multiple Syndromal Diagnoses		
Speechley & Tinetti 1991[38]		Classification in 3 groups: frail (≥4 frailty criteria), transition group (not meeting the criteria of either frail or vigorous), vigorous (<2 frailty criteria). Frailty criteria: age>80, depression, use of sedatives, impaired vision, balance and mobility problems, low walking activity, diminished shoulder strength, diminished knee strength, disability at lower extremities

Author(s)	Definition	Criteria
Multiple Syndromal Diagnoses		
Buchner & Wagner 1992[39]	State of diminished physiological reserve capacity, that increases the risk of disability	Deficits in 3 frailty components: neurological control, mechanical functioning, energy metabolism
Ory et al. 1993[40]		Diminished strength, impaired mobility, balance and endurance
Rockwood et al. 1994[14]	Vulnerable, dynamic condition, that is caused by a precarious balance between health maintaining abilities and deficits that are a health threat	Deficits in 5 frailty components: functional independence, reduced mobility, low self-rated health, limited social contacts
Campbell & Buchner 1997[41]	Syndrome that is the result of a diminished reserve capacity in multiple physiological systems. Increases the risk of disability and death in the case of small environmental stressors	Limitations in 4 frailty components: muscle and skeletal system, respiratory capacity, cognitive/ neurological and nutrition
Dayhoff et al. 1998[42]	Diminished functioning combined with low self-rated health	Score of >20 on WHO 'Assessment of Functional Capacity'
Strawbridge et al. 1998[4]	A grouping of problems and losses of capability in multiple domains of functioning, which make the individual more vulnerable to environmental challenge	Experiencing problems or difficulties in 2 or more of the following domains: Physical functioning - Sudden loss of balance - Weakness in arms - Weakness in legs - Get dizzy or faint when stand up quickly Nutritive function - Loss of appetite - Unexplained weight loss Cognitive functioning - Difficulty paying attention - Trouble finding the right word - Difficulty remembering things - Forgetting where put something Sensory problems - Difficulty reading a newspaper - Recognizing a friend across the street - Reading signs at night - Hearing over the phone - Hearing a normal conversation - Hearing a conversation in a noisy room
Chin et al. 1999[43]	Inactivity combined with low energy intake, weight loss or low BMI	Inactivity <210 minutes a week, energy intake <7.6 MJ per day, 5 kg weight loss in the previous 5 years, BMI < 23.5 kg/m2

Author(s)	Definition	Criteria
Multiple Syndromal Diagnoses		
Fried et al. 2001[2]	Biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiological systems, and causing vulnerability to adverse outcomes	The presence of 3 or more of the following components: Weight loss, weakness, poor endurance and energy, slowness, and low physical activity level
Puts et al. 2005[44]		≥3 frailty markers with a score above the cut-off out of 9 frailty selected frailty markers: body weight, peak expiratory flow, cognition, vision and hearing problems, incontinence, sense of mastery, depressive symptoms, and physical activity
Rolland et al. 2006[45]		3 operational definitions; scores in the lowest quartile of: 1. SPPB score 2. Walking speed 3. Handgrip strength
Ensrud et al. 2008[18]		SOF-index (based on the criteria of Fried et al. (2001)[2]; ≥2 of the following 3 components: - Weight loss - Inability to rise from a chair 5 times without using arms - Reduced energy level
Sarkisian et al. 2008[46]	In addition to the physical phenotype, multiple sub-dimensions: cognition, IL-6 en CRP levels, subjective weakness and anorexia	≥4 out of the following 10 criteria: - Slower gait - Weaker grip - Lower physical activity - Weight loss - Exhaustion - Lower cognitive function - Subjective weakness - Anorexia - Higher IL-6 - Higher CRP

Author(s)	Definition	Criteria
Scales		
Raphael et al. 1995[21]	Diminished ability to carry out the important practical and social activities of daily living	Measurement of the ability to carry out practical (21 items) and social activities (9 items)
Brown et al. 2000[2]	Difficulty with fundamental tasks	Based on an adapted version of the MPPT
Mitnitski et al. 2002[24]	A range of symptoms/deficits that represent a loss of functional activity, sensory damage and overall medical-, health-, and behavioral problems	Frailty-index based on a list of 21 deficits (symptoms, signs, damage and limitations), obtained from structured clinical geriatric research into: vision, hearing, mobility, vascula, gait speed, vibration sense, toileting, cooking, bathing, going out, grooming, skin, resting tremor, sleep, dressing, urinating, gastro-intestinal condition, diabetes, hypertension, limb tone
Jones et al. 2004[23]	Based on Rockwood et al 2002.[47]: a vulnerable state that is caused by a complex interaction between medical and social difficulties, resulting in a diminished ability to deal with stressors and is accompanied by diminished functioning	Frailty index (FI-CGA) based on the presence of 70 deficits in the following domains: cognitive status, mood and motivation, communication, mobility, balance, bowel and bladder function, IADLs and ADLs, nutrition, social resources and the number of comorbidities
Mitnitski et al. 2004[30]	Two variables: chronological age and a frailty-index	PBA (self-report frailty-index): a scale with a range of 0-1, based on the weighted impact of 40 self-reported health related variables
Schuurmans et al. 2004[3]	A loss of resources in several domains of functioning, which leads to a declining reserve capacity for dealing with stressors	GFI: a 15-item screening instrument that screens for loss of function in 4 domains: 1. Physical (mobility functions, multiple health problems, physical fatigue, vision, hearing) 2. Cognitive 3. Social (emotional isolation) 4. Psychological (depressed mood and feelings of anxiety)
Studenski et al. 2004[19]		CGIC-PF includes 6 intrinsic domains (mobility, balance, strength, endurance, nutrition, and neuro-motor performance) and seven consequences domains (medical complexity, healthcare utilization, appearance, self-perceived health, activities of daily living, emotional status, and social status)

Author(s)	Definition	Criteria
Scales		
Mitnitski et al. 2005[48]	A proportion of deficits greater than average for age	Frailty index (0-1) as a proportion of all potential deficits (symptoms, signs, laboratory abnormalities, disabilities)
Rockwood et al. 2005[25]		CSHA Clinical Frailty Scale: a 7-point scale ranging from very fit to severely frail, based on clinical judgment
Rolfson et al. 2006[49]		EFS samples 9 domains: cognition, overall health (self reported and number of hospital admissions in the last year), functional independence, social support, medication use, nutrition, mood, incontinence and a timed up-and-go test
Abellan van Kan et al. 2008[50]	Various existing frailty definitions (Fried et al., 2001[2]; Rockwood et al., 1999[35]; Rolland et al., 2006[45])	The Geriatric Advisory Panel proposed the FRAIL Scale that consists of 5 domains: Fatigue, Resistance (ability to climb 1 flight of stairs), Ambulation (ability to walk 1 block), Illnesses (greater than 5), Weight Loss (>5%)
Ravaglia et al. 2008[51]		Frailty score based on 9 variables from different domains that predict mortality: age >80, physical inactivity, male gender, daily use of ≥3 drugs, sensory deficits, calf circumference ≥31 cm, IADL limitations, gait and balance test score <24, pessimism about one's own health
Gobbens et al. 2010[52]	Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes	TFI: questionnaire (25 questions) in 2 parts. Part A: 10 questions about determinants of frailty, and in part B : 15 questions about 3 components of frailty (physical, psychological and social)

Abbreviations: MNA, Mini Nutritional Assessment; ADL, Activities of Daily Living; SPPB, Short Physical Performance Battery; IADL, Instrumental Activities of Daily Living; WHO, World Health Organization; BMI, Body Mass Index; SOF, Study of Osteoporotic Fractures; IL-6, Interleukin-6; CRP, C-Reactive Protein; MPPT, Modified Physical Performance Test; FI-CGA, Frailty Index-Comprehensive Geriatric Assessment; PBA, Personal Biological Age; GFI, Groningen Frailty Indicator; CGIC-PF, Clinical Global Impression of Change in Physical Frailty; CSHA, Canadian Study of Health and Aging; EFS, Edmonton Frail Scale; FRAIL-scale, Fatigue Resistance Ambulation Illnesses Loss of weight-scale; TFI, Tilburg Frailty Indicator

Discussion

First, it can be concluded that despite an exponential growth in the amount of articles regarding frailty, there is no consensus about how frailty is defined and how frailty should be operationalized. In a recent international consensus meeting these concerns were not resolved.[50] Second, literature regarding frailty in gerontopsychiatric literature is scarce. The available studies are cross-sectional and point to an association between frailty and depression; information about causality and/ or confounding due to symptom overlap is lacking.

Points of discussion
Important topics for discussion are whether frailty should be defined according to solely biomedical factors (physical phenotype), or whether psychosocial factors should also be included in the definition of frailty. Furthermore, it remains unclear whether frailty can be regarded as a unidimensional disease concept with unique pathophysiology, or whether frailty is an epidemiological construct that consists of a combination of criteria that together are more predictive of adverse health outcomes than the sum of those criteria (statistical interaction). Finally, it can be discussed whether frailty consists of a number of individual components associated with aging, that should not be considered in clusters.[53]

Regarding the second point of discussion, no consensus will be reached on short term. Currently, several aging mechanisms exist[54] on both a molecular/ genetic level (e.g. telomere length), as well as a systemic level (e.g. inflammation, hormonal changes). Presumably, all these mechanisms contribute to the occurrence of frailty. Considering the many frailty definitions that have a predictive value with regard to adverse health outcomes,[55] and the various existing aging mechanisms, it seems unlikely that a final common pathway will be found.

For fundamental frailty research within a psychiatric setting we advocate the use of the physical phenotype of frailty. First, because this offers the possibility for studying frailty in relation to psychiatric disorders without including psychiatric disorders such as depression in the (broad) definition of frailty. Second, because underlying mechanisms associated with and moderating psychiatric disorders can be studied. In order to enable comparison with previous studies, it is preferred that the physical frailty definition by Fried and colleagues is applied.[2] It should be noted that unifying the operationalization of the components of physical frailty is an important step forward, as is the validation of these frailty criteria in various populations. In these validation studies, negative health outcomes should be limited to mortality, because mortality is least susceptive to cultural and socio-economical differences.

Disadvantages of the broad frailty phenotype
Based on our reasoning, the question arises whether the broad frailty phenotype only

creates confusion. Nevertheless, the popularity of the broad phenotype seems to gradually grow[8, 56] which is because of its compatibility with clinical practice. The broad frailty phenotype forces clinicians to assess factors like social context, cognitive functioning and psychiatric disorders.[56] Physical and cognitive training programs contribute to healthy aging[57] and may prevent frailty.[36, 58, 59] Furthermore, interventions that focus on multiple, reciprocally influencing factors have yielded good results in vulnerable older persons.[60, 61] Important components of these interventions were physical activity and therapy aimed at balance skills and strength, and regular visits by a social worker.

Both quantitative and qualitative research into the relations between frailty and psychiatric disorders are scarce, merely because lifestyle factors are important etiological factors in the occurrence of frailty.[16] Psychiatric diseases are often accompanied by an unhealthy lifestyle[62] and systemic aging mechanisms such as elevated inflammatory markers.[63] Adequate treatment of psychiatric disorders may be a key element in preventing frailty.

Conclusion
Frailty deserves a prominent place in old age psychiatry research. The proliferation of operational definitions forces clinicians to carefully substantiate the definition that is used to assess frailty. In psychiatric research, a physical frailty definition is preferred in order to prevent symptom overlap and confounding with psychiatric disorders. Future research will have to show whether older psychiatric patients with frailty will benefit from specific treatment strategies, as is increasingly the case in somatic medicine.[64]

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Chapter 3

Prevalence of frailty in community-dwelling older persons: a systematic review

Abstract

Objectives- To systematically compare and pool the prevalence of frailty, including prefrailty, reported in community-dwelling older people overall and according to sex, age and definition of frailty used.

Design- Systematic review of the literature using the keywords elderly, aged, frailty, prevalence and epidemiology.

Setting- Cross-sectional data from community-based cohorts.

Participants- Community-dwelling adults older aged 65 years and older.

Measurements- In the studies that were found, frailty and prefrailty were measured according to physical phenotype and broad phenotype, the first defining frailty as a purely physical condition and the second also including psychosocial aspects.

Results- Reported prevalence in the community varies enormously (range 4.0–59.1%). The overall weighted prevalence of frailty was 10.7% (95% confidence interval (CI) = 10.5–10.9; 21 studies; 61,500 participants). The weighted prevalence was 9.9% for physical frailty (95% CI = 9.6–10.2; 15 studies; 44,894 participants) and 13.6% for the broad phenotype of frailty (95% CI = 13.2–14.0; 8 studies; 24,072 participants) (chi-square ($\chi2$) = 217.7, degrees of freedom (df)=1, P < .001). Prevalence increased with age ($\chi2$ = 6067, df = 1, P < .001) and was higher in women (9.6%, 95% CI = 9.2–10.0%) than in men (5.2%, 95% CI = 4.9–5.5; $\chi2$ = 298.9 df = 1, P < .001).

Conclusion- Frailty is common in later life, but differential operationalization of frailty status results in widely different prevalence rates between studies. Improving the comparability of epidemiological and clinical studies constitutes an important step forward.

Key words: frailty, prevalence, elderly

Introduction

Not everyone can achieve successful aging. Decreasing well-being and increasing levels of frailty often accompany increasing age.[1] Although chronological and bio-logical age correlate,[2] individuals with the same chronological age may vary widely in health and functional status.[3] The concept of frailty attempts to explain this hetero-geneity in older adults and is thus an important concept for clinical practitioners and policy-makers. From a clinical perspective, frailty is important because it constitutes a condition of greater risk of adverse health outcomes, such as falls, less mobility, less independence, hospitalization, disability and death.[1] The explanation for these increased health risks is sought in a reduction of the reserve capacity of various physiological systems. Frailty appears when the reserve capacity has decreased to a critically low point, where even small disturbances can lead to a series of compli-cations.[4] Frailty is important from a societal perspective because it identifies groups of people in need of extra medical attention. Frailty is also important when considering financial health care planning.

Although it is generally assumed that the prevalence of frailty increases with age, is higher in women than men, and is more prevalent in the presence of chronic disease,[1, 5, 6] no consensus exists about the prevalence rates of frailty. The definition of frailty can at least partly explain discrepancies. Two groups of researchers mainly dominate the ongoing discussion about the definition of frailty. One group defines frailty according to a physical phenotype and has attracted the most attention of researchers.[7] In this phenotype, frailty is defined as a purely physical condition and therefore consists of solely physical components. For example, the Fried Frailty Index (FFI) requires the presence of three or more out of five components: weight loss, exhaustion, weakness, slowness, and low physical activity.[1] The other group defines frailty by a broader definition, including social and psychological aspects.[8] For example, the Frailty Index (FI) is based on the routinely used Comprehensive Geriatric Assessment (CGA) and consists of a count of impairments in various areas such as mood, cognition and incontinence.[9] In addition to these two operationalizations of frailty, many variations on these definitions can be found in the literature.[10-12] Most definitions also include a prefrailty state[1, 13] -a state in between frail and nonfrail-acknowledging the dimensional aspect. This latter aspect has further stimulated the development of several instruments to measure the frailty status[14-17] , which in turn has indicated the dynamic nature of frailty over time.[18]

The objectives of this literature review were to systematically compare the prevalence of frailty with regard to definition, sex and age reported in community-dwelling older persons and to pool these rates to overall frailty and prefrailty prevalence.

Methods

The process of reviewing was divided into three steps: obtaining, extracting and assessing data. First, the literature was systematically searched in the PubMed database using the keywords *elderly, aged, frailty, prevalence and epidemiology.* If applicable to the keyword, Medical Subject Heading terms were included and then combined with the search. References of the included articles were checked to find studies that had not been found with the search string.

Inclusion criteria were community-based study, cross-sectional study design or reporting of frailty prevalence at the baseline assessment of longitudinal studies, sufficient information regarding the definition of frailty that was used, a minimum of age of 65 years of participants in the cohorts, and no upper age limit for participants. Studies that also enrolled younger subjects were included in the present study, as long as prevalence was specifically given for persons aged 65 and over. Studies that did not report frailty prevalence but only, for example, mean frailty scores on a measurement instrument were excluded. In the case of multiple studies using the same cohort, the study was chosen that provided the most detailed information on the subjects and frailty definition or included the largest number of subjects.

Prevalence was calculated for frailty and prefrailty. If a study compared various definitions of frailty and therefore provided multiple different prevalence rates, the FFI prevalence was used for the calculation for the overall frailty and prefrailty prevalence. If a study did not use the FFI, the lowest prevalence rates were chosen for the overall calculations, to be conservative. The variables of interest for the subgroup analyses were the definition of frailty (physical frailty versus the broad phenotype of frailty), age and sex.

Two authors (RC and RCOV) independently extracted the data. Results were compared and differences were resolved by consensus.

Statistical Methods

Data analyses were performed using SPSS, version 16.0 (SPSS, Inc., Chicago, IL). Prevalence was taken directly from the articles. Weighted average rates were calculated by weighting the results according to the number of participants in the study. In each of the studies in this review, frailty has its own unique variance. These variances were included in the calculation of the 95% confidence intervals (CIs). Important variables, such as age and sex, were subsequently compared using analyses of variance (continuous variables) and chi-square (χ2) statistics (categorical variables).

Results

The search strategy yielded 507 hits, of which 54 were eligible articles. Of these, 33 were excluded because they described a double study sample that was already included. A total of 21 community-based studies was included. Four studies provided results according to age group and 10 studies according to sex (Table 1). One additional study was used for the calculation of frailty prevalence according to sex but could not be used for the overall frailty prevalence calculation because prevalence rates were given only according to sex.[19] No new studies were found in the references of the articles.

The prevalence of frailty in community-dwelling older adults varied from 4.0% to 59.1%. The FFI[1] was the most frequently used definition of frailty (n=14). Two studies compared two frailty indexes.[13, 20] Another study compared three self-report screening instruments.[21] The studies that reported the highest prevalence rates, used self-report questionnaires.[21, 22]

The wide range in the results was considerably reduced by arranging the studies according to the frailty definition used. In studies that used a frailty definition according to the physical phenotype, frailty prevalence ranged from 4.0% to 17.0%. In studies that used broad definitions or measurement instruments, prevalence varied from 4.2% to 59.1%.

The proportion of women was calculated across 15 studies including 53,322 participants. There were slightly more women (51.3%, 95% CI = 50.9–51.7%) than men in the studies ($\chi2$ = 1506.7, df = 1, P < .001). Weighted mean age, derived from 20 studies with a total of 56,183 participants, was 74.9 (95% CI = 74.8–74.9). Table 1 shows the details of the studies.

The overall weighted average prevalence of frailty was 10.7% (95% CI = 10.5–10.9%; 21 studies; 61,500 participants). The overall weighted average prevalence of prefrailty was 41.6% (95% CI = 41.2–42.0%; 15 studies; 53.727 participants).

Table 1 Prevalence of Frailty and Prefrailty in Community-Dwelling Elderly Adults

Author	Year	Study Group	Country	N	Female %	Data Stratified According to Age	Data Stratified According to Sex	Frailty Definition	Prevalence, % Prefrailty	Prevalence, % Frailty
Strawbridge et al.[23]	1998	ACS	USA	574	57	Yes	Yes	Problems in ≥2 functional domains (physical, nutritive, cognitive, and sensory)		26.1
Fried et al.[1]	2001	CHS	USA	5317	58	Yes	Yes	FFI	46.6	6.9
Gutman et al.[24]	2001	CSHA	Canada	8914	60	No	Yes	FS	27.7	5.3
Ble et al.	2006	InCHIANTI	Italy	827	54	No	No	FFI	37.8	6.5
Cawthon et al.[25]	2007	MrOS	USA	5993	0	No	Yes	FFI	40.0	4.0
Avila-Funes et al.[26]	2008	3C	France	6078	61	No	Yes	FFI	47.6	7.0
Blyth et al.[27]	2008	CHAMP	Australia	1705	0	No	No	FFI	40.6	9.4
Ensrud et al.[13]	2008	SOF	USA	6701	100	No	No	SOF index and FFI	36 / 47	17 / 16
Gallucci et al.[28]	2009	TRELONG	Italy	668	53	No	No	SOF index and FFI	39.2	16.3
Kiely et al.[20]	2009	MBS	USA	765	64	No	No	Chair stands and walking speed tests / SOF index and FFI	18.7 / 38.8	4.2 / 10.0
Ma et al.[22]	2009		USA	230	82	No	No	ACOVE		44
Ottenbacher et al.[29]	2009	HEPESE	USA	2049	58	No	No	FFI	47.6	7.6
Santos-Egginman et al.[30]	2009	SHARE	10 European countries	7510	ND	No	No	FFI	42.3	17.0
Chen et al.[31]	2010	SHLSET	Taiwan	2238	49	Yes	Yes	FFI	40.0	4.9
Espinoza et al.[32]	2010	SALSA	USA	606	58	No	No	FFI	53.1	9.8
Hubbard et al.[33]	2010	ELSA	UK	3055	56	No	Yes	FFI		8.1
Hyde et al.[34]	2010	HMS	Australia	3616	0	No	Yes	FRAIL scale	46.2	15.2
Melzelthin et al.[21]	2010		Netherlands	532	59	No	No	GFI / TFI / SPQ		46.3 / 40.2 / 59.1
Song et al.[35]	2010	NPHS	Canada	2740	61	No	No	FI		22.7
Syddall et al.[36]	2010	HCS	UK	642	50	No	Yes	FFI		6.3
Wong et al.[37]	2010	MUNS	Canada	740	68	Yes	No	FFI	49.7	7.4

Abbreviations: ACS, Alameda County Study; CHS, Cardiovascular Health Study; CSHA, Canadian Study of Health and Aging; FFI, Fried Frailty Index; FS, Frailty Scale; MrOS, Osteoporotic Fractures in men Study; 3C, Three-City Study; CHAMP, Concord Health and Ageing in Men Project; SOF, Study of Osteoporotic fractures; TRELONG, Treviso Longeva study; MBS, MOBILIZE Boston Study; ACOVE, Assessing Care of Vulnerable Elders; HEPESE, Hispanic Established Populations for Epidemiologic Studies of the Elderly; SHARE, Survey of Health, Aging and Retirement in Europe; ND, no data; SHLSET, Survey of Health and Living Status of the Elderly in Taiwan; SALSA, San Antonio Longitudinal Study of Aging; ELSA, English Longitudinal Study of Ageing; HMS, Health in Men Study; GFI, Groningen Frailty Indicator; TFI, Tilburg Frailty Indicator; SPQ, Sherbrooke Postal Questionnaire; NPHS, National Population and Health Survey; FI, Frailty Index; HCS, Hertfordshire Cohort Study; MUNS, Montreal Unmet Needs Study.

Subgroup analyses

Definition of frailty
In studies that used physical frailty definitions, the weighted average was 9.9% for frailty (95% CI: 9.6-10.2%; 15 studies; 44,894 participants) and 44.2% for prefrailty (95% CI: 44.2-44.7%; 13 studies; 41,197 participants). The weighted frailty and prefrailty rates were also calculated for studies that applied the broad frailty phenotype. The weighted average prevalence of frailty prevalence in this group was 13.6% (95% CI: 13.2-14.0%; 8 studies; 24,072 participants) and 33.5% had a prefrail state (95% CI: 32.9-34.1%; 4 studies; 19,996 participants).The difference between weighted rates of frailty according to physical phenotype (9.9%) versus broad phenotype (13.6%) was statistically significant (χ^2=217.7, df=1, P< .001).

Sex
The 11 studies that described frailty prevalence according to sex enrolled 17,746 women and 22,596 men. In women, the weighted average prevalence of frailty was statistically significantly higher (9.6%, 95% CI = 9.2–10.0%) than in men (5.2%, 95% CI = 4.9–5.5%; χ^2= 298.9, df =1, P< .001).

Prefrailty prevalence was addressed in six studies involving 10,683 female participants and 17,160 male participants. Prefrailty was more prevalent in women (39.0%, 95% CI = 38.1–39.9%) than in men (37.3%, 95% CI = 36.6–38.0%; χ^2 = 8,629, df = 1, P= .003). Mean age was 75.7 for women and 75.0 for men (t = −33.15, df = 19,877, P< .001; 7 studies; 20,236 participants).

Age
Four studies presented the data according to age group, resulting in increasing prevalence rates according to age (χ^2=6,067, df= 1, P< .001). For two studies, the age groups of 85-89 years and 90 and older had to be combined. Figure 1 shows weighted average rates of frailty overall and for each subgroup.

Figure 1 Prevalence of Frailty and 95% Confidence Intervals

Systematic review of frailty prevalence
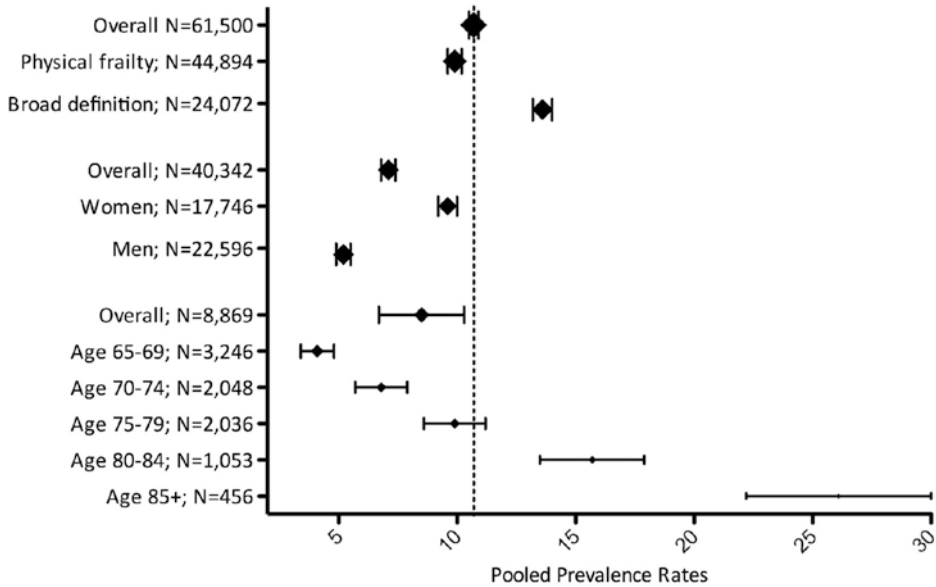
Discussion

Based on 21 cohorts involving 61,500 subjects, on average 10.7% of community-dwelling older persons are frail and another 41.6% prefrail. Nevertheless, the reported prevalence rates differed substantially, ranging from 4.0% to 59.1%.

The range of frailty rates found in the included studies was wide, but arranging the results according to frailty definition reduced this variety. Studies using a physical frailty definition consistently report lower prevalence of frailty than those using a broad frailty definition. Most studies reporting on the physical phenotype of frailty used the original or slightly adjusted FFI as applied in Cardiovascular Health Study CHS, making a comparison of the studies within this group easier. The diversity in frailty criteria of broad frailty definitions thus appears to have contributed to the wide range of prevalence found in literature. Although the broad phenotype of frailty has its roots in Canadian population surveys, it has stimulated researchers around the world to develop their own (broad) criteria for frailty. Therefore, the often-proposed FI of broad phenotype research groups did not dominate among studies applying the broad phenotype.[35, 38]

The smaller range of frailty rates in studies that used a physical frailty definition implies more consensus between researchers searching for physical frailty and or

a more-reliable definition of frailty. These findings argue for the use of a physical definition of frailty, because by employing the narrower but more-consistent physical definition of frailty, comparability of studies will be improved. In the case of a distinct preference for the use of a broad frailty definition, the different aspects within this definition should be examined separately (physical, social, psychological). Not only does this approach provide more information about who needs special care in specific domains, it also enables researchers to examine underlying pathophysiological processes of frailty more accurately.

Another finding is that frailty increases with age. This pattern of increasing frailty prevalence has also been confirmed in previous studies that divided the cohort into age groups. In the present study, the prevalence for the oldest-old persons were 15.7% (aged 80-84) and 26.1% (≥85). This contrasts with prevalence of 40% as estimated by the American Medical Association,[39] which institutionalization of frail older persons in these higher age groups could explain, whereas the current results are community based. Older persons, especially when frail, account for the highest costs in health care in developed countries.[40] This makes it absolutely necessary that policy-makers explicitly state their target population (age group, sex), when applying these rates of frailty.

Women had higher rates of frailty than men. This finding is not unexpected, given that women have lower average amounts of lean body mass and muscle strength.[1] The relationship between frailty and sarcopenia has been confirmed in previous research.[6]

In another study, it was shown that men have a higher likelihood of dying suddenly than women, the latter showing a more-steady, progressive decline.[41] This decline could lead to frailty, providing women with more frailty characteristics.

Another, possible explanation is the longer life expectancy of women. As a result of which the women in the age groups were older than the men. Because frailty increases with age, this could contribute to the differences between the sexes. Only one study mentioned an age difference between men and women.[23]

One of the limitations of this systematic review is that it included slightly more women (51.3%) than men, so the overall prevalence of frailty may be overestimated. The review showed that age in men and women in the studies may not have differed in a clinically significant matter but differed significantly statistically, leading to a potential confounder of the findings in studies that did not correct for age differences between men and women. Nevertheless, women were not overrepresented when

compared with the distribution of older men and women in the community. Because not all studies provided information on sex distribution, it was impossible to control for this difference. Future researchers should be aware of and, if possible, control for differences in age between men and women.

Secondly, the included studies enrolled subjects from different countries. It has been reported that frailty prevalence might be higher in Mexican older adults[32] and among inhabitants of southern European countries.[30] If true, this may have led to an overestimation of the overall frailty prevalence, although the inclusion of studies from Europe, as well as the United States, Australia and Asia, enhances the generalizability of the results. The exclusion of studies from countries with higher prevalence of frailty would have decreased the robustness of the findings.

In conclusion, this systematic review finds that approximately one in 10 independently living adults aged 65 years and older is frail and confirms sex differences.

The aim of the concept of frailty is to predict adverse health outcomes. Previous research showed that two different frailty definitions (a broad and a physical definition) had the same predictive value concerning adverse outcomes, such as falls, hip fracture and death,[13] although the results of this review suggest that the physical definition of frailty leads to a lower estimation of prevalence but is likely more easily comparable between studies that use a physical definition of frailty.

The next step is to recognize frail elderly adults and to prevent adverse outcomes with special multidisciplinary treatments. To enable preventive interventions, it should be clear which frailty characteristics or underlying processes predict each outcome most accurately. Fundamental research therefore not only warrants summary scores or categorical definitions of frailty, but should also consider the separate components and their dimensional aspects. As long as no consensus has been reached about the operationalization of frailty, clinicians and policy-makers should be aware of these differences and should take these differences into account.[7] Consequences of these differences are amount, content, and type of collaborative care projects but also planning of somatic, mental, or integrated healthcare centers. A physical model of frailty should be used in fundamental research and a multidimensional model in studying healthcare organization and planning. Improving the comparability of epidemiological and clinical studies by consensus regarding these two operationalizations of frailty constitutes an important step forward.

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Part II:

Is physical frailty associated with late-life depression?

59

Chapter 4

Physical frailty: vulnerability of patients suffering from late-life depression

Abstract

Objectives- Frailty, a state of increased risk of negative health outcomes, is increasingly recognized as a relevant concept for identifying older persons in need of preventative geriatric interventions. Even though broader concepts of frailty include psychological characteristics, frailty is largely neglected in mental health care. The aim of the present study is to examine the prevalence of physical frailty in depressed older patients and its potential overlap with depression criteria.

Methods- Cross-sectional observational study including 378 older adults with depression according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and 132 non-depressed adults, all aged ≥60 years. Physical frailty was defined as ≥3 out of 5 criteria (handgrip strength, weight loss, poor endurance, walking speed, low physical activity).

Results- Prevalence rates of physical frailty were 27.2% and 9.1% among depressed and non-depressed participants, respectively, which remained significant after controlling for relevant covariates (odds ratio [OR]=2.66 [95% confidence interval [C.I.] =1.36-5.24], p=.004). Physical frailty in depression was associated with more severe depressive symptoms; this association remained significant in subsequent analyses with purely physical proxies for frailty (handgrip strength, walking speed) and different severity measures of depressive symptoms.

Conclusion- A quarter of depressed older patients is physically frail, especially the most depressed group. This cannot be explained by overlap in criteria and should be examined in future studies, primarily on its presumed clinical relevance.

Keywords: depression, frailty, elderly, Netherlands Study of Depression in Older persons (NESDO)

Introduction

Frailty is conceptualized as a state of increased risk of adverse health outcomes, such as falls, reduced mobility, reduced independence, hospitalization, disability and death.[1] The explanation of the increased health risks is sought in a reduction of the reserve capacity of various physiological systems. Frailty is prevalent when the reserve capacity has decreased to a critically low point, where even small disturbances can lead to a series of complications. As this theoretical foundation is not (yet) supported by a clear underlying pathophysiological process, research has led to various operationalizations of frailty and prevalence rates vary widely.[1-3] Among community-dwelling older persons, meta-analysis showed a prevalence rate of frailty of 9.9% for physical frailty and 13.6% for the broader operationalization of frailty.[4] The latter also includes psychological and psychosocial characteristics.

Irrespective of the exact conceptualization of frailty, prospective studies have unequivocally demonstrated a worsening of prognosis of somatic conditions in the presence of frailty.[5, 6] Quite recently, the clinical relevance is further substantiated by several randomized controlled trials, showing that interventions targeted at frailty components, improve health outcomes of frail older persons.[7-10] For example: high-intensity progressive resistance training reduced mortality and nursing home admission after hip fracture surgery.[11] In physically frail older persons, a home-based physical therapy targeted at underlying impairments in physical ability, significantly reduced functional decline.[12] Finally, a home-based self-administered exercise program with protein supplementation led to significantly less decline in walking ability and instrumental activities of daily living.[13]

Although hardly examined, frailty can be assumed to be of special relevance in older persons suffering from psychiatric diseases, especially depressive disorders that are also associated with increased mortality rates and negative health outcomes, such as somatic diseases and increased risk of suicide.[14, 15] However, the disparity between body and mind has probably led to the ignorance of physical frailty in psychiatric patients. Broader concepts of frailty include several psychiatric symptoms next to physical symptoms, thereby not discriminating anymore between them. Empirical data indeed show some overlap between frailty and late-life depression,[16] but also underline that frailty and depression represent distinct syndromes rather than a single construct.[17] To improve treatment of older depressed persons it is important to further study frailty in this specific group.

Objectives
The objective of the present study is to determine the prevalence of physical frailty in depressed older and non-depressed older adults, adjusted for potential confounders.

For this purpose, frailty should be defined in purely physical terms. Therefore, a definition was chosen that did not contain depression as a characteristic of frailty. The definition of Fried and colleagues[1] is widely used in geriatric research and encompasses a physical phenotype of frailty.[1, 3, 18, 19] Nevertheless, as included physical symptoms such as exhaustion, weight loss and slowness, may also be related to depression, we further explored whether the hypothesized association between depression and physical frailty can be explained by shared characteristics.

Methods

Ethics statement

The study was approved by the Ethical Review Board of the VU University Medical Center in Amsterdam. Since this was a multi-center study, the ethical review boards of the other participating institutes approved of the local feasibility of the study, of which the details are described elsewhere.[20] Participants received written and oral information about the study. They had the opportunity to ask questions and it was checked by the research nurses whether the participants understood the consequences of the study. All participants were competent to consent to participation. Written informed consent was obtained from all participants.

The present study was embedded within a prospective cohort study: the Netherlands Study of Depression in Older persons (NESDO).[20] The aims for NESDO are to examine the (determinants of the) course and consequences of depressive disorders in older persons, and to compare the course and determinants of late-life depression with that of early-life depression.

The NESDO sample consists of 378 depressed participants with a current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%), of which 26.5% have two depressive disorders. The comparison group consists of 132 non-depressed participants, aged 60 through 93 years. Persons with a primary diagnosis of dementia, a Mini Mental State Examination score (MMSE) under 18 or an organic or psychotic disorder were excluded, since the course of these persons will be largely determined by the primary disorder. Insufficient mastery of the Dutch language is also an exclusion criterion.[20]

Of the depressed participants, 86.2% was recruited from mental health institutes (both in- and outpatients) and 13.8% from primary care. The non-depressed comparison group was recruited from 14 primary care practices and screened for absence of depression.

All participants underwent a baseline examination at one of the research locations or at the homes of the participants. A questionnaire including several of the written measurement instruments was sent to the homes of the participants prior to the baseline examination and when necessary, the assessment was spread over two appointments.

Measures

Depression

The Composite International Diagnostic Interview (CIDI), version 2.1; life time version was used in order to determine depression classification according to the criteria of DSM-IV and the criteria of the International Classification of Diseases-10 (ICD-10).[21] The CIDI has high validity for depressive disorders.[22] To determine the research DSM-IV diagnosis of current minor depression, questions were added to the CIDI, as in The Netherlands Study of Depression and Anxiety (NESDA).[23]

Severity of depression was measured by the 30-item self-rating Inventory of Depressive Symptomatology (IDS), which has acceptable psychometric properties.[24, 25] IDS sum score (range 0 – 84) was used as a continuous variable. The clinical interpretation of the IDS sum score is as follows: 0–13=normal, 14–25=mild depression, 26–38=moderate depression, 39–48=severe depression and 49–84=very severe depression.[26] Principal component analysis and confirmatory factor analysis of the IDS-SR indicated a three-factor model of which two factors could be optimized with Rasch analyses to function as homogenous measures of depressive symptoms dimensions: the mood/cognition factor and the anxiety/arousal factor (age range 18-65).[27]

Frailty

Frailty was assessed according to the criteria of Fried et al.,[1] which are weight loss, weakness, poor endurance and energy, slowness and low physical activity level. A person is classified as frail when ≥3 criteria are present, classified as prefrail when 1 or 2 criteria are present and classified as robust when none of the criteria are present.

Unintentional weight loss was defined as a positive response on the CIDI question about unwanted weight loss of a minimum of one kilogram a week, during two or more consecutive weeks or a body mass index (BMI) of less than 18.5 kg/ m².

A handgrip dynamometer was used to assess weakness. Participants were asked to perform two squeezes with the dynamometer, using their dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Cutoff scores were stratified by gender and BMI quartiles according to Fried at al.[1] Participants unable to perform the test were also considered weak.

Poor endurance and energy (exhaustion) were determined by two questions from the Center for Epidemiologic Studies-Depression scale (CES-D),[28] similar to other studies[1, 18]: "I felt that everything I did was an effort" and "I could not get going." The items asked "How often in the last week did you feel this way?" and subjects responded on a four-point scale: 0=rarely or never (<1 day), 1=some or a little of the time (1–2 days), 2=a moderate amount of the time (3–4 days), 3=most of the time (5–7 days). Participants answering 2 or 3 to either of these two items were categorized as positive for this item.

Slowness was measured by a six-meter walking test. For men ≤173 centimeters (cm) tall the cutoff time was 9 seconds, for men >173 cm the cutoff time was 8 seconds. The cutoff time on this criterion for women with a height of ≤159 cm was 9 seconds, for women >159 cm the cutoff time was 8 seconds (extrapolated from the data of Fried and colleagues).[1]

Low physical activity level was defined as no daily activities such as walking and gardening, or sports activity less than once weekly. The last-seven-days short form of the self-administered version of the International physical Activities Questionnaire (IPAQ),[29] consisting of seven items, was used to collect the physical activity data. Psychometric properties of the short and long version of the IPAQ are acceptable.[29]

In addition to the syndromal definition of frailty based on the Fried criteria, we also included two unidimensional proxies for frailty based on previous research into physical frailty, i.e. muscle weakness[30] and gait velocity.[31] Muscle weakness was defined as the handgrip strength, as described above. Gait velocity was based on the six-meter walking test, as described above.

Covariates
Demographic data were collected during the interview (age, gender, living circumstances and educational level).

Somatic comorbidity was assessed using a self-report questionnaire about the presence of somatic diseases (lung disease, cardiovascular disease, diabetes, arthritis, rheuma-tism, cancer, ulcer, intestinal disorder, liver disease, epilepsy, allergy, thyroid gland disease and (head) injury), as originally developed by Statistics Netherlands (Centraal Bureau voor de Statistiek, www.cbs.nl). This questionnaire has high accuracy for chronic somatic disease as previously reported.[32]

Global cognitive functioning was assessed by the MMSE.[33] MMSE score (range 0-30) will be measured as a continuous variable, with higher scores indicating better

cognitive functioning. Interrater reliability and test-retest reliability are good.[34, 35]

Statistical analyses

Demographics and clinical characteristics of the participants with and without depression were examined using independent samples t-tests for normally distributed, continuous variables, nonparametric Mann Whitney U tests for skewed continuous variables, and χ^2 tests for categorical variables. The association between physical frailty and depression diagnoses (yes/no) as the dependent variable was subsequently assessed by multivariate logistic regression analysis corrected for age, gender, educational level, living circumstances, number of comorbid somatic diseases and MMSE score.

Multicollinearity was tested by calculating the bivariate correlation coefficient of all pairs of independent variables. These tests showed no multicollinearity problems.

The second objective was evaluated within the depressed subgroup only. Multiple logistic regression analyses were used to investigate the association between severity of depression (independent variable) and physical frailty (dependent variable). First, the variable was tested univariately. Subsequently, the regression analyses were corrected for the following potential confounders: age, gender, educational level, living circumstances, number of comorbid somatic diseases and MMSE score (model 1).

To examine whether overlap in criteria may explain some of the associations, analyses were repeated with different definitions of frailty and depressive symptoms. Frailty was operationalized with two unidimensional proxies for frailty, namely weakness[30] and slowness,[31] as these definitions do not overlap with symptoms of depression.

Severity of depression was included in the model in different ways. First by calculating the IDS sum score excluding all items that overlap with physical frailty (i.e. items 11-14 [appetite and weight change], item 20 [energy level], item 23 [feeling slowed down] and item 28 [physical energy]). Secondly, by the two IDS subscale scores as identified by Wardenaar and colleagues.[27]

All p values were two-tailed, and the level of statistical significance was set at p< .05. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS), version 16.0.

Results

Comparison depressed patients and non-depressed comparison group
The mean age [standard deviation (SD)] of the 510 participants was 70.6 [7.3] years, and 64.9% was female. Table 1 presents the characteristics of both the depressed and non-depressed group.

Table 1 Demographics, Clinical Characteristics and Frailty

Characteristic	Depressed Group (N=378)	Comparison Group (N=132)	P Value[a]
Age, mean (SD)	70.7 (7.4)	70.1 (7.2)	.371
Age, range	60 – 90	60 – 93	
Gender, % female	66.1	61.4	.322
Living alone, %	54.0	34.8	<.001
Education, % low education	79.1	60.6	<.001
MMSE score, mean (SD)	27.6 (2.5)	28.3 (1.6)	<.001
Chronic diseases, mean (SD), no	1.54 (1.21)	1.14 (0.99)	.001
Frailty, %	27.2	9.1	<.001
• Weight loss, %	35.4	3.8	<.001
• Weakness, %	25.1	19.7	.205
• Exhaustion, %	45.8	3.8	<.001
• Slowness, %	26.5	18.9	.084
• Low activity level, %	42.3	34.8	.132
Number of frailty criteria:			<.001
• % 0	15.6	48.1	
• % 1	30.8	32.8	
• % 2	26.3	9.9	
• % 3	18.8	7.6	
• % 4	6.6	1.5	
• % 5	1.6	0.0	

Abbreviation: MMSE, Mini Mental State Examination.
[a] Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables) and U tests (continuous, skewed variables).

Four participants had missing data on one physical frailty criterion (weakness). However, frailty status could be computed based on the four remaining criteria. In order to be classified as frail, three or more out of five criteria had to be present. Two of the

participants with missing data were considered frail (because of 3 out of 4 positive criteria) and two participants were classified nonfrail (because of 0 or 1 positive criteria, respectively).

The prevalence of physical frailty was significantly higher in the depressed group compared to the non-depressed comparison group (27.2% versus 9.1%; χ^2=18.5, df=1, p< .001). Logistic regression analysis, adjusted for age, gender, and all baseline characteristics that differed between both groups (number of somatic diseases, educational level, MMSE score and living status), showed an increased odds ratio (OR) of frailty for depression (OR=2.66, 95% confidence interval [CI] =1.36-5.24, p=.004).

Comparison of frail and nonfrail depressed older persons
Compared to nonfrail depressed older persons (n=275), frail depressed elderly (n=103) were significantly older, had fewer years of education, lower cognitive functioning, more comorbid somatic diseases, and were more severely depressed (Table 2). Including all characteristics in a multivariate logistic regression model with physical frailty (yes/no) as the dependent variable, age (OR=1.10, 95% CI=1.06-1.14, p<.001) and severity of depression (OR=1.07, 95% CI=1.05-1.10, p<.001) were significantly associated with physical frailty in the depressed group.

Table 2 Characteristics of Frail and Nonfrail Depressed Participants

Characteristic	Depressed Participants (N=378)		
	Frail Group (N=103)	Nonfrail Group (N=275)	P Value[a]
Age, mean (SD), y	73.8 (8.0)	69.6 (6.9)	<.001
Female gender	68.9	65.1	.482
Living alone	57.3	52.7	.429
Education, mean (SD), y	9.7 (3.2)	10.7 (3.5)	.008
Cognition (MMSE score), mean (SD)	27.1 (2.5)	27.8 (2.5)	.008
Chronic diseases, mean (SD), no	2.1 (1.5)	1.5 (1.1)	.001
IDS score, mean (SD)	37.2 (12.4)	27.5 (12.3)	<.001

Abbreviations: MMSE, Mini Mental State Examination; IDS, Inventory of Depressive Symptomatology.
[a] Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables) and U tests (continuous, skewed variables).

The proportion of women was equal in both the frail and the nonfrail group ($\chi^2=$ 0.49, df=1, p=.482) (Figure 1). Frailty did increase with age in the depressed group ($\chi^2=25$, df=5, p<.001) (Figure 2). Frailty prevalence between health care setting did not differ significantly ($\chi^2=2$, df=2, p=.407) (Figure 3).

Figure 1 Frailty Prevalence in the Depressed Subgroup
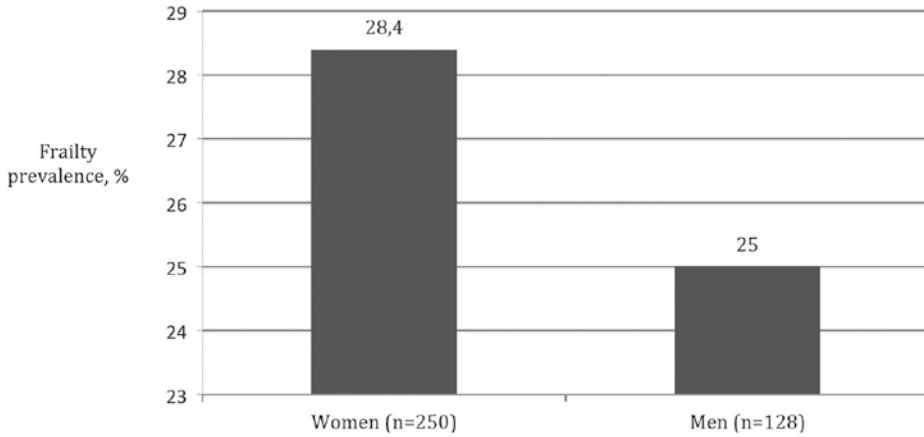
Figure 2 Frailty Prevalence in Depressed Elderly According to Age Groups
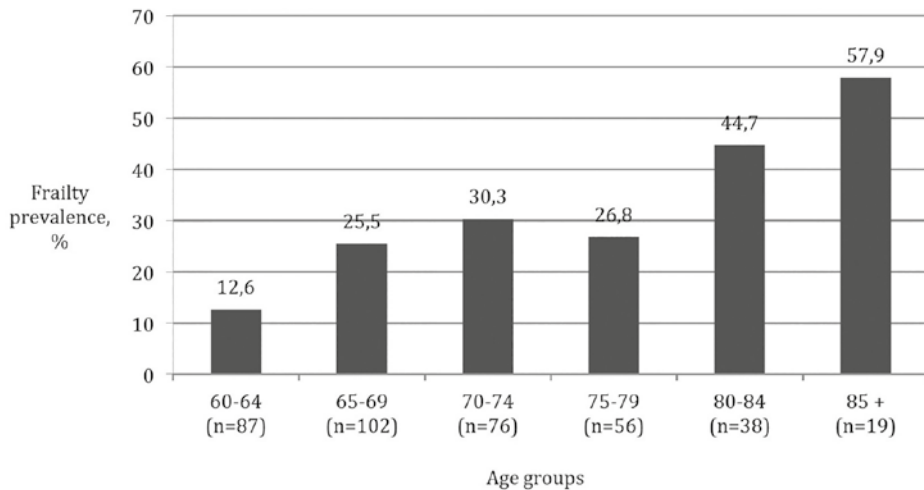
Figure 3 Health Care Setting and Frailty Prevalence in Depressed Elderly
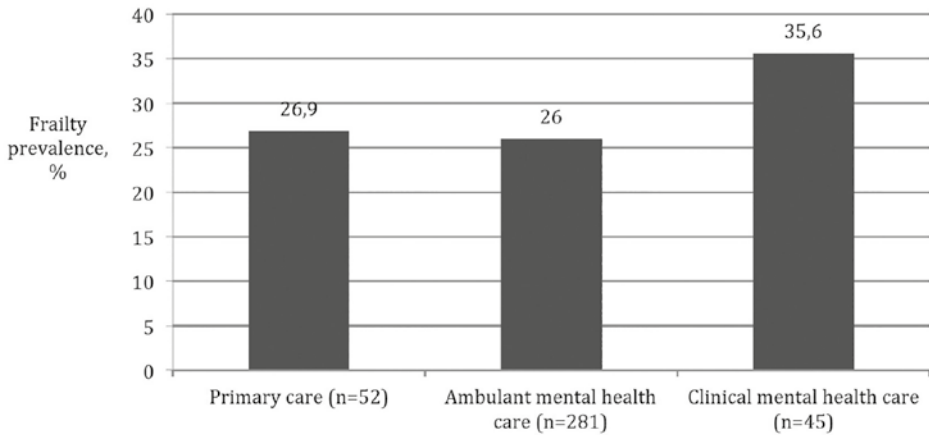
Deconstructing frailty

In order to disentangle the relationship between physical frailty and depression, the analyses were repeated with two unidimensional proxies for frailty: weakness (operationalized as grip strength) and slowness (operationalized as gait velocity). As both variables had a skewed distribution that could not be transformed to a normal distribution and outliers were considered informative (a very low grip strength certainly points to frailty and should not be excluded), analyses were performed on dichotomized scores of cutoff points of both dependent variables. These analyses yielded similar results compared to the analyses using the Fried Frailty Index as indicator for frailty (Table 3).

Deconstructing depression

Since the severity of depressive symptoms was significantly higher among frail depressed elderly compared to their nonfrail counterparts, finally all analyses were repeated using the adapted IDS sum score (without overlapping frailty items) as well as the total scores on two IDS subscales. As shown in Table 4, all measures of depressive symptoms were significantly associated with frailty in depressed patients, irrespective of the used definition of frailty.

Table 3 Association Between Severity of Depression (IDS) and Frailty, Weakness and Slowness in Depressed Persons Aged 60 Years and Older

N=373 Severity of depression	Frailty OR (95% CI)	P Value	Weakness OR (95% CI)	P Value	Slowness OR (95% CI)	P Value
Unadjusted	1.07 (1.05, 1.09)	<.001	1.02 (1.01, 1.04)	.001	1.03 (1.02, 1.05)	<.001
Adjusted[1]	1.07 (1.05, 1.10)	<.001	1.02 (1.00, 1.04)	.025	1.03 (1.01, 1.04)	.005

Abbreviation: IDS, Inventory of Depressive Symptomatology.
[1] Adjusted for age, gender, living circumstances, level of education, number of somatic comorbidities and Mini Mental State Examination (MMSE) score.

Table 4 IDS Adapted Sum Score without Overlapping Frailty Items and Two IDS Subscales Yielded by Factor Analysis[27]: Association with Frailty, Weakness and Slowness (Adjusted for Age, Gender, Living Circumstances, Level of Education, Number of Somatic Comorbidities and MMSE Score)

N=373	Frailty OR (95% CI)	P Value	Weakness OR (95% CI)	P Value	Slowness OR (95% CI)	P Value
IDS adapted sum score	1.08 (1.06, 1.11)	<.001	1.04 (1.01, 1.06)	.005	1.05 (1.02, 1.08)	<.001
IDS subscales						
1. Mood/cognition	1.13 (1.08, 1.19)	<.001	1.05 (1.01, 1.10)	.022	1.08 (1.03, 1.13)	.002
2. Anxiety/arousal	1.21 (1.13, 1.29)	<.001	1.07 (1.01, 1.14)	.028	1.13 (1.06, 1.21)	<.001

Abbreviations: IDS, Inventory of Depressive Symptomatology; MMSE, Mini Mental State Examination.

Discussion

With an overall prevalence of 27.0%, the prevalence of physical frailty was significantly higher among depressed compared to non-depressed older persons. Higher age and severity of depression were independently associated with physical frailty in depressed older adults.

This raises the question whether depressed frail persons might have inflated depressive symptom scores (due to the shared characteristics of both syndromes). Therefore, the construct of depression was decomposed (using the IDS sum score without items that might overlap with physical frailty, as well as using IDS subscale scores) and different measures of frailty were used (weakness and slowness). These analyses, however, still revealed a significant association between all measures of depressive symptom severity and all measures of frailty. It is thus unlikely that the higher severity of depressive symptoms in frail compared to nonfrail depressed older persons can be explained by shared characteristics.

A review on the relationship of depression and frailty in later life suggests that depression and frailty might be bi-directionally related.[36] Included studies, however, neither measured depression according to state-of-the-art diagnostic criteria nor considered the use of antidepressants.[36] Another recent study found that depressive symptoms as well as antidepressant drug use were indeed associated with frailty after three years of follow-up.[37] Indirect evidence points to several explanations for the association between physical frailty and the severity of depressive symptoms in late-life depression. First, it may be hypothesized that severely depressed patients are more prone to developing frailty by both lifestyle factors associated with depression (inactivity and non-compliance of medication in case of somatic comorbidity), as well as physiological disturbances associated with depression (for example hypo- and hyper-cortisolemia affecting the endothelium or autonomic nervous system disturbances[38]). Secondly, frailty may result in a more severe depressed state due to its association with chronic somatic diseases and functional limitations. At population level, depression is more strongly associated with consequences of chronic disease than with the disease.[39] We a priori chose to include only somatic comorbidity as a confounder, because of the risk of overcorrecting. Nevertheless, additional adjustment for functional limitations (as assessed with the WHO-Disability Assessment Schedule[40]), yielded similar results to the analyses with somatic comorbidity only (data available on request). A third explanation may be common underlying processes, related to both frailty and depression. Low-grade inflammation, for example, is generally considered one of the underlying mechanisms of both frailty[41] and late-life depression.[42, 43]

Irrespective of the mechanisms by which frailty and late-life depression are related, late-life depression with comorbid frailty is challenging in clinical practice. First, an older person with frailty can easily be misclassified as suffering from a depressive disorder during a period of (physiological) low mood. Such a person may inappropriately receive antidepressant drugs and may be withhold appropriate strategies to prevent negative health outcomes, associated with frailty. Secondly, although not examined yet, it is possible that treatment of depression among frail older persons benefits from adapted treatment strategies. In somatic conditions it has already been shown that the optimal treatment needs to be different for frail and for nonfrail persons.[44] Nursing health promotion, proactively provided to frail older adults, increases quality of life and reduces depressive symptoms of frail older persons, while not increasing the overall healthcare costs.[45] The benefits of integrated, multidisciplinary geriatric care have been determined in several studies.[46-48] Frailty highlights the need to individualize and integrate guidelines for treatment, and to prevent adverse outcomes by choosing health care interventions fit for such frail elderly.[49] By differentiating between frail and nonfrail elderly, it will be easier to treat frail older adults with the appropriate, multidisciplinary interventions. Such treatment opportunities seem especially important in late-life depression with comorbid frailty, as lifestyle is supposed to be the greatest contributor to the onset of frailty[50] and late-life depression negatively affects lifestyle behavior.[51, 52]

Methodological considerations

Some strengths and limitations of this study should be mentioned. A major strength of this study is the use of two proxies for physical frailty (weakness and slowness) in addition to a multi-component measure of frailty.[1] Furthermore, where other studies use questionnaires as a substitute for depression diagnosis, this study used a formal diagnosis of depression according to DSM-IV criteria. Decomposing of the severity of depressive symptoms makes it unlikely that the higher severity of depression can be explained by overlapping concepts. Finally, since participants were recruited from primary care as well as in- and outpatient secondary care clinics, our sample covers the whole spectrum of depressive disorders, varying from mildly depressed, independent living older adults to severely depressed inpatients. This enhances the generalizability of the results, specifically the second aim of the study. Interestingly, frailty prevalence did not differ across the different echelons of our health care system.

A limitation of the study was the small size of the 85+ group. Therefore, specific conclusions about this generally frail subgroup cannot be drawn. Furthermore, the comparison group was recruited among non-depressed general practice visitors, who can be assumed to have more illnesses and medical complaints than community-dwelling elderly. The difference between depressed and non-depressed persons in

our study should thus be considered conservative. On the other hand, the found prevalence rates of frailty in our comparison group resembled those found in a recent meta-analysis on the prevalence of frailty in community-dwelling elderly[4] suggesting no or only limited selection bias.

Finally, this study provides the opportunity of adequate control of potential confounders, but it cannot be ruled out that the association between physical frailty and depression is confounded by unknown variables. Moreover, the cross-sectional nature of our study precludes causal interpretation of the association demonstrated.

Future perspective
The high prevalence of physical frailty among depressed elderly persons and potential benefits of targeting frailty argues for the need of screening of this particularly vulnerable group of persons. As frail depressed older patients were more severely depressed than nonfrail depressed patients, it may be required that especially the frail subgroup should be treated in secondary mental health care in which integrative geriatric care is more likely to be available. Future research should examine underlying mechanisms and consequences of frailty in late-life depression, as well as effectiveness of screening for frailty. Multidisciplinary interventions focused on lifestyle and behavioral activation to reduce the negative impact of frailty within this particularly vulnerable group of patients, should also be examined.

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Chapter 5

The role of frailty in the association between depression and somatic comorbidity: results from baseline data of an ongoing prospective cohort study

Published
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Abstract

Background- Depression and physical frailty in older persons are both associated with somatic diseases, but are hardly examined in concert.

Objectives- To examine whether depression and physical frailty act independently and/or synergistically in their association with somatic diseases.

Design- Baseline data of an ongoing observational cohort study including depressed cases and non-depressed comparison subjects.

Settings- Netherlands Study of Depression in Older persons (NESDO).

Participants- 378 depressed older persons confirmed by the Composite International Diagnostic Interview (CIDI), version 2.1, and 132 non-depressed comparison subjects.

Methods- Multiple linear regression analyses adjusted for socio-demographic and lifestyle characteristics were conducted with the number of somatic diseases as the dependent variable and depression and physical frailty as independent variables. Physical frailty was defined as ≥3 of the following characteristics, slowness, low physical activity, weight loss, exhaustion, and weakness.

Results- Depression and physical frailty did not interact in explaining variance in the number of somatic diseases (p=.57). Physical frailty, however, partly mediated the association between depression and somatic diseases, as the strength of this association decreased by over 10% when frailty was added to the model (B=0.47, p=.003, versus B=0.41, p=.01). The mediation effect was primarily driven by the frailty criterion exhaustion. Of the remaining frailty components, only slowness was associated with the number of somatic diseases; but this association was fully independent of depression.

Conclusions- Our results suggest that depression and physical frailty have common pathways towards somatic diseases, as well as unique pathways. As no high-risk group was identified (no significant interaction), mental health nurses should regularly monitor for physical frailty within their caseload of depressed patients.

Keywords: depression, frailty, aged, somatic diseases, Netherlands Study of Depression in Older persons (NESDO)

Introduction

Depression not only deteriorates the symptom burden of chronic somatic diseases, but also places persons at higher risk of new-onset somatic diseases like cardiovascular diseases, diabetes, overweight, and even cancer.[1] The wide range of somatic consequences of depression, as well as an increasing strength of these associations in later life, suggest common underlying mechanisms associated with accelerated aging.[2, 3] Several explanations for the relationship between depression and somatic comorbidity can be put forward, such as an unhealthy lifestyle, non-compliance to treatment in case of existing somatic diseases, as well as physiological dysregulations like overactivity of the hypothalamic-pituitary-adrenal axis, autonomic nervous system dysregulation, and immune activation.[1, 4] Interestingly, many of these explanations are also thought to be the basis of frailty. Frailty is a condition of increased risk of adverse health outcomes.[5] This risk is presumed to be caused by a reduction of the reserve capacity of various physiological systems, due to declines in molecular, cellular and physiological systems of the aged body.[6] Negative consequences of depression, such as somatic comorbidity, may thus occur as a result of the development of frailty.

Depression, frailty and somatic morbidity are highly prevalent in later life, and their mutual relationship is complex. Meta-analytic studies have estimated that 10.7% in community dwelling elderly aged 65 and over meet the criteria for frailty[7] and between 1.8% and 9.3% for major depressive disorder.[8, 9] Empirical data have shown that although frailty and depression share overlapping characteristics, both represent distinct syndromes.[10] Similar to the bidirectional association between depression and somatic diseases, a recent review also pointed to a potential bidirectional association between depression and frailty.[11] Interpretation remains difficult as all studies in this review relied on depression severity scales (prone to confounding by frailty) instead of formal diagnostic criteria.

Up until today, no research has been conducted into the triangle depression – frailty – somatic morbidity. In order to prevent somatic morbidity, knowledge of the interplay between depression and physical frailty is crucial. In outpatient mental health care, specialized nurses generally care for the most vulnerable patients among which those with chronic depression, frailty, physical disabilities and unhealthy lifestyle. Mental health care nurses who care for depressed elderly are very capable of detecting frailty and monitoring the development of frailty.[12, 13] Moreover, effective frailty interventions to date are usually based on nursing skills, such as assistance in daily living and improving exercise frequency.[14]

In this study, we first aimed to confirm that somatic diseases are more prevalent among depressed patients, compared to non-depressed controls. Secondly, assuming several

physiological pathways potentially underlie both frailty and depression, we hypothesize that frailty is an explanatory factor (in statistical terms a mediator) of the association between depression and somatic disease. Furthermore, we will also explore a moderating effect of frailty that might be explained by a reinforcing effect of two underlying pathways when depression and physical frailty occur simultaneously. In order to avoid contamination between frailty and depression, frailty will be defined as physical frailty, as done by the frequently used Fried Frailty Index (FFI) of Fried et al.[5]

Methods

Study participants came from NESDO (the Netherlands Study of Depression in Older persons). This cohort study consists of 378 depressed patients with a current DSM-IV diagnosis of major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%), of which 26.5% have two depressive disorders, and 132 non-depressed participants, aged 60 through 93 years.[15]

Recruitment of depressed participants took place in five regions in the Netherlands. Participants were recruited from mental health institutes (both in- and outpatients) and from primary care, in order to include persons with late-life depression in various developmental and severity stages.[15] The non-depressed comparison group was recruited from primary care practices.

Persons with a clinical diagnosis of dementia, a Mini Mental State Examination score (MMSE) under 18 or an organic or psychotic disorder were excluded, since the course of depression in these persons will be largely determined by the primary disorder. Insufficient mastery of the Dutch language was also an exclusion criterion.

All participants received written and oral information about the study and were competent to consent to participation. Written informed consent was obtained from the participants. The ethical review boards of the participating institutes approved of this study.

All participants underwent a baseline examination at one of the participating clinics or at the homes of the participants. This examination included an interview with internationally accepted, frequently used measures, among which measures of demographic variables, depression, somatic comorbidity and physical tests such as gait speed. Trained research professionals, mainly consisting of mental health care nurses and psychologists, conducted all interviews and physical examinations. Details of NESDO are described elsewhere.[15]

Measures

Depression

The Composite International Diagnostic Interview (CIDI), version 2.1 was used in order to determine the presence of depression.[16] The CIDI is a structured interview that diagnoses psychiatric disorders in adults according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the criteria of the International Classification of Diseases-10 (ICD-10). The CIDI has high validity for depressive and anxiety disorders.[17, 18] To determine the research DSM-IV diagnosis of current minor depression, questions were added to the CIDI, as in Netherlands Study of Depression and Anxiety (NESDA).[19] Severity of depression was measured by the well-validated 30-item self-rating Inventory of Depressive Symptomatology (IDS).[20]

Somatic comorbidity

Somatic comorbidity was assessed by Statistics Netherlands (Centraal Bureau voor de Statistiek, www.CBS.nl) questionnaire: a self-report questionnaire about the presence of chronic diseases. In order to enhance its reliability, the questionnaire was conducted by the interviewers. Compared to general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate and independent of cognitive impairment.[21] We used the number of reported diseases (not necessarily under treatment) as a continuous variable. This variable included the following diseases or disease categories: lung disease (asthma, chronic bronchitis, pulmonary emphysema), cardiovascular disease (cardiac events, heart failure, heart infarction, cardiac arrhythmia, coronary heart disease, angina pectoris, vascular abnormalities), stroke, diabetes, arthritis/rheumatism (osteoarthritis, rheumatism), gastro intestinal disease (ulcer, irritable bowel syndrome, Crohn's disease, colitis ulcerosa, constipation), cancer, epilepsy and thyroid disease. Presence of separate diseases/categories was dichotomized (by present yes/ no).

Frailty

Physical frailty was operationalized by the criteria of Fried et al.[5] Conform these criteria physical frailty is present if three out of the following five criteria are met: 1) slowness, 2) low physical activity, 3) weight loss, 4) exhaustion, and 5) weakness. In this study, we included frailty as a dichotomized variable and as a dimensional variable based on the number of criteria present (range 0 – 5).

Slowness was measured by a six meter walking test. For men ≤173 centimetres (cm) tall the cutoff time was 9 seconds, for men >173 cm the cutoff time was 8 seconds. The cutoff time for this criterion for women with a height of ≤159 cm was 9 seconds, for women >159 cm the cutoff time was 8 seconds (extrapolated from the data of Fried and colleagues).[5]

Low physical activity level was defined as no daily activities such as walking and gardening, or the performance of sports less than once weekly. The last-seven-days self-administered version of the International Physical Activities Questionnaire (IPAQ),[22] consisting of eight items, was used to collect the physical activity data.

The presence of unintentional weight loss or low body mass index was used for the weight loss criterion. The CIDI question about unwanted weight loss was used to determine the loss of a minimum of one kilogram a week, during two or more consecutive weeks. BMI was defined as weight in kilograms divided by height in meters squared. With a BMI of $<18,5$ kg/ m^2 weight loss was also considered to be present.

Exhaustion (poor endurance and energy) was determined by two questions from the Center for Epidemiologic Studies-Depression scale (CES-D),[23] similar to other studies[5, 24-27]: "I felt that everything I did was an effort" and "I could not get going." The items asked "How often in the last week did you feel this way?" and subjects responded on a four-point scale: 1=rarely or never (<1 day), 2=some or a little of the time (1–2 days), 3=a moderate amount of the time (3–4 days), 4=most of the time (5–7 days). Participants answering 3 or 4 to either of these two items were categorized as positive on this criterion.

A handgrip dynamometer was used to assess muscle weakness. Participants were asked to perform two squeezes with the dynamometer, using the dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Cutoff scores were stratified by gender and BMI quartiles according to Fried et al.[5] Participants unable to perform the test were also considered weak.

A total of four participants (3 depressed, 1 non-depressed) had missing data on one frailty criterion (weakness criterion) and were excluded from analyses with frailty as a dimensional characteristic. Nonetheless, the dichotomised frailty status could be classified based on the available criteria.[28]

Covariates
Potential confounders were selected a priori, based on their relationship with depression or frailty as well as with somatic diseases in general[29] and included socio-demographic variables,[9, 30] and lifestyle characteristics.[31]

Demographics data were collected during the interview (age, gender, partner status and educational level).

Lifestyle variables included smoking status, use of alcohol, physical exercise and BMI. Smoking status was divided into two categories: non-smoker and current smoker. The Alcohol Use Disorder Identification Test (AUDIT) is designed to detect hazardous and harmful alcohol consumption.[32] AUDIT score was divided into three categories, no alcohol use, moderate alcohol use and problematic alcohol use. These categories were based on the first two questions assessing the frequency drinking and the number of units taken on a typical drinking day. Physical exercise was measured with the IPAQ,[22] by calculating energy expenditure based on sports and daily activities in MET minutes/week. METs are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed. Missing values in the IPAQ questionnaire were imputed by mean scores of age-sex stratified samples (n=90).

Statistical analysis

Demographics and clinical characteristics of the participants with and without depression were compared using independent samples t-tests for normally distributed, continuous variables, nonparametric Mann Whitney U tests for skewed continuous variables, and χ^2 tests for categorical variables.

Multiple linear regression analyses were conducted to examine associations of the number of somatic diseases (dependent variable) with depression (independent variable) adjusted for socio-demographic variables (age, gender, educational level, partner status, income) and lifestyle factors (smoking status, alcohol use, BMI, and physical exercise). First, we checked whether the associations between depression and somatic comorbidity were dependent on frailty by including interaction terms between frailty and depression in the fully adjusted models. We tested both, frailty as a dichotomous characteristic (present yes/no) and as a dimensional variable based on the number of criteria present. A significant interaction term between depression and frailty (yes/no) implies that the association between depression and somatic diseases is different in patients with and without frailty. In case of a significant interaction term with the number of frailty criteria present, the association between depression and frailty differs among the different levels of frailty. Subsequently, it was tested whether frailty was an explanatory factor in the association between depression and somatic diseases by assessing whether B decreased with 10% or more when adding frailty to the fully adjusted model.

Subsequently, we performed in-depth analyses to examine whether identified effects were driven by individual frailty criteria as well as whether frailty effects could also be identified in explaining the presence of individual somatic diseases. First, we analyzed

components of frailty in a linear regression analysis with the number of somatic diseases as the dependent variable and depression as the independent variable, in the fully adjusted model. Next, we assessed whether depression was associated with individual diseases (disease present yes/no) with logistic regression analysis with disease category as the dependent variable and depression as the independent variable. Only diseases that differed (in the unadjusted analysis) between depressed and non-depressed participants were analyzed. Frailty (both dichotomized and continuous frailty) was evaluated as an explanatory factor of the association between depression and type of somatic disease.

All p-values were tested two-tailed and p values ≤.05 were considered statistically significant. Data were analysed using Statistical Package of the Social Sciences (SPSS), version 20.0.

Results

The mean age [standard deviation (SD)] of the 510 participants was 70.6 [7.3] years, and 64.9% was female. Table 1 presents the characteristics of both the depressed and non-depressed group. The two groups differed significantly with respect to educational level, partner status, prevalence of frailty, smoking status, depression severity, physical activity and somatic disease burden. Depressed persons suffered from more somatic diseases than the non-depressed persons. Regarding the type of disease, the two groups differed with respect to lung disease, stroke and gastrointestinal disease.

Associations between depression, frailty and somatic diseases
Multiple regression analyses adjusted for socio-demographic and lifestyle characteristics showed that the number of somatic diseases (dependent variable) was associated with depression (B (SE)=0.47 (0.16); p=.003) as well as with frailty (presence of frailty: B (SE)=0.64 (0.17); p<.001; frailty dimensional: B (SE)=0.27 (0.06), p<.001). Moreover, multiple logistic regression analyses adjusted for socio-demographic and lifestyle characteristics also revealed that depression (dependent variable) was significantly associated with frailty (presence of frailty: OR=2.9 [95% CI: 1.3–6.7], p=.012; frailty dimensional: OR=2.2 [95% CI: 1.6–2.9]. p<.001).

Table 1 Sample Characteristics And Differences Between Amount and Type of Somatic Diseases

Characteristic	Depressed Group (N=378)	Comparison Group (N=132)	P Value[a]
Age, mean (SD), y	70.7 (7.4)	70.1 (7.2)	.371
Female gender, %	66.1	61.4	.322
Married or with partner, %	52.4	75.0	**< .001**
Education, mean (SD), years	10.4 (3.4)	12.5 (3.5)	**< .001**
Frailty, %	27.0	9.1	**< .001**
Smoking, %			**< .001**
Non smoker	29.9	31.8	
Former smoker	42.9	59.8	
Smoker (<20)	19.3	6.8	
Heavy smoker (≥20)	7.1	1.5	
Alcohol use, %			**< .001**
No alcohol use	39.7	12.9	
Moderate alcohol use	50.5	63.6	
Problematic alcohol use	8.7	20.5	
IDS score, mean (SD)	30.1 (13.0)	7.8 (6.4)	**< .001**
BMI, mean (SD)	27.0 (4.6)	26.3 (4.1)	.138
Physical exercise: MET minutes/week, mean (SD)	2391 (2460)	3324 (2909)	**< .001**
Walking speed, s/6m	7.7	6.9	**.025**
Handgrip strength, kg	27.2	30.2	**.007**
Chronic diseases, mean (SD)	2.1 (1.5)	1.5 (1.1)	**.001**
Type of disease, %			
Lung	15.3	7.6	**.023**
Cardiovascular	29.9	24.2	.215
Stroke	11.4	2.3	**.002**
Diabetes	12.7	18.2	.119
Arthritis/rheumatism	52.4	47.7	.343
Cancer	19.6	18.9	.863
Gastro-intestinal	14.0	6.8	**.029**
Epilepsy	1.3	0.0	.184
Thyroid	10.3	6.1	.143

Abbreviations: IDS, Inventory of Depressive Symptomatology; BMI, Body Mass Index.
[a] Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables) and U tests (continuous, skewed variables).

Frailty as a moderating factor
Whether the association between depression and number of somatic diseases was dependent on frailty status, was examined by adding the interaction term of depression by frailty to the fully adjusted linear regression models. Depression neither interacted with the presence of frailty (yes/no) (p=.57), nor with the number of frailty components present (p=.25).

Frailty as an explanatory factor
In order to examine whether frailty was an explanatory factor of the association between depression and somatic diseases, frailty was added to the different (fully adjusted) regression models that regarded the association between depression and somatic diseases (Table 2, models 2a through 2g). Adding the presence of physical frailty (yes/no) to the linear regression model reduced the association between depression and somatic diseases by 14.7%, indicating that frailty explained a substantial part of the association between depression and somatic diseases. Nonetheless, the association between depression and somatic diseases remained significant, indicating an association between depression and somatic diseases independent of frailty. Comparable effects were found when frailty was added as a continuous variable.

In-depth analyses
Only the frailty criteria "exhaustion" and "slowness" were associated with the number of somatic diseases. In the depressed group 45.8% reported exhaustion and 26.5% was slow, compared to 3.8% and 18.9% respectively in the non-depressed group. Of these two criteria, exhaustion mediated the association between depression and somatic diseases, whereas the effect of slowness was fully independent of the presence of depression (Table 2).

With regard to individual categories of somatic diseases, only lung disease, stroke and gastro intestinal disease were univariately associated with the presence of depression (Table 1). After adjustment for potential confounders, however, only stroke remained significantly associated with depression in our study (Table 3). Subsequently, we tested whether this association was mediated by frailty. However, the presence of frailty (yes/no) was not identified as an explanatory factor in the relation between depression and stroke (Table 3). Nonetheless, when frailty was entered as a continuous variable, it was an explanatory factor of the association between depression and stroke (Table 3).

Table 2 Depression and Frailty as Determinants of the Total Number of Somatic Diseases [a]

N=510	B(SE)	Beta	P Value	ΔB
Model 1[b]:				
- Depression	0.484 (0.161)	.15	**.003**	
Model 2a[c]:				
- Depression	0.413 (0.159)	.13	**.010**	- 14.7%
- Frailty (yes/no)	0.590 (0.166)	.17	**.001**	
Model 2b[c]:				
- Depression	0.333 (0.163)	.10	**.041**	- 31.2%
- Number of frailty components	0.243 (0.061)	.21	**.001**	
Model 2c[c]:				
- Depression	0.473 (0.165)	.14	**.004**	- 2.3%
- Frailty: Weight loss criterion	-0.003 (0.150)	< -.01	.983	
Model 2d[c]:				
- Depression	0.485 (0.161)	.15	**.003**	+ 0.2%
- Frailty: Handgrip strength criterion	0.191 (0.158)	.06	.225	
Model 2e[c]:				
- Depression	0.254 (0.167)	.08	.129	- 47.5%
- Frailty: Exhaustion/ poor energy criterion	0.552 (0.140)	.18	**.001**	
Model 2f[c]:				
- Depression	0.467 (0.158)	.14	**.003**	- 3.5%
- Frailty: Slowness criterion	0.632 (0.161)	.19	**.001**	
Model 2g[c]:				
- Depression	0.474 (0.160)	.14	**.003**	- 2.1%
- Frailty: Low activity level criterion	0.105 (0.149)	.04	.481	

[a] Multiple linear regression analyses with number of somatic diseases as the dependent variable, adjusted for age, sex, years of education, partner status, average income, smoking status, alcohol consumption, physical activity and body mass index.
[b] Model 1: Association between depression and the number of somatic diseases.
[c] Model 2: Independent effect of depression and frailty (different definitions) added simultaneously in one linear regression analyses with the number of somatic diseases as the dependent variable.

Table 3 Depression and Frailty as Determinants of Individual Somatic Disease Categories[a]

N=510	OR (95% C.I.)	B	P Value	ΔB
Lung disease				
Model 1[b]:				
- Depression	0.50 (0.21, 1.22)	-0.687	.130	
Stroke				
Model 1[b]:				
- Depression	0.29 (0.08, 1.00)	-1.255	**.049**	
Model 2[c]:				
- Depression	0.34 (0.10, 1.23)	-1.068	.100	- 14.9%
- Number of frailty components	1.30 (0.97, 1.76)	0.264	.083	
Gastro-intestinal disease				
Model 1[b]:				
- Depression	0.45 (0.19, 1.05)	-0.802	.065	

[a] Multiple logistic regression analyses with type of somatic disease as the dependent variable, adjusted for socio-demographic and lifestyle characteristics.
[b] Model 1: Adjusted association of depression (independent variable) and type of somatic disease
[c] Model 2: Independent effect of depression and frailty when added simultaneously in one logistic regression analyses with the type of somatic disease as the dependent variable.

Discussion

As expected, somatic diseases were more prevalent among depressed patients than in the non-depressed comparison group.[33, 34] Confirming our hypothesis, an accumulation of frailty characteristics, such as the frailty criteria of Fried et al.[5] indeed partly explained the relation between depression and the number of somatic diseases. Since depression and frailty remained associated with the number and presence of somatic diseases, independently of each other, our results imply that depression and frailty have common relations with somatic diseases as well as unique relations. As frailty did not moderate the relation between depression and somatic diseases (interaction), the presence of frailty does not aggravate the negative health effects already associated with the depression itself.

Frailty as explanatory factor
Although physical frailty defined by the criteria of Fried et al.[5] partly explained the association between depression and somatic diseases, this effect was primarily driven by the criterion "exhaustion". This is not surprising, as the operationalization of the criterion is based on two items of a depression severity scale, i.e. the CES-D. This

overlap between operationalization of frailty and depression probably explains its mediating effects (in clinical terms). Even attempts to define frailty in pure biomedical terms thus still overlap with depression, stressing the need to measure both mental illness and frailty simultaneously when trying to evaluate long-term negative health outcomes. This approach can help us disentangle unique effects of depression and frailty.

The fact that of the other four frailty criteria, only slowness (or gait speed) was associated with the number of somatic diseases is an interesting finding. This association was completely independent from the presence of depression, implying that gait speed does have underlying pathophysiological mechanisms leading to somatic diseases or vice versa, which are different from mechanisms associated with depression. Gait speed as well as handgrip strength are the only two performance-based frailty criteria, and both have also been used as simplified measures of frailty in other studies.[35, 36] Our results suggest that when studied in concert with depression, gait speed may be preferred to disentangle the relationship between frailty, depression and somatic diseases. Interestingly, gait speed can be quantified as done in our study, but mental health nurses can also easily observe gait speed. These observations and especially changes in gait speed, may trigger nurses for further assessment and treatment.

The discussion about how frailty should be operationalized is ongoing.[7] When interested in pathophysiological mechanisms that are involved in both depression and physical frailty, the FFI can be used, but a simple measure of "vital exhaustion" may be even better. The pathophysiological mechanisms underlying vital exhaustion probably explain the shared impact of depression and frailty with respect to the negative health outcomes. This is in line with findings from a recent review, where it was stated that atypical depression, that is characterized by exhaustion, is more related to biological dysregulations than the melancholic subtype of depression.[1] Both the depression and the biological dysregulations may lead to somatic health decline.[1] The shared pathway may lead to the hypothesis that shared mechanisms may fully account for the negative health effects of depression. Nonetheless, this seems unlikely, as depression also remained independently associated with the number of somatic diseases and it has been shown before that the relation between depression and frailty is not fully explained by overlap between these two syndromes.[28]

Clinical relevance
Depression is a highly prevalent condition among elderly and recurrence or relapse are not uncommon.[37] Since frailty is a potentially reversible factor,[29] of which the negative health impact can be reduced by specific interventions, assessment of frailty in depression is relevant for clinical practice. The other way around, somatic comorbidity is often accompanied by depression and in those cases associated

with increased levels of disability.[38] Nurses are particularly likely to be caring for persons with chronic somatic diseases[39] and their work also requires knowledge of depression and frailty as well as their reciprocal relations with somatic diseases. Better recognition of frailty in older patients suffering from depression and/or chronic somatic conditions by nurses is also important, as nurse-led health promotion to frail older persons enhances quality of life, while not increasing the overall health care costs.[12, 14] This implies the need for a constant state of alertness towards the severity of frailty in depressed patients by nurses treating depressed elderly. Regarding this, it is noteworthy that simple screening tools for daily practice are available to confirm the presence of frailty.[40]

Strengths and weaknesses
Some strengths and limitations of this study have to be mentioned in order to allow proper interpretation of the results. Whereas other studies use questionnaires as a substitute for depression diagnosis, this study used a formal diagnosis of depression according to DSM-IV criteria. This is an important strength of our study as formal criteria of depression are less prone to confounding by symptoms or signs of somatic diseases and frailty compared to (self-report) questionnaires assessing depressive symptoms. Furthermore, our findings also point to the importance of physical frailty within a psychiatric sample. Since participants were recruited from primary care as well as in- and outpatient secondary care clinics, this sample covers a large spectrum of depressive disorders. The fact that we did not find strong results for one or two specific chronic diseases, adds to our hypothesis of general underlying pathways relating depression and frailty towards different somatic comorbidity. Nonetheless, we must acknowledge that due to low prevalence rates of some of the individual diseases, statistical power is probably too low for more definitive conclusions. Another limitation might be that somatic diseases were assessed by a self-report measure which may have led to bias, however previously the reliability of this questionnaire has shown to be adequate.[21]

Finally, as with any cross-sectional design it is not appropriate to draw causal conclusions. The relation between depression, frailty and somatic comorbidity is a complicated one, with reciprocal associations between all entities, and possibly other factors influencing these associations. Therefore, the relation between depression, frailty and somatic comorbidity should be further examined in prospective designs.

Final conclusion
This study confirms the relation between depression and somatic comorbidity. Frailty partly explains this relationship, but depression also remains an independent determinant of the somatic condition. As the prevalence of frailty is almost three times higher

among depressed older persons compared to non-depressed older persons,[28] our findings argue for integral assessment of frailty in depressed older persons and mental health nurses should regularly monitor for physical frailty within their caseload of depressed patients. Analogue to the impact of frailty on the course of somatic diseases [41, 42] the presence of frailty in depression probably also complicates the course and treatment of late-life depression. This, however, should be subject to further study, as well as future projects examining whether the effects of (nurse-led) interventions to prevent or reduce frailty in depressed older adults indeed improves both depression outcome and the negative health effects of depression.

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Chapter 6

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

Abstract

Objectives- To determine whether physical frailty is associated with low-grade inflammation in older adults with depression, because late-life depression is associated with frailty and low-grade inflammation.

Design- Baseline data of a cohort study.

Setting- Primary care and specialized mental health care.

Participants- Individuals aged 60 and older with depression according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (N=366).

Measurements- The physical frailty phenotype, defined as three out of five criteria (weight loss, weakness, exhaustion, slowness, and low physical activity level), and three inflammatory markers (C-reactive protein (CRP), interleukin-6 (IL-6) and neutrophil gelatinase-associated lipocalin (NGAL) were assessed.

Results- The physical frailty phenotype was not associated with inflammatory markers in linear regression models adjusted for sociodemographic charateristics, lifestyle characteristics and somatic morbidity. Of the individual criteria, handgrip strength was associated with CRP (β=-0.21, p=.002) and with IL-6 (β=-0.25, p<.001), and gait speed was associated with NGAL (β=0.15, p=.02). Principal component analysis identified two dimensions within the physical frailty phenotype: performance-based physical frailty (encompassing gait speed, handgrip strength and low physical activity) and vitality-based physical frailty (encompassing weight loss and exhaustion). Only performance-based physical frailty was associated with higher levels of inflammatory markers (CRP: β=0.14, p=.03; IL-6: β=0.13, p=.060; NGAL: β=0.14, p=.03).

Conclusion- The physical frailty phenotype is not a unidimensional construct in individuals with depression. Only performance-based physical frailty is associated with low-grade inflammation in late-life depression, which might point to a specific depressive subtype.

Keywords: frailty, depressive disorder, inflammation, C-reactive protein, interleukin-6, lipocalin-2, NGAL.

Introduction

Frailty is a medical syndrome describing persons at greater risk of adverse health outcomes when exposed to a stressor.[1] Frailty is considered an important syndrome for geriatric health care, because frail persons are high users of community resources, hospitalization, and nursing homes. Therefore, early intervention may improve quality of life and reduce costs of care.[1] The mean prevalence rate of physical frailty is estimated 9.9% in community-dwelling persons aged 65 and older (range 4.0–17.0%).[2]

Although the criteria for physical frailty and depression partly overlap, both represent unique, but reciprocally related constructs.[3] Two models of physical frailty are dominant.[4,5] The deficit model of Rockwood consists of adding together an individual's number of impairments and conditions to create a Frailty Index.[4] The physical frailty phenotype of Fried, as included in the current study, consists of a constellation of three out of five possible criteria (weight loss, exhaustion, weakness, slowness, and reduced physical activity).[5] It was recently shown that 27% of older persons with depression met the criteria for the physical frailty phenotype.[6] The physical frailty phenotype is assumed to mark an underlying physiological state of multisystem and energy dysregulation.[7] Depressive disorder is increasingly recognized as a disorder of accelerated aging,[8] sharing at least some underlying pathophysiological mechanisms with physical frailty.[9]

It has been proposed that immunosenescence is one of the mechanisms underlying frailty. Aging of the immune system results in a condition of chronic low-level inflammation, also called "inflamm-aging",[10] characterized by high levels of the inflammatory cytokine interleukin-6 (IL-6) and the non-specific acute phase reactant C-reactive protein (CRP).[11] Frailty and depression have been associated with higher serum CRP and IL-6 levels.[12] High circulating levels of neutrophil gelatinase-associated lipocalin (NGAL), an acute phase protein, have recently been found in aging-related disorders such as mild cognitive impairment, Alzheimer's disease and late-life depression.[13,14] The association between inflammation and frailty has been reported consistently, in contrast to the association between inflammation and late-life depression.[12,15] Low-grade inflammation in late-life depression might thus depend on the level of frailty.

The present study examined whether the physical frailty phenotype is associated with low-grade inflammation in older adults with depression. It was hypothesized that inflammatory markers would be found to be associated with the physical frailty phenotype and that the frailty criteria that do not overlap with the depression criteria (muscle strength and gait speed) would be found to determine this association.

Methods

Study population
The present study was embedded within the Netherlands Study of Depression in Older persons (NESDO).[16] The NESDO sample consists of 378 subjects aged 60 years and older with a current diagnosis of 6-month major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%). Diagnoses were established according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) using the Composite International Diagnostic Interview version 2.1.[17] Three hundred twenty-six of the participants (86.2%) were recruited from mental health institutes (in- and outpatients) and 52 (13.8%) from primary care.

Exclusion criteria were a diagnosis of dementia, a Mini Mental State Examination (MMSE) score less than 18, an organic or psychotic disorder, and finally insufficient mastery of the Dutch language.[16]

All participants underwent a baseline examination at one of the five research locations (University Medical Center Groningen, Free University Medical Center Amsterdam, Leiden University Medical Center, Radboud university medical center, Mental Health Care Center GGNet) or at the home. The ethical review boards of all participating study centers approved of the study protocol, and all participants provided written informed consent.[16]

Physical frailty phenotype
The physical frailty phenotype was assessed according to the criteria of Fried et al.[5] A person is classified as frail when at least three out of the following five criteria are present:[6]
- Unintentional weight loss: unwanted weight loss of 1 kg/wk or more during two or more consecutive weeks or a body mass index (BMI) of less than 18.5 kg/m^2.
- Weakness: based on the maximum handgrip strength of the dominant hand assessed using a handgrip dynamometer. The best out of two trials was stratified according to sex and BMI quartile according to Fried et al.[5] Participants unable to perform the test were also considered weak.
- Exhaustion: determined according to two questions from the Center for Epidemiologic Studies Depression scale,[18] as in previous studies:[5] "I felt that everything I did was an effort" and "I could not get going." Participants answering "3 or more days a week" to either of these two items were categorized as positive.
- Slowness: measured using the 6-m walking test, using sex- and body height-stratified cutoffs as extrapolated from Fried et al.[5] (9 seconds for men ≤173 cm and women ≤159 cm tall; 8 seconds for men >173 cm and women >159 cm).[5]
- Low physical activity level: no daily activities such as walking and gardening

and sports activity less than once weekly, as assessed according to short form of the International physical Activities Questionnaire (IPAQ).[19]

Inflammatory markers
Fasting blood samples were obtained and kept at −80°C for subsequent analyses. Plasma CRP, IL-6 and NGAL levels were assessed. Plasma levels of high-sensitivity CRP were measured in duplicate using a immunoturbidimetric assay (Tina-quant CRPHS; Roche Diagnostics, Mannheim, Germany). Intra- and interassay coefficients of variation were both 2%. Plasma IL-6 levels were measured in duplicate using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit (PeliKine Compact ELISA; Sanquin, Amsterdam, the Netherlands). Intra- and interassay coefficients of variation were 8% and 12%, respectively.

Finally, the plasma NGAL levels (ng/ml) were measured in duplicate using an ELISA kit (R&D Systems, Minneapolis, MN).[14] The intra- and interassay coefficients of variation were 2% and 5%, respectively.

Covariates
Demographic data were collected on age, sex, and years of education, as well as lifestyle and disease-related characteristics that are potentially associated with either inflammatory markers or physical frailty.

Lifestyle characteristics included smoking (yes/no), alcohol intake (no drinking/moderate drinking/problematic drinking (5 – 10 units on a typical drinking day regardless of the frequency of drinking or 3 or 4 units on a typical drinking day at least 4 days a week)), physical activity (measured using the IPAQ in metabolic equivalent minutes (ratio of energy expenditure during activity to rest times the number of minutes performing the activity per week), and BMI.

Disease-related covariates included global cognitive functioning (MMSE, range 0-30), somatic comorbidity, depression severity, and medication use. The total number of self-reported chronic diseases as determined by well-validated algorithms[20] (lung disease, cardiovascular disease, diabetes mellitus, osteoarthritis or rheumatic disease, cancer, ulcer, intestinal problems, liver disease, epilepsy, and thyroid gland disease) was included. Severity of depression was measured using the 30-item self-rating Inventory of Depressive Symptomatology (IDS).[21] Finally, antidepressant drug use as well as antiinflammatory drugs (amino salicylic acid and similar agents, antiallergic agents, systemically applied corticosteroids, antiinflammatory and antirheumatic products, other analgesics and antipyretics, statins) drug use was controlled for.

Data analysis

Multiple linear regression analyses were conducted to examine the association between the different measures of physical frailty (independent variable) and each inflammatory marker (dependent variable) separately adjusted for all covariates described above. Because CRP and IL-6 values were positively skewed, ln-transformed values were used in all analyses.

The different measures of physical frailty included the presence of the physical frailty phenotype (yes/no), the number of the individual frailty criteria met (sum score), and five criteria (yes/no) individually. Associations with gait speed and handgrip strength (as two continuous proxies for frailty) were subsequently examined.

Finally, a non-linear principal components analysis (PCA) was conducted on the five binary criteria of the Fried Frailty Index (FFI). The purpose of PCA is data reduction. In PCA, relations between variables (in this case, the five FFI criteria) are analyzed, and underlying common factors are defined. So, factors are broadly formulated features that cover more than one variable.[22] PCA was chosen over factor analysis as PCA results in continuous latent factors (rotated axes) with purely binary variables (unrotated axes). Factor scores were calculated on the basis of unstandardized item factor loadings, the five criteria of the FFI in this case, and transformed into standardized z scores (using the Anderson-Rubin method) to increase their interpretability.[23]

Results

Sample

Of the 378 older persons with depression, three were excluded because they had missing values for one of the frailty criteria. Another nine were excluded due to missing data on all inflammatory markers because they refused or failed blood withdrawal. The mean age of the remaining 366 patients was 70.8 ± 7.4, and 242 (66.1%) were female. Table 1 presents the characteristics the study population for frail (n=97, 26.5%) and nonfrail participants separately.

IL-6 levels were available for all patients, whereas CRP levels were missing for four and NGAL levels for one because of invalid laboratory results. CRP level was significantly associated with IL-6 (r=0.24, p<.001) and NGAL level (r=0.20, p<.001), whereas Il-6 and NGAL levels were not associated (r=0.04, p=.46). The severity of depressive symptoms (IDS sum score) were not associated with any of the inflammatory markers (CRP: Pearson correlation coefficient (r)=0.01, p=.83; IL-6: r<0.01, p=.94; NGAL: r=0.04, p=.50).

Table 1 Characteristics of the Study Population According to Frailty Status

Characteristic	Frail (N=97)	Nonfrail (N=269)	P Value
Sociodemographic			
Age, mean ± SD	74.0 ± 8.0	69.4 ± 6.7	<.001[b]
Female, n (%)	68 (70.1)	174 (64.7)	.33[c]
Education, years, mean ± SD	10.0 (3.2)	10.8 (3.5)	.01[b]
Somatic and cognitive functioning			
Mini Mental State Examiniation score, mean ± SD	27.3 ± 2.3	28.0 ± 1.7	.003[b]
Number of somatic diseases, mean ± SD	2.6 ± 1.7	1.9 ± 1.4	<.001[b]
Use of medication, n (%)[a]			
Antidepressant	76 (78.4)	189 (70.3)	.13[c]
SSRI	29 (29.9)	70(26.0)	.47[c]
TCA	33 (34.0)	56 (20.8)	.71[c]
Other	33 (34.0)	72 (26.8)	.16[c]
Antiinflammatory	12 (12.4)	32 (11.9)	.90[c]
Statin	27 (27.8)	59 (21.9)	.24[c]
Lifestyle characteristics			
Current smoker, n (%)	22 (22.7)	73 (27.1)	.44[c]
Alcohol use, n (%)			.08[c]
No	44 (45.4)	100 (37.2)	
Moderate	45 (46.4)	138 (51.3)	
Severe	4 (4.1)	29 (10.8)	
Physical activity (metabolic equivalent minutes), mean ± SD	1,099.9 ± 1,497	2,884.8 ± 2,519.9	<.001[b]
Body Mass Index, kg/m2, mean ± SD	26.8 ±4.8	26.1 ± 4.1	.14[b]
Depression			
Inventory of Depressive Symptoms sum score, mean ± SD	36.3 ± 12.0	27.4 ± 12.0	<.001[b]
Late-onset depression, n (%)	33 (34.0)	79 (29.4)	.40c
Frailty			
Fried Frailty Index, mean ± SD	3.4 ± 0.6	1.1 ± 0.8	<.001[b]
Handgrip Strength, kg, mean ± SD	19.9 ± 8.8	30.6 ± 10.8	<.001[b]
Gait speed, seconds, median (IQR)	9.0 (7.0)	6.4 (2.0)	<.001[d]
Inflammatory markers			
C-reactive protein, mg/L, median (IQR)	2.20 (5.05)	1.87 (4.76)	.26[d]
Interleukin-6 ,pg/L, median (IQR)	0.56 (10.80)	0.46 (5.64)	.17[d]
Neutrophil gelatinase-associated lipocalin, ng/ml, mean ± SD	68.4 ± 26.5	59.9 ± 21.3	.01[b]

[a] Medications were defined according to the Anatomical Therapeutic Chemical classification system: selective serotonin reuptake inhibitor (SSRI) (N06AB), serotonin-norepinephrine reuptake inhibitor (N06AX16, N06AX21), tricyclic antidepressant (TCA)(N06AA) tetracyclic antidepressant (N06AX03, N06AX05, N06AX11), antiinflammatory drug (including amino salicylic acid and similar agents) (A07EC), antiallergic agents (A07EB), systemically applied corticosteroids (H02A), antiinflammatory and antirheumatic products (M01) and other analgesics and antipyretics (N02B), and statins (C10AA, C10B).
P-values were calculated using [b]t-tests, [c]chi-square tests, or [d]Mann-Whitney-U tests.
SD= standard deviation; IQR= interquartile range.

Table 2 Associations Between C-Reactive Protein (CRP), Interleukin-6 (IL)-6, and Neutrophil Gelatinase-Associated Lipocalin (NGAL) and the Physical Frailty Phenotype

Frailty Characteristics	CRP	IL-6	NGAL
	β (P Value)		
Unadjusted			
Frailty (0=no, 1=yes)	0.06 (.26)	0.05 (.36)	0.13 (.01)
Frailty sum score (range 0-5)	0.10 (.05)	0.08 (.13)	0.20 (<.001)
Individual frailty criteria (dichotomous)			
Weight loss	-0.03 (.53)	-0.02 (.71)	-0.03 (.56)
Weakness	0.15 (.004)	0.12 (.02)	0.10 (.06)
Exhaustion, poor energy	0.02 (.77)	-0.02 (.78)	0.11 (.04)
Slowness	0.15 (.005)	0.11 (.04)	0.26 (<.001)
Low activity level	<0.01 (.95)	0.03 (.64)	0.12 (.03)
Performance-based criteria (dimensional)			
Handgrip strength	-0.13 (.01)	-0.15 (.004)	-0.08 (.14)
Gait speed	0.13 (.01)	0.12 (.03)	0.24 (<.001)
Fully adjusted[a]			
Frailty (0=no, 1=yes)	0.04 (.56)	0.04 (.47)	0.02 (.73)
Frailty sum score (range 0-5)	0.10 (.13)	0.08 (.21)	0.10 (.12)
Individual frailty criteria (dichotomous)			
Weight loss	<0.01 (.99)	-0.03 (.64)	-0.07 (.20)
Weakness	0.12 (.03)	0.09 (.10)	0.03 (.61)
Exhaustion, poor energy	-0.01 (.91)	<0.01 (.95)	0.07 (.23)
Slowness	0.11 (.08)	0.08 (.22)	0.17 (.006)
Low activity level	<0.01 (.95)	0.06 (.39)	0.06 (.38)
Performance-based criteria (dimensional)			
Handgrip strength	-0.21 (.002)	-0.25 (<.001)	-0.04 (.57)
Gait speed	0.09 (.18)	0.11 (.12)	0.15 (.02)

[a] Adjusted for age, sex, years of education, severity of depressive symptoms (Inventory of Depressive Symptomatology sum score), cognitive functioning (Mini Mental State Examination score), number of chronic diseases, antiinflammatory drug use (including statins), antidepressants (selective serotonine reuptake inhibitors, tricyclic antidepressants, other), alcohol use (none, moderate, severe), smoking (yes/no), body mass index, physical activity (metabolic equivalent minutes).

Association between inflammatory markers and the physical frailty phenotype
Bivariate and multivariate associations between inflammatory markers and the physical frailty phenotype are shown in Table 2. In the fully adjusted models, only handgrip strength and gait speed were significantly associated with inflammatory markers (handgrip strength with CRP and IL-6, gait speed with NGAL).

Principal component analysis of physical frailty criteria
The scree plot of eigenvalues and the number of complex items revealed a two-factor solution as the optimal solution (KMO-measure of sampling adequacy: .575; Bartlett's test of sphericity: chi-square=50.1, degrees of freedom=10, p<.001). Handgrip strength, gait speed and low activity level loaded on Factor 1 (explained variance: 28.7%, factor loadings 0.75, 0.65, 0.55, respectively); this dimension was called 'performance-based physical frailty'. Weight loss and exhaustion loaded on Factor 2; this dimension was labeled 'vitality-based physical frailty' (explained variance: 20.2%, factor loadings 0.84 and 0.54, respectively).

The frailty dimensions did not correlate with each other (r=-0.08, p=.13). Associations between each dimension of physical frailty and the three inflammatory markers are shown in Table 3.

Table 3 Associations Between C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Dimensions of the Physical Frailty Phenotype

	CRP	IL-6	NGAL
Physical Frailty		β (P Value)	
Unadjusted			
Performance-based	0.14 (.01)	0.11 (.06)	0.16 (.003)
Vitality-based	-0.03 (.56)	-0.01 (.89)	-0.09 (0.7)
Fully adjusted[a]			
Performance-based	0.14 (.03)	0.13 (.06)	0.14 (.03)
Vitality-based	0.01 (.93)	-0.02 (.69)	-0.10 (.07)

[a] Adjusted for age, sex, years of education, severity of depressive symptoms (Inventory of Depressive Symptomatology sum score), cognitive functioning (Mini Mental State Examiniation score), number of chronic diseases, antiinflammatory drug use (including statins), alcohol use (none, moderate, severe), smoking (yes/no), body mass index, physical activity (metabolic equivalent minutes).

Discussion

Main findings

The physical frailty phenotype was not associated with high levels of inflammatory markers in older adults with depression participating in the NESDO study. Nonetheless, performance-based measures such as handgrip strength and gait speed were associated with markers of low-grade inflammation. The criteria of the FFI represent two dimensions of physical frailty in a population with depression. Only one dimension, including the criteria based on the handgrip strength and gait speed, was associated with inflammation independent of somatic illnesses, medication use or lifestyle characteristics.

Physical frailty phenotype in late-life depression

This first dimension, based on the criteria for weakness, slowness and low activity level, was called "performance-based physical frailty". Weight loss and exhaustion represented a second dimension, called "vitality-based physical frailty".

Measures of handgrip strength and gait speed are often used as indicators of sarcopenia,[24] which is considered to be an important mechanism underlying physical frailty.[25] The physical frailty criteria of exhaustion and of low physical activity may also be indicators of sarcopenia, but their relationship with sarcopenia is not straightforward. The physical frailty criterion of exhaustion may simply reflect a symptom of depression in the current sample for two reasons. First, this criterion is derived from a self-report instrument assessing depression severity[18] and overlaps with the DSM-IV criteria for major depressive disorder. Second, exhaustion has many different causes in old age, of which sarcopenia is only one, among others such as anemia, endocrine disorders, sleep disorders, pain and polypharmacy.

The frailty component of low physical activity can be cause and consequence of depression or sarcopenia. Because low physical activity loads on the same dimension as handgrip strength and gait speed, it seems to reflect sarcopenia the current study population.

Finally, unintended weight loss may reflect sarcopenia but again, in the current study population probably, may be more likely a symptom of depression. Therefore, the dimension of vitality-based physical frailty has face validity for being a marker of depression severity instead of a true (second) dimension of physical frailty. Nonetheless, this hypothesis needs further validation.

Inflammation and frailty in late-life depression

Although the physical frailty phenotype was not associated with any of the three inflammatory markers, IL-6 and CRP were significantly associated with handgrip

strength and NGAL with gait speed. These findings suggest differential patterns between specific inflammatory markers and specific frailty criteria. Nonetheless, all three inflammatory markers were associated with the performance-based physical frailty dimension. Low-grade inflammation may thus be a general mechanism underlying performance-based physical frailty.

The association between NGAL and vitality-based physical frailty is also of interest. In the NESDO study, only NGAL levels were higher in participants with depression than in those without.[26] NGAL seems to be an inflammatory marker associated not only with frailty in depression, but also specifically with depression.

Associations between high IL-6 and CRP levels and depression have not been found consistently.[27,28] It might be that low-grade inflammation in depression is conditional on the level of frailty in the population under study, but this needs further investigation.

Methodological considerations
Strengths of the current study are the large number of older persons with depression and the comprehensive assessment of depression characteristics and confounding factors. However, some limitations should also be acknowledged. First, the cross-sectional study design precludes causal interpretations. It is generally assumed that depressive symptoms and frailty are reciprocally associated.[3] Low-grade inflammation might be involved in both directions. Frailty-associated inflammatory processes may drive the pathway from frailty to depression by activating the hypothalamo-pituitary-adrenocortical axis.[12,29] Conversely, low physical activity and low protein intake due to a depressive disorder may result in sarcopenia, which in itself is associated with inflammation[30] and may culminate in the physical frailty phenotype. Longitudinal studies with repeated measurement of physical frailty, depression and inflammatory markers should be conducted to evaluate the sequence of events. Second, although negative cognitions (e.g. self-report symptoms of physical functioning) do not negatively bias performance-based measures of fhysical frailty, poorer performance due to lack of motivation during testing cannot be fully excluded, although research assistants were specifically trained to enhance motivation and performance as much as possible.

Conclusion
The operationalization of the physical frailty phenotype should be adapted in an older population with depression, with a more prominent role for criteria associated with low-grade inflammation that does not overlap with the criteria of depressive disorder. An interesting question that merits further investigation is to examine whether late-life depression with physical frailty represents a specific depressive subtype.

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Part III:

Does physical frailty affect the incidence and course of late-life depression?

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Chapter 7

Frailty as a predictor
of the incidence and course
# of depressed mood

Abstract

Background- Late-life depression and physical frailty are supposed to be reciprocally associated, however longitudinal studies are lacking.

Objectives- This study examines whether physical frailty predicts a higher incidence of depression, as well as a less favorable course of depression.

Methods- A population-based cohort study of 888 people aged 65 years and over with follow-up measures at 3, 6 and 9 years. Cox proportional hazards models adjusted for age, sex, education, smoking, alcohol usage and global cognitive functioning were applied to calculate the incidence of depressed mood in those non-depressed at baseline (n=699) and remission in those with depressed mood at baseline (n=189). Depressed mood onset or remission was defined as crossing the cutoff score of 20 points on the Center for Epidemiological Studies-Depression Scale (CES-D) combined with a relevant change in CES-D score. Physical frailty was based on the presence of ≥3 out of 5 components (i.e. weight loss, weakness, slowness, exhaustion and low physical activity level).

Results- A total of 214 out of 699 (30.6%) non-depressed persons developed depressed mood during follow-up. Physical frailty predicted the onset of depressed mood with a hazard rate of 1.26 (95% confidence interval: 1.09-1.45, p=.002). Of the 189 persons with depressed mood at baseline, 96 (50.8%) experienced remission during follow-up. Remission was less likely in the presence of a higher level of physical frailty (hazard rate =0.72, 95% confidence interval: 0.58–0.91, p=.005).

Conclusions- Because physical frailty predicts both the onset and course of late-life depressed mood, physical frailty should receive more attention in mental health care planning for older persons as well as its interference with treatment. Future studies into the pathophysiological mechanisms may guide the development of new treatment opportunities for these vulnerable patients.

Keywords: depression, frailty, older persons, InCHIANTI

Introduction

Late-life depression places a great burden on patients and society,[1] partly due to its often chronic course and high relapse rates.[2-5] Not only depressive disorder, but also clinically relevant depressive symptoms have high impact on well-being, disability and utilization of health care services.[1] Late-life depression is a complex mood disorder with various etiological pathways and high comorbidity rates with cognitive decline and physical diseases.[6-9] These high comorbidity rates suggest involvement of general aging mechanisms. In an earlier study, we showed that 27% of depressed older patients can be classified as physically frail.[10] Recently, a consensus conference concluded that physical frailty is an important medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death.[11] Promising ideas were the optimism about the possibility to prevent and treat frailty and, thus, the need to take frailty into account in geriatric medicine.

Despite shared underlying pathophysiological mechanisms of depression and frailty,[12] the concept of frailty has received little attention in mental health care for older persons. This can partly be explained by overlapping criteria of frailty and psychiatric diseases, which is most apparent for broader frailty concepts (including both physical and psychosocial components, such as depressive symptoms). The physical frailty phenotype for example remained significantly associated with late-life depression when overlapping criteria were omitted.[13] Accordingly, latent class analyses have shown that physical frailty and depression identify distinct, but overlapping subpopulations.[14] For research into the relations between depression and frailty, the physical frailty phenotype by Fried et al.,[15] defined as the presence of ≥3 out of the following 5 criteria: weight loss, weakness, slowness, exhaustion and low physical activity level, is particularly useful, as depressive symptomatology is not part of this frailty definition. This is in line with the conclusions from the earlier mentioned consensus conference.[11]

If frailty indeed can be distinguished from late-life depression, it may be expected that physical frailty will be predictive for the onset of depression (as an adverse health effect). Additionally, it may be expected that frailty in depression is associated with negative health effects independent of the adverse effects of late-life depression itself, such as a more persistent course. Such data will contribute to the relevance of physical frailty in late-life mental health, and may ultimately lead to different interventions for frail and nonfrail persons, as previously have been suggested in general medicine. [16, 17] To date, the impact of physical frailty on incident depression has been examined twice using a prospective study design. Both studies identified

physical frailty as an independent predictor of incident depression.[18, 19] Generalization to a Western society, however, may be limited as both studies were conducted in an Asian population. Moreover, one of them had a duration of follow-up limited to 15 months.[19]

The objectives of the present study are, therefore, to investigate whether in a Western society, physical frailty also predicts a higher incidence of depressed mood in non-depressed community-dwelling older persons and, whether physical frailty decreases the chance on remission of depressed mood in persons with depressed mood at baseline.

Methods

Data are from the InCHIANTI (Invecchiare in Chianti, aging in the Chianti area) Study, a prospective, population-based cohort study. Details of the study are described elsewhere.[20] Briefly, the baseline data collection started in 1998 and was completed in 2000. It included an interview at the homes of the participants and a medical examination at the study clinic. The medical examination was conducted within 21 days after the home interview. Follow-up assessments took place at 3, 6 and 9 years after baseline. After explaining the study procedures to the participants, they were asked to sign informed consent. The ethics committee of the Italian National Institute of Research and Care on Ageing approved of the study protocol.

The InCHIANTI study included 1155 persons aged 65 years and older. Because of missing data on depressed mood at baseline (N=76) or lack of follow-up data with respect to depressive symptoms (N=191), the present study included 888 participants. Persons with missing data were significantly older (82.3 (standard deviation [SD] 7.6) versus 73.4 (6.3) years, p<.001), less educated (4.2 (3.2) versus 5.6 (3.3) years, p<.001), had more somatic diseases (1.18 versus 0.89, p=.002), and were more likely to be frail (20.2% versus 6.8%, p<.001). The two groups did not differ with respect to gender and depressed mood status at baseline.

Depressed mood
Depressive symptoms were assessed at baseline, 3 years, 6 years and 9 years of follow-up, using the Center for Epidemiological Studies-Depression Scale (CES-D). The CES-D is a self-report 20-item measurement scale for depressive symptoms experienced during the previous week.[21] It has been shown to be a valid and reliable instrument for identifying depressed mood in community-dwelling older persons.[22]

The sum score ranges from 0 through 60, whereas a score of 20 was the best indicator

of clinically relevant depressive symptoms within the InCHIANTI sample.[23, 24] Crossing the cutoff of 20 points combined with a relevant change on the CES-D was considered the primary outcome variable (i.e. onset of depressed mood in case of no depressed mood at baseline and remitted depressed mood in case of depressed mood at baseline). A relevant change was defined as a decrease or an increase of at least 4 points (one-half a standard deviation) on the CES-D between 2 measurements. This criterion of a minimum change of 4 points was chosen to avoid random fluctuations or clinically irrelevant changes of symptoms leading to a respondent being identified as either incident depressed or remitted from depressed mood.

Frailty
Frailty was defined according to the widely used criteria of Fried and colleagues.[15] In this definition frailty is operationalized as the presence of ≥3 out of the following 5 criteria: weight loss, weakness, slowness, exhaustion and low physical activity level. In the analyses, however, frailty was used as a continuous variable based on the number of criteria met (range 0 – 5). Each criterion was operationalized using previously published methods.[25, 26]

- Weight loss was defined as the unintentional weight loss of >4.5 kilogram in the past year.
- Handgrip strength was used to assess weakness. If handgrip strength corresponded to the lowest quintile for stratified gender and body mass index groups, weakness was considered present.
- Slowness was measured by a 4-m walking test, and was considered to be present when walking speed corresponded to the lowest quintile of stratified gender and height groups.
- Exhaustion was evaluated by a CES-D question ("How often in the last week did you feel that everything you did was an effort?"). If the participants answered "often" or "most of the time", exhaustion was considered present.
- Low physical activity was assessed during the home interview. It was defined as sedentary state or performing light intensity activity (i.e. walking) less than 1 hour a week.

Covariates
The following covariates were included in the analyses: socio-demographic variables, lifestyle variables and cognitive functioning. Socio-demographic variables included age, gender and years of education. Lifestyle variables included smoking (non-smoker/ former smoker/ current smoker) and alcohol use (<3 or ≥3 drinks a day). Cognitive functioning was measured by the Mini Mental State Examination (MMSE).[27]

The number of somatic diseases was established using standardized criteria that combined information from self-report history, medical records and a clinical examination (including heart failure, coronary heart disease, stroke, chronic obstructive lung disease, hypertension, diabetes, cancer, Parkinson's disease and hip arthritis).

Statistical analyses
All analyses will be presented for persons with depressed mood (CESD score ≥20) and non-depressed (CESD score <20) persons at baseline. Demographics and clinical characteristics of the participants with and without frailty (yes/no) were compared using independent samples t-tests for normally distributed, continuous variables, nonparametric Mann Whitney U tests for skewed continuous variables, and χ^2 tests for categorical variables. All predictors and covariates (primary variables) that were included in the models were checked for normality and collinearity.

Missing data of determinants and covariates was handled by multiple imputations using the fully conditional specification method with IBM SPSS statistics (SPSS Inc, Chicago, IL), whereas the outcomes (depressed mood status) were not. Appendix 1 and 2 show the variables in the imputation model and their role in the model (predictor, imputed variable or both).

In the non-depressed group 43 datasets were created because 43% of the cases had missing data on at least 1 variable. In the depressed mood group 58 datasets were created.[28] Analyses on the imputed dataset were considered the primary analyses. Nonetheless, results of the original data (complete cases) were also shown.[28, 29]

Cox proportional hazards models adjusted for age, gender, education, smoking status, alcohol use, number of somatic diseases and MMSE score were used to examine whether frailty predicts incidence of depressed mood during follow-up (either at 3, 6 or 9 years of follow-up, CES-D scores of ≥20 combined with a relevant change) [24] among those originally not depressed at enrollment. The proportionality of hazards assumption was checked for the primary variables by log minus log plots.

Only subjects with data from at least one follow-up measure were included in the analysis. First, the number of frailty components (range 0 -5) was used as a continuous predictor variable. Subsequently, the impact of the individual frailty components was examined by including each component in a separate model.

Among persons with depressed mood at baseline, a similar strategy was applied. We used Cox proportional hazards models to examine whether frailty status at baseline predicted remission of depressed mood during follow-up.

Interactions with gender were tested because the prevalence rates for both frailty and depression are higher in women than in men. Finally, because the exhaustion criterion from the physical frailty definition is derived from a depression scale (CES-D), we performed a sensitivity analysis by excluding the exhaustion criterion from the frailty definition. The sum score was re-calculated on the remaining 4 frailty components. With this measure of frailty, the analyses were repeated. All statistical procedures were performed using IBM SPSS version 20. Final outcomes were considered statistically significant if P values were ≤.05.

Results

The mean age [SD] of total study population (n=888) was 73.4 [6.3] years and 56.3% was female. At baseline, 21.3% had depressed mood and 6.8% were frail. Table 1 presents the characteristics of both the depressed mood and the non-depressed group by frailty status.

Persons with baseline depressed mood were significantly older, were more often female, were less frequently a smoker, drank less alcohol, had lower cognitive functioning, were more likely to be frail and were more likely to have depressed mood at follow-up.

Incidence of depressed mood

Incidence of depressed mood was assessed in persons who were not depressed at baseline (n=699). Of these persons 92.4% (n=646) had CES-D data available at 3 years of follow-up, 81.4% (n=569) at 6 years follow-up and 64.2% (n=449) at 9 years follow-up. Of the persons not depressed at baseline, 30.6% (n=214) developed depressed mood during the 9-year follow-up. The risk of becoming depressed was increased for persons with frailty, compared to the nonfrail persons in the unadjusted analyses. When the analyses were corrected for age, gender, educational level, smoking status, alcohol use, number of somatic diseases and MMSE score, this increased risk remained present (hazard rate (HR)=1.26 [95% CI: 1.09–1.45], p=.002). Subsequently, frailty components were analyzed separately. Only low physical activity level significantly increased the risk of incident depressed mood (Table 2).

Remission in depressed mood group

Remission of depressed mood was assessed in persons who had depressed mood at baseline (n=189). Follow-up data were available for 93.7% (n=177) at 3 years follow-up, for 73.0% (n=138) at 6 years follow-up and for 49.7% (n=94) at 9 years follow-up. Of the persons with initially depressed mood, 50.8% (n=96) experienced remission during follow-up.

Table 1 Sample Characteristics (complete cases)

| | Participants (n=888), % | | | | | |
| Characteristic | Depressed Mood at Baseline (n=189), 21.3 | | | No Depressed Mood at Baseline (n=699), 78.7 | | |
	Frail (n=31), 16.4	Nonfrail (n=158), 83.6	P Value[a]	Frail (n=29), 4.1	Nonfrail (n=670), 95.9	P Value[a]
Sociodemographics						
Age, mean (SD), y	79.9 (6.2)	74.6 (6.4)	<.001	77.0 (7.1)	72.6 (6.0)	<.001
Female gender, %	77.4	77.8	.958	48.3	50.6	.807
Education, mean (SD), y	4.3 (2.7)	5.4 (3.4)	.072	5.4 (3.1)	5.7 (3.3)	.622
Health indicators						
Smoking, %			.560			.120
Never smoked	77.4	72.8		37.9	54.3	
Former smoker	9.7	17.1		34.5	30.4	
Current smoker	12.9	10.1		27.6	15.2	
Alcohol use, ≥3 drinks a day, %	3.2	12.0	.145	13.8	22.8	.253
MMSE score, mean (SD)	23.3 (2.9)	25.3 (2.8)	<.001	24.4 (3.4)	25.9 (2.7)	.023
Somatic diseases, mean no (SD)	1.4 (1.1)	0.9 (1.0)	.007	1.7 (1.2)	0.8 (0.9)	<.001
Frailty indicators						
Weight loss, %	25.8	3.8	<.001	27.6	3.1	<.001
Weakness, %	58.1	11.4	<.001	75.9	13.0	<.001
Slowness, %	80.6	16.4	<.001	86.2	10.9	<.001
Exhaustion, %	83.9	46.8	<.001	65.5	7.5	<.001
Low physical activity level, %	80.6	24.1	<.001	72.4	8.2	<.001
Amount of frailty criteria present, mean (SD)	3.3 (0.5)	1 (0.7)	<.001	3.3 (0.5)	0.4 (0.7)	<.001

Abbreviations: MMSE, Mini Mental State Examination
[a] Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables) and U tests (continuous, skewed variables).

With regard to remission during follow-up, Cox regression analysis showed that frailty strongly predicts lower remission during follow-up (Table 3). This increased likelihood of remission remained present, also in the fully adjusted model (HR=0.72 [95% CI: 0.58–0.91], p=.005). When frailty was decomposed into components, only absence of low physical activity level predicted remission of depressed mood in the fully adjusted model (Table 3). No significant interactions between frailty*gender were found (non-depressed mood group: p=.919, depressed mood group: p=.621).

Sensitivity Analysis
The analyses were repeated after excluding the exhaustion criterion from the frailty definition. Frailty without exhaustion remained significantly associated with incident

depressed mood and remission in the fully adjusted model (incidence: HR=1.31 [95%CI: 1.10–1.56], p=.003, remission: HR=0.70 [0.53–0.92], p=.010).

Table 2 Cox Proportional Hazards Model for Incidence of Depressed Mood in the Group Not Depressed at Baseline[a]

N=699 Frailty (N=29)[b]:	Imputed Data HR (95% CI)	P Value	Complete Cases HR (95% CI)	P Value
Unadjusted	1.41 (1.24, 1.60)	<.001	1.43 (1.23, 1.60)	<.001
Fully adjusted	1.26 (1.09, 1.45)	.002	1.25 (1.08, 1.46)	.003
Components of frailty[c]:				
Weight loss (N=29)	1.49 (0.80, 2.76)	.205	1.48 (0.79, 2.75)	.218
Weakness (N=115)	1.21 (0.85, 1.73)	.279	1.20 (0.84, 1.71)	.329
Slowness (N=106)	1.39 (0.95, 2.03)	.087	1.36 (0.92, 2.02)	.123
Exhaustion (N=69)	1.40 (0.95, 2.08)	.090	1.40 (0.95, 2.08)	.090
Low physical activity level (N=76)	1.68 (1.17, 2.42)	.005	1.68 (1.17, 2.42)	.005

[a]Number of events: 214, number of person years: 4668 (45.8 events/ 1000 person years).
[b]Frailty was used as a continuous variable.
[c]Frailty components were analyzed separately and adjusted for age, gender, level of education, smoking status, alcohol use, number of somatic diseases and Mini Mental State Examination score.

Table 3 Cox Proportional Hazards Model for Remission in the Group Depressed Mood at Baseline[a]

N=189 Frailty (N=31)[b]:	Imputed Data HR (95% CI)	P Value	Complete Cases HR (95% CI)	P Value
Unadjusted	0.73 (0.60, 0.90)	.003	0.73 (0.59, 0.90)	.004
Fully adjusted	0.72 (0.58, 0.91)	.005	0.74 (0.58, 0.93)	.010
Components of frailty[c]:				
Weight loss (N=15)	1.17 (0.54, 2.50)	.688	1.22 (0.58, 2.57)	.600
Weakness (N=41)	0.66 (0.35, 1.24)	.195	0.65 (0.34, 1.24)	.190
Slowness (N=53)	0.55 (0.30, 1.01)	.052	0.55 (0.30, 1.02)	.057
Exhaustion (N=100)	0.75 (0.49, 1.13)	.169	0.75 (0.49, 1.13)	.169
Low physical activity level (N=63)	0.55 (0.33, 0.94)	.028	0.55 (0.33, 0.94)	.0.28

[a]Number of events: 96, number of person years: 999 (96.1 events/ 1000 person years).
[b]Frailty was used as a continuous variable.
[1]Frailty components were analyzed separately and adjusted for age, gender, level of education, smoking status, alcohol use, number of somatic diseases and Mini Mental State Examination score

Discussion

Main findings

This study describes the longitudinal association between physical frailty and depressed mood; focusing on incidence as well as remission of depressed mood. It is confirmed that the severity of frailty negatively interferes with both the onset and remission of late-life depressed mood independent of age, sex, level of education, lifestyle, somatic diseases and global cognitive functioning.

Comparison with literature

Our findings are fully in line with a recent systematic review on the relationship between frailty and depression.[30] The authors concluded that frailty, its components and functional impairments are risk factors for depression.[30] In most of the included cohort studies, however, frailty was defined by Activities of Daily Living indices. None of these cohort studies used a definition of frailty according to the physical phenotype. This is important, as physical frailty should reflect the biological age of a person and should be distinguished from disabilities and multimorbidity.[11] Not included in this review are two recent studies on the longitudinal association between physical frailty and depression.[18, 19] Both studies find that physical frailty predicts the incidence of depressive symptoms in an Asian population. In 1 study, the persistence of depressive symptoms is also investigated, and frailty is identified as an independent predictor of persistence of depressive symptoms.[18] Our findings not only confirm these findings for a Western population, but also extend to these findings by determining the contribution of frailty to remission in a group that has depressed mood at baseline. Furthermore, the risk of depression in the case of frailty is also confirmed for a relatively long follow-up period (9 years).

With regard to components of frailty; weight loss, slowness, exhaustion and low physical activity seem to contribute to the impact of frailty on the onset of depressed mood, whereas the impact of weakness seems to be less strong. Nonetheless, only low physical activity significantly increased the risk of depressed mood onset in the fully adjusted models. The association between low physical activity and incident depression is in line with previous studies.[31]

Among older persons suffering from depressed mood, frailty was associated with a lower chance on remission during follow-up. The impact of frailty on remission of depressed mood seems to be driven by slowness and low physical activity level whereas an impact of weight loss was reverse. Previous research showed the same (non-significant) inverse association of weight loss with depressed mood.[18] Nonetheless, again only (absence of) low physical activity level was an independent predictor of remission in the fully adjusted models.

So, what do the findings among depressed and non-depressed persons tell us about the concept of frailty? The physical frailty phenotype according to the criteria of Fried et al.[15] is a widely used and well-validated concept.[11] In our study, the construct of frailty is consistently associated with depressed mood. Results with respect to the individual frailty components also seem consistent. With respect to the prediction of depressed mood, all components pointed towards the same direction. Regarding remission of depressed mood, the association with weight loss is opposite to the direction of the association of the other frailty components. When the unidimensionality of physical frailty is examined with respect to its association with late-life depression, zooming in on frailty components may help revealing the validity of the concept of frailty. Future studies therefore, should pay more attention to the relationship between adverse outcomes and the individual components of frailty.

In recent research it was found that overlap between depression and frailty was highest for the somatic and severely depressed subgroups; almost three quarters of the severely depressed older persons was also frail.[32] The co-occurrence of frailty and depressed mood is confirmed in the present study. The frailty prevalence of 6.8% in the present study, however, is lower than the prevalence rate we found before in a meta-analysis of frailty prevalence among community dwelling older persons (10.7%).[10] This difference can almost completely be explained by the higher prevalence of frailty (20.2%) among the persons that were excluded due to missing data. Nonetheless, another less weighty explanation for this finding may be the lower age of the InCHIANTI participants, compared to the mean age of the participants in the meta-analysis, as the prevalence of frailty increases with age.

What underlies this compound between physical frailty and depression? Shared mechanisms include low-grade inflammation, nutritional deficits among which vitamin D deficiency, lack of exercise and sarcopenia, and/or age-related hormonal changes, which all have been associated with frailty as well as depression.[31, 33-40] These pathophysiological mechanisms add to the multi-facetted pathways to both frailty and depression. Moreover, when depression and frailty are simultaneously present, disentangling causes and consequences of either one from another becomes challenging. For instance, a factor like lack of exercise can be part of the path towards frailty and depression, as well as a result of one or both of these syndromes. All factors may even occur in a complicated vicious circle. Nonetheless, the longitudinal association between frailty and depression is clearly present in this study. Therefore, treatment of frailty deserves a more prominent role in late-life depression, as it may prevent depression or shorten the duration of depression. Older persons that are not only depressed, but also frail confer specific complex care needs.[41, 42]

Strengths and limitations

Our study has some important strengths. The association between frailty and depressed mood was examined within a prospective design, with data of 9 years of follow-up. A large, community-based sample was used, providing the opportunity to investigate onset, as well as persistence of depressed mood. Frailty was included as a continuous variable, reflecting the dimensional nature of physical frailty.[43] Relations were further disentangled by examining components of frailty separately.

Because the dropout of study participants during follow-up is selective when studying older persons (in our case the most frail participants dropped out during follow-up, data not shown), the strength of the association between frailty and depressed mood may decrease at the end of the follow-up time (9 years). Cox regression analysis takes this into account by censoring the data at time of dropout.

Nonetheless, the findings have to be interpreted in light of the study limitations also. In our sample, persons with missing data on baseline depressive symptoms or all follow-up data on depressive symptoms were excluded prior to the analyses. The persons with missing data were older, less educated, more frail and had more somatic diseases, as compared to persons with no missing data. This implies that the most frail and unhealthy persons were not included in the analyses, and therefore the findings may be biased towards an underestimation of the association between frailty and depressed mood.

Depressive symptoms were assessed with the CES-D; a self-report questionnaire. With a score of ≥20 combined with a relevant change in symptoms (≥4 CES-D points), a person was considered to have depressed mood. Although a CES-D score of 20 points or more reflects clinically relevant depressive symptoms,[22, 44] it is not necessarily a psychiatric diagnosis of major depressive disorder.[22] Our results should therefore be confirmed by future studies assessing depressive disorder according to DSM-5 or International Classification of Diseases-10th revision criteria. Finally, the history of depression was unknown and some of the persons in the non-depressed group may have suffered from depressed mood in the past.

Clinical implications

This study confirms that frailty predicts incidence of depressed mood and not being frail predicts remission. In long-term care, both frailty and depression are highly prevalent,[45, 46] and these findings may change the perspective on the treatment of late-life depression and frailty. Our results imply that interventions proven to improve the frailty status, such as exercise, nutritional intervention and vitamin D suppletion,[11] might be relevant for old age psychiatry and for prevention of frailty. Future research

should guide interventions for persons suffering from frailty and depression, especially the influence of treating frailty and the consequences for depression.

Appendices

Appendix 1:
Missing data patterns in persons with depressed mood at baseline

Variable N=189	N (%) Cases With Missing Values	Role
Age	0 (0)	Predictor
Gender	0 (0)	Predictor
Education	0 (0)	Predictor
Smoking status	0 (0)	Predictor
Alcohol use	0 (0)	Predictor
MMSE score	0 (0)	Predictor
Somatic diseases	0 (0)	Predictor
Weight loss	8 (4.2)	Predictor and imputed
Grip strength	22 (11.6)	predictor and imputed
Walking speed	27 (14.3)	Predictor and imputed
Exhaustion	0 (0)	Predictor
Low activity level	0 (0)	Predictor
CES-D follow-up 1	12 (6.3)	Predictor
CES-D follow-up 2	51 (27.0)	Predictor
CES-D follow-up 3	95 (50.3)	Predictor
CES-D baseline	0 (0)	Predictor

When patterns of missing data were analyzed, it showed that data was missing by a random pattern and therefore the Fully Conditional Specification Method was used. We created 58 datasets, as 58% of the cases had at least 1 missing value.[29] In total, 7.1% of the data were missing. The imputation included the variables that were used in the final model.

Appendix 2:

Missing data pattern in the group non depressed at baseline

Variable N=699	N (%) Cases With Missing Values	Role
Age	0 (0)	Predictor
Gender	0 (0)	Predictor
Education	0 (0)	Predictor
Smoking status	0 (0)	Predictor
Alcohol use	0 (0)	Predictor
MMSE score	0 (0)	Predictor
Somatic diseases	0 (0)	Predictor
Weight loss	5 (0.7)	Predictor and imputed
Grip strength	35 (5.0)	predictor and imputed
Walking speed	48 (6.9)	predictor and imputed
Exhaustion	0 (0)	Predictor
Low activity level	0 (0)	Predictor
CES-D follow-up 1	53 (7.6)	Predictor
CES-D follow-up 2	130 (18.6)	Predictor
CES-D follow-up 3	250 (35.8)	Predictor
CES-D baseline	0 (0)	Predictor

When patterns of missing data were analyzed, it showed that data was missing by a random pattern and therefore the Fully Conditional Specification Method was used. We used the Fully Conditional Specification Method and created 43 datasets, as 43% of the cases had at least 1 missing value. [29] In total, 4.7% of the data were missing. The imputation included the variables that were used in the final model.

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Chapter 8

Frailty as a predictor of the course of late-life depression: findings from the Netherlands Study of Depression in Older persons

Abstract

Background- Understanding the associations between frailty and depression may help to improve treatment outcome of late-life depression. The aim of this study is to test whether frailty predicts non-remission of late-life depression.

Methods- A cohort study (N=285) of depressed older persons aged ≥60 years with two years follow-up. Depression was classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Severity of depression was assessed with the Inventory of Depressive Symptomatology (IDS). Frailty was defined as physical frailty (weakness, slowness, weight loss, exhaustion, low physical activity).

Results- Frailty predicted non-remission of depression with an odds ratio of 1.21 [95% CI=0.99-1.49] (p=.064) for each additional component of physical frailty. A higher level of frailty was associated with a higher severity of depressive symptoms over the two years. Linear mixed models showed that motivational and somatic symptom severity improved significantly more over time in frail patients (p<.001 and p=.003), although the overall level of motivational and somatic symptoms remained higher over time.

Limitations- Due to the naturalistic aspect of the cohort no differentiation could be made between the type of treatment offered to patients. Despite a large sample size, power seems to be limited to draw firm conclusions.

Conclusions- Although the faster decline of motivational and somatic symptoms of depression in patients suffering from a higher severity of physical frailty suggests some overlap between frailty and depression, physical frailty still negatively impacts the course of late-life depression. This may point to the potential importance of incorporating multi-facetted interventions in the treatment of late-life depression. Further understanding of the mediating mechanisms underlying the association between frailty and depression may further guide the development of these interventions.

Keywords: depression, frailty, older persons, Netherlands Study of Depression in Older persons (NESDO)

Introduction

Depressive disorder is a highly prevalent condition among older persons[1] and constitutes an important worldwide health issue due to its often chronic course.[2, 3] To optimize treatment of late-life depression, understanding the processes involved in the course of this mental illness is essential. An important step would be to identify risk factors that predict an unfavorable course of depression; frailty may be such a risk factor.[4, 5]

Frailty is a condition of increased risk of adverse health outcomes.[6] In a recent consensus meeting it has been concluded that physical frailty is an important medical syndrome with multiple causes and contributors.[7] Physical frailty is defined as the presence of three or more of the following five characteristics: weight loss, weakness, slowness, exhaustion and low activity level.[6] The dimensional nature of frailty is acknowledged by including a prodromal frailty state in this definition; prefrailty, which is defined as the presence of only one or two of the characteristics. When no frailty characteristics are present an older person is classified as robust.[6] Meta-analytic research has shown that approximately one out of ten persons over 65 years can be classified as physically frail.[8] Recently, we showed that more than a quarter of clinically depressed older persons fulfill criteria for physical frailty.[9]

The association between physical frailty and depressive symptoms in the population is assumed to be bidirectional.[9, 10] This leads to the question whether frailty and late-life depression are causal factors for each other, or whether they simply share similar underlying mechanisms that may also influence the presentation of one another. Suggestions for the latter hypothesis involve both psychosocial factors and stress-related pathophysiological dysregulations.[4] Latent class analyses on the individual components of physical frailty and depression suggests that the most appropriate model for understanding depression and frailty is one of comorbidity.[11] To date, three longitudinal studies in the general population have identified physical frailty as an independent predictor of the increase and protracted course of depressive symptoms.[4, 5, 12] Because these studies focused on depressive symptoms instead of a depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria results may be confounded by overlap between self-report depressive symptoms and signs of frailty. Moreover, these community-based findings cannot be extrapolated to a psychiatric population. The next step would be to assess frailty and the course of depression in a clinically depressed sample.

In the present study the effect of physical frailty on the course of late-life depression is examined. More specifically, we first examined whether physical frailty predicts non-remission of depressive disorder at two years follow-up, and second, whether

physical frailty predicts the course of depressive symptoms over time. Additionally, we zoomed in on depressive symptoms subscales. Hypothesizing a negative effect of physical frailty on depression outcome, we expect lower remission rates at follow-up and a more adverse course of depressive symptoms over time. Furthermore, we expect less improvement on the mood subscale compared to the motivation and somatic subscales with a higher level of frailty, indicating a true effect on depression that cannot be explained by symptom overlap.

Methods

Study participants came from the Netherlands Study of Depression in Older persons (NESDO),[13] an ongoing cohort study aimed at examining the long-term course and consequences of depressive and anxiety disorders in older persons (aged ≥ 60 years). The NESDO study has included 378 depressed subjects (age range: 60 through 93 years) from mental health institutes (both in- and outpatients) and from primary care who suffered from a current DSM-IV diagnosis of major depressive disorder (95%), dysthymia (26.5%), or minor depression (5.6%), of which 26.5% have two types of depressive disorders. Persons with a primary diagnosis of dementia, a Mini Mental State Examination score (MMSE) under 18 or an organic or psychotic disorder were excluded, since the course of these persons will be largely determined by the primary disorder. Insufficient mastery of the Dutch language was another exclusion criterion. All participants were competent to consent to participation and all gave written informed consent. The ethical review boards of the participating institutes approved of this study.

Data collection included an examination at one of the participating clinics or at the homes of the participants, including a structured diagnostic interview, physical tests (such as blood pressure and gait speed), and paper and pencil questionnaires. These assessments were conducted at baseline (n=510) as well as at two year follow-up (overall attrition rate of 21.4%). The course of late-life depression was followed up every six months by means of a postal assessment, including questionnaires on the severity of depressive symptoms and physical health in the past six months.

The present study was performed on all participants from the depressed group. Because of missing data on follow-up measures (n=93), this study consisted of 285 participants.[14] Persons that were lost to follow-up had lower cognitive functioning (MMSE score 27.2 versus 27.9, p=.014) and more frailty characteristics (2.2 versus 1.7, p=.002). No baseline differences with regard to age, gender, educational level, severity of depression and number of diseases were found between persons that participated in follow-up and persons that did not participate in follow-up.

Measures

Depression

The Composite International Diagnostic Interview (CIDI), version 2.1 was used in order to determine the presence of depression at baseline, as well as at two years follow-up.[15] The CIDI is a structured interview that assesses psychiatric disorders in adults according to the criteria of DSM-IV. The CIDI has good validity and reliability for depressive and anxiety disorders.[16, 17] To determine the research DSM-IV diagnosis of current minor depression, questions were added to the CIDI, as in the Netherlands Study of Depression and Anxiety (NESDA).[18] Diagnosis of depression after two years consisted of major depression and dysthymia in the past six months, and minor depression in the past month. Severity of depression was measured by the well-validated 30-item self-rating IDS,[19] which in older persons has three subscales; a mood, motivation and somatic subscale.[20] In the IDS, items are scored on a four point scale, with each item equally weighted and summed up to a total score. A higher total score indicates more severe depression.

Frailty

Physical frailty was operationalized by the following five criteria of Fried et al.[6]; 1) slowness, 2) low physical activity, 3) weight loss, 4) exhaustion, and 5) weakness. As a dimensional measure we used the number of criteria present (range $0 - 5$). Subsequently, components of frailty were analyzed. For clinical interpretation, a frailty score of 0 is considered robust; a score of 1 or 2 is considered prefrail whereas a score of 3 or more is considered physically frail.

- Slowness was measured by a 6-m walking test. For men ≤173 centimetres (cm) tall the cutoff time was 9 seconds, for men >173 cm the cutoff time was 8 seconds. The cutoff time for this criterion for women with a height of ≤159 cm was 9 seconds, for women >159 cm the cutoff time was 8 seconds (extrapolated from the data of Fried and colleagues).[6]
- Low physical activity level was defined as no daily activities such as walking and gardening, or the performance of sports less than once weekly. The self-administered version of the International Physical Activities Questionnaire (IPAQ),[21] was used to collect physical activity data over the last seven days.
- The presence of unintentional weight loss or low body mass index was used for the weight loss criterion. The CIDI question about unwanted weight loss was used to determine the loss of a minimum of one kilogram a week, during two or more consecutive weeks. Body Mass Index (BMI) was defined as weight in kilograms divided by height in meters squared. With a BMI of <18.5 kg/ m² weight loss was also considered to be present.
- Exhaustion (poor endurance and energy) was determined by two questions from

the IDS,[19] about energy level and leaden paralysis/physical energy. Participants answering positive on either of these two questions were categorized as exhausted.

- A handgrip dynamometer was used to assess muscle weakness. Participants were asked to perform two squeezes with the dynamometer, using the dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Cutoff scores were stratified by gender and BMI quartiles according to Fried et al.[6] Participants unable to perform the test were also considered weak.

Covariates
Demographic data were collected during the baseline assessment (age, gender, and educational level). Global cognitive functioning was assessed by the MMSE.[22] MMSE score (range 0-30) was used as a continuous variable, with higher scores indicating better cognitive functioning. Interrater reliability and test-retest reliability of the MMSE are good.[23, 24] Health indicators included smoking status, use of alcohol and the number of somatic diseases present. Smoking status was divided into two categories: non-smoker and current smoker. The Alcohol Use Disorder Identification Test (AUDIT) is designed to detect hazardous and harmful alcohol consumption.[25] AUDIT score was used as a continuous score. Somatic comorbidity was assessed using a self-report questionnaire about the presence of somatic diseases (lung disease, cardiovascular disease, diabetes, arthritis, rheumatism, cancer, ulcer, intestinal disorder, liver disease, epilepsy, allergy, thyroid gland disease and (head) injury), as originally developed by Statistics Netherlands (Centraal Bureau voor de Statistiek, www.cbs.nl). This questionnaire has high accuracy for chronic somatic disease as previously reported.[26]

Statistical analyses
Baseline demographics and clinical characteristics of the depressed participants were compared using independent samples t-tests for normally distributed, continuous variables, nonparametric Mann Whitney U tests for skewed continuous variables, and χ^2 tests for categorical variables. Logistic regression analyses were used to assess whether frailty score at baseline (predictor) was associated with depression during follow-up (dependent variable). Analyses were performed unadjusted, and subsequently adjusted for socio-demographics (age, gender, education) and health indicators (MMSE score, smoking status, alcohol use and number of somatic diseases). Multi-collinearity of variables included in the final model was tested with correlation matrices. All correlations between variables were <0.60, therefore none of the variables were excluded from the final model. Finally, fully adjusted linear mixed models were used to examine the association between frailty (predictor) and IDS total score during 5 time points (dependent variable). The three IDS subscales were also analyzed.[20]

Frailty and all covariates were entered as fixed factors. Subjects were treated as random factors. The interaction term frailty by time was added to the final model to assess whether the course of depression differed according to the level of frailty.

When estimated mean scores of depression severity and depressive subscales were calculated, frailty was used as a nominal variable with three categories (robust, prefrail and frail) for graphical purposes. In all other analyses frailty was used as a continuous variable. All p-values were tested two-tailed and p values ≤.05 were considered statistically significant. Data were analysed using Statistical Package of the Social Sciences (SPSS), version 20.0.

Results

The mean age of the participants was 70.7 (Standard deviation (SD) =7.4) years and 66.1% was female. One participant had more than two missing items on the frailty count and was therefore considered missing. Baseline characteristics of the participants are shown in Table 1. Participants with frailty were older, less educated, had lower cognitive functioning, used less alcohol, and were more severely depressed than participants without frailty at baseline. After two years, 40.4% of the participants had a depressive disorder in the past six months, 25.3% had dysthymia in the past six months and 3.9% had a minor depression in the past month. Of the participants with depression at baseline, 21.1% had two types of depression (major depression and dysthymia) during follow-up.

Depression diagnosis after two years
Persons depressed and frail at baseline suffered from depression after two years more often than their non-frail counterparts in the unadjusted model. This association lost significance in the fully adjusted model (odds ratio (OR)=1.21 [95% CI: 0.99-1.49], p=.064, Table 2). Nonetheless, the OR was borderline significant in this final model. Removing somatic comorbidity from the model resulted in a significant association (OR=1.25 [95%CI: 1.02-1.53], p=.028). With regard to the five frailty components, only exhaustion and low physical activity level at baseline were significantly associated with depression diagnosis after two years.

Chronicity of depressive symptoms
The presence of frailty at baseline predicted chronicity of depressive symptoms, also after adjusting for socio-demographics and health indicators simultaneously. An interaction effect with time was also found, implying that the course of depressive symptoms differed according to frailty status at baseline (Figure 1). Figure 1 presents the course of depressive symptoms graphically for robust (score 0), prefrail (score 1 or 2)

Table 1 Sample Characteristics (N=285)

Characteristics	Frailty at baseline (N=76, 26.7%)	No frailty at baseline (N=209, 73.3%)	P Value[a]
Age, mean (SD), y	73.5 (8.3)	69.6 (6.9)	<.001
Female gender, %	72.4	63.2	.148
Education, mean (SD), years	9.9 (3.0)	10.8 (3.6)	.046
MMSE score, mean (SD)	27.4 (2.1)	28.1 (1.6)	.014
Smoker, %	20	35.9	.268
Alcohol use, mean AUDIT score (SD)	1.8 (2.7)	2.9 (3.7)	.010
No of diseases, mean (SD)	1.8 (1.4)	1.4 (1.10)	.030
IDS score, mean (SD)	37.2 (12.5)	27.0 (11.8)	<.001
Frailty components:			
- Weight loss, %	57.9	26.3	<.001
- Weakness, %	65.8	6.3	<.001
- Slowness, %	57.3	12.6	<.001
- Exhaustion, %	90.7	41.5	<.001
Low physical activity level, %	74.7	24.1	<.001

Abbreviations: IDS, Inventory of Depressive Symptomatology; MMSE, Mini Mental State Examination; WHODAS, WHO-Disability Assessment Schedule
[a] Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables) and U tests (continuous, skewed variables).

and frail (score ≥3) depressed older persons. It shows that robust persons have rather consistent depressive symptom levels over time, in contrast to prefrail and frail depressed persons who show persistent elevated levels of depressive symptoms despite higher symptom reduction over two years.

When subscales of the IDS were analyzed (mood, motivation and somatic subscale), frailty was associated with higher severity on all three subscales (Table 3). Mood symptoms of depression reduced equally over the two years follow-up for all categories of frailty in depressed older persons (Figure 2). Frailty predicted more decline of motivational and somatic symptoms of depression (Figures 3 and 4). In all subscales, frail depressed older persons had increased depressive subscale symptom levels over two years follow-up.

Table 2 Logistic Regression Analysis of the Association Between Frailty and Depression Diagnosis After Two Years of Follow-up

N= 285

Frailty:	*OR (95% CI)*	*P Value*
Unadjusted	1.23 (1.02, 1.49)	.028
Adjusted[1]	1.21 (0.99, 1.49)	.064
Frailty components[1]:		
Weight loss	0.72 (0.43, 1.19)	.200
Weakness	1.05 (0.58, 1.90)	.886
Slowness	1.55 (0.82, 2.92)	.175
Exhaustion	1.90 (1.15, 3.12)	.012
Low physical activity level	1.81 (1.09, 3.02)	.021

[1] Adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use and somatic diseases.

Table 3 Linear Mixed Model Analysis of the Longitudinal Association Between Frailty and Depressive Symptoms, and Depressive Symptoms Subscales

N=285	Depressive Symptoms		Mood Subscale		Motivation Subscale		Somatic Subscale	
Frailty	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value
Unadjusted	3.51 (0.48)	<.001	1.10 (0.19)	<.001	0.61 (0.11)	<.001	1.09 (0.16)	<.001
Model[1]	3.24 (0.50)	<.001	1.09 (0.20)	<.001	0.61 (0.11)	<.001	0.93 (0.16)	<.001

[1] Adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use and somatic diseases.

Figure 1 Course of Depressive Symptoms (Estimated Means) Over Two Years for Robust (Score 0), Prefrail (Score 1 or 2) and Frail (Score≥3) Depressed Older Persons (N=285)[1, 2]

Abbreviation: IDS, Inventory of Depressive Symptomatology
[1] Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use and somatic diseases.
[2] Interaction effect frailty*time: p=.001.

Figure 2 Course of Depressed Mood Symptoms (Estimated Means) Over Two Years for Robust (Score 0), Prefrail (Score 1 or 2) and Frail (Score≥3) Depressed Older Persons (N=285)[1, 2]

Abbreviation: IDS, Inventory of Depressive Symptomatology
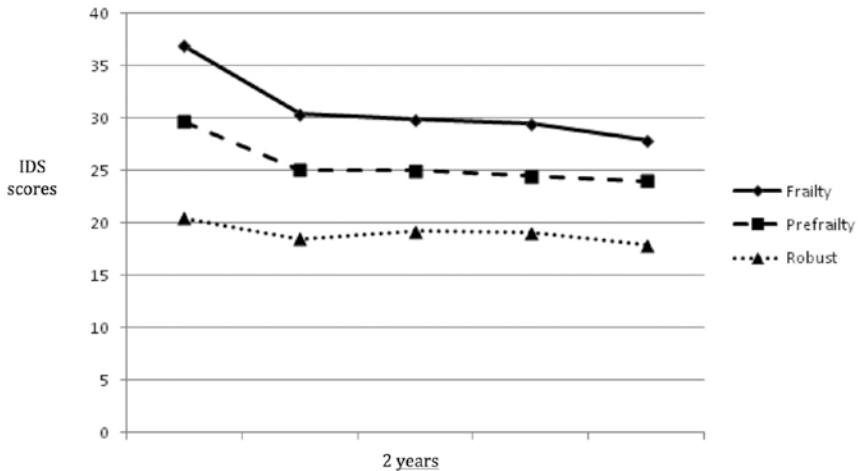[1] Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use and somatic diseases.
[2] Interaction effect frailty*time: p=.198.

Figure 3 Course of Motivational Symptoms (Estimated Means) Over Two Years for Robust (Score 0), Prefrail (Score 1 or 2) and Frail (Score ≥3) Depressed Older Persons (N=285)(N=285)[1, 2]

Abbreviation: IDS, Inventory of Depressive Symptomatology
[1] Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use and somatic diseases.
[2] Interaction effect frailty*time: p<.001.

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Figure 4 Course of Somatic Symptoms (Estimated Means) Over Two Years for Robust (Score 0), Prefrail (Score 1 or 2) and Frail (Score ≥3) Depressed Older Persons (N=285)[1, 2]
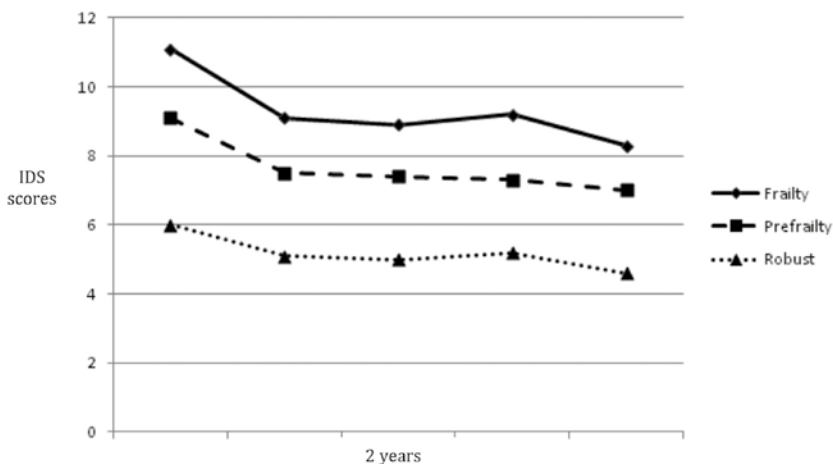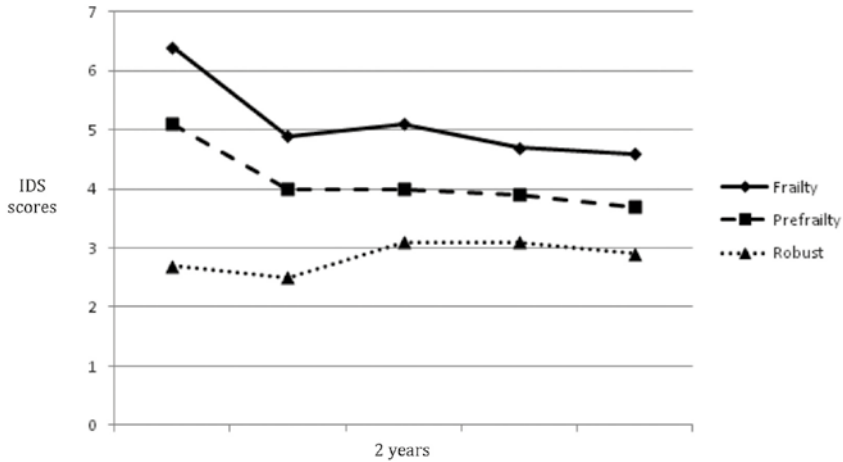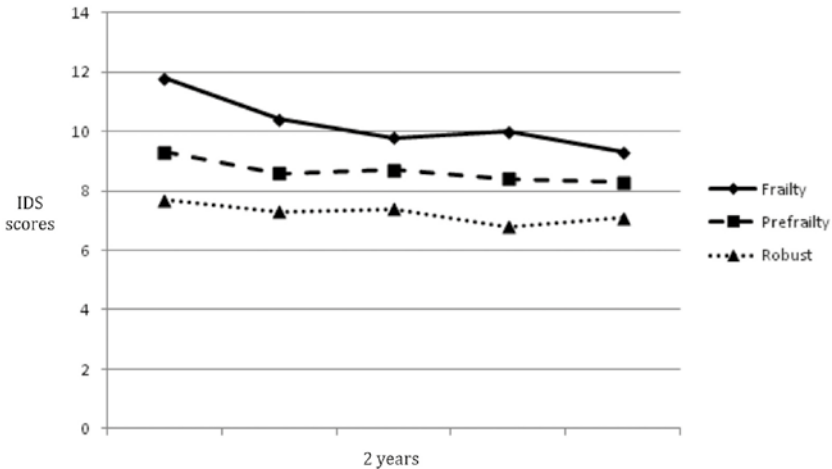

Abbreviation: IDS, Inventory of Depressive Symptomatology
[1] Based on linear mixed model analyses adjusted for age, gender, level of education, Mini Mental State Examination score, smoking status, alcohol use and somatic diseases.
[2] Interaction effect frailty*time: p=.003.

Discussion

Main findings

The present study, to our knowledge, is the first to examine the longitudinal association between physical frailty and depressive disorder in a sample of clinically depressed older persons. Our results confirm that late-life depression is a highly persisting disorder with half of the patients not achieving remission at two years follow-up. A higher level of physical frailty predicted non-remission of depression at two year follow-up, although the fully adjusted model did not reach statistical significance (p=.064). This may, however, be explained by overcorrection by somatic co-morbidity, which is associated with physical frailty as well. With respect to frailty components, both exhaustion and low physical activity level predicted non-remission of depression at two years.

Physical frailty was also associated with a higher level of depressive symptoms over time. In contrast to our hypothesis, a higher level of frailty predicted more decline in depression severity over time. This finding was driven by the motivational and somatic symptoms of depression, which may point to some overlap between both syndromes, as has been remarked before.[11, 27]

Comparison with literature

Our results are in line with findings from a recent literature review on the relation between frailty and depression, that finds that in all prospective studies, frailty is a predictor of (persistence of) depressive symptoms.[10] However, included studies mainly defined frailty as activities of daily living (ADL) indices or used a simplified proxy for frailty, such as gait speed. Results from that same review suggest a bidirectional relation between frailty and depression, which might imply a vicious frailty-depression circle. Even more recently, three longitudinal studies, not included in this review, showed that physical frailty was an independent predictor of depressive symptoms in community-dwelling older adults.[4, 5, 12] However, one study included middle aged and older adults (aged ≥55 years)[4], and the second had a relatively short follow-up period (15 months).[12] Our study extends these findings to a clinically depressed population, emphasizing the importance of physical frailty for geriatric psychiatry.

Physical frailty was associated with higher depressive symptom severity over the two years follow-up. Interestingly, motivational and somatic symptoms of depression decline faster with increasing frailty, an effect not found with respect to the mood symptoms of depression. These findings may point to an aggravation of frailty-related motivational and somatic depressive symptoms at baseline as measured by the IDS. However, despite the faster decline of motivational and somatic symptoms over time, depressed patients with physical frailty still suffered from a higher depressive symptom severity at two year follow-up.

In clinical practice, remaining symptoms will often be regarded as residual depressive symptoms that need further (intensifying of) psychiatric treatment. However, our results suggest that these symptoms might also be accounted to frailty. If true, these symptoms simply warn for more aggressive depression treatment, as physical frailty is a high-risk state for adverse effects. These results imply that assessment of physical frailty at the start of and during the treatment of the depression may guide treatment choices. Persons suffering from this type of frail-depression may be eligible for specialized care, targeting both frailty and depression.

Interventions on reducing frailty could be promising, because previous research shows that frailty is a reversible condition[28] that can be treated with assistance in daily living, vitamin D suppletion, and improving exercise frequency.[29-33] Furthermore, polypharmacy is recognized as a major contributor to the pathogenesis of frailty, and evaluation of inappropriate medication use seems beneficial for frailty status, as well as health care costs.[7] Growing evidence suggests the effectiveness of these interventions not only for frailty, but also for the treatment of depression.[34, 35] Since late-life depression and frailty frequently co-occur, these interventions may be particularly beneficial for the frail-depressed subgroup.

Diagnosis of depression is often complicated by the presence of somatic comorbidity, pain and frailty.[11, 35, 36] Underlying mechanisms of the association between frailty and depression may include inflammatory processes, sarcopenia, and lifestyle factors such as smoking and lack of exercise, because these have all been associated with both frailty and depression.[35, 37-40] Since the analyses in this study were corrected for smoking and somatic comorbidity, a possible explanation for the chronic course of depression in the case of co-existing frailty could lie in the hampering effect of frailty-induced inflammation and sarcopenia on the recovery from late-life depression. Previous studies have shown the negative effect of inflammation and sarcopenia on the course of depression.[35, 39]

Strengths
This study has some important strengths. We prospectively examined whether frailty predicts a chronic course of depression. Furthermore, we included a sample of older persons with a DSM-IV confirmed depression diagnosis, contrary to previous studies that used questionnaires as an indicator of depression status.[4, 5, 11, 12] In addition to the formal depression diagnosis, this study used a well-validated measure of severity of depressive symptoms (IDS) that included symptom profiles of depression, in order to perform in-depth analysis of the associations that were found between frailty and depression diagnosis after two years.

Limitations
A limitation of this study is the naturalistic aspect of the cohort, in which no differentiation was made between the types of treatment that depressed older persons received. It is not certain whether persons had the same treatment and if the treatment persons received was the most appropriate treatment. Futhermore, the lower frailty scores of participants in the analytical sample as compared to those who dropped out, suggest that the most frail participants were not followed up. This may bias our results towards an underestimation of the association between frailty and depression at two years of follow-up, and provides an explanation for the fact that we found only a trend towards significance regarding this association in the fully adjusted analysis. The most important limitation, however, may be that we still cannot disentangle symptoms of frailty and symptoms depression definitively as both constructs have been measured at the same time.

Clinical implications
In closing, our results clearly show that depression with comorbid frailty is less likely to resolve. Taking previous studies into account, it seems that frailty and depression are intertwined and that frailty contributes to a chronic, more severely depressed subtype. Frailty and depression might thus stimulate each other's occurrence, but once both are present, multiple interactive processes may arise, worsening the depression as well as the frailty status more and more.[10, 11, 41]
This indicates that frailty may be an important element in the treatment of depression in older persons and that multi-facetted interventions are needed for this particularly vulnerable subgroup of depressed older persons.

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Chapter 9

Summary and general discussion

The main aim of this thesis was to study the concept of frailty in relation to late-life depression, the association between depression and somatic diseases, and the explanatory role of frailty in this association. Inflammation is examined as a potential mechanism, underlying these complex associations.

The thesis consists of three parts. In part I we focused on the concept and epidemiology of frailty by conducting systematic reviews and calculating pooled prevalence rates. In part II we described the cross-sectional association between frailty and depression in a sample of clinically depressed persons from the Netherlands Study of Depression in Older persons (NESDO).[1] We also tested whether the association between depression and somatic diseases was mediated by frailty and evaluated the association between physical frailty and inflammation. In part III we focused on longitudinal associations between frailty and depression in a community-dwelling sample of older persons (Invecchiare nel CHIANTI; aging in the Chianti area: InCHIANTI)[2] and in NESDO.

In this chapter findings from the preceding chapters will be summarized and discussed within the context of current scientific knowledge. Next, some notes will be given on methodological issues, clinical implications and recommendations for future research. Finally, we will discuss the case report from the Introduction (Chapter 1) in the light of the findings from this thesis.

Summary of the findings

The concept of frailty
The ongoing scientific discussion about the definition of frailty limits the use of the concept in clinical practice. This discussion is mainly dominated by two groups of researchers. One group defines frailty as a purely physical condition, whereas the other group proposes a broader definition of frailty also including psychosocial components. Despite this lack of consensus about the definition, there is no reason why frailty is of less importance for older patients with mental disorders compared to older persons with somatic diseases. Frailty may thus enable the early detection of a particularly vulnerable group of older psychiatric patients, at risk of (somatic) complications. An issue for implementation of frailty in old age psychiatry however, is the overlap between psychiatric disorders and frailty, especially the broad frailty definitions.

In Chapter 2 we contributed to this discussion by giving an overview of existing frailty definitions. In addition, we described the relation between frailty and psychiatric disorders. In total, 35 operationalizations of frailty were found by means of a systematic literature review. These consisted of single measurements as a proxy for frailty (n=4),

syndrome diagnoses (n=18), subdivided in single (n=5) and multiple syndrome diagnoses (n=13), and dimensional operationalizations for which measurement instruments were used (n=13).

Only six studies reported on the relation between frailty and psychiatric disorders. These studies revealed an association between frailty and psychopathology, in particular depression. Whether depression and frailty share the same pathophysiological mechanisms or whether depression leads to frailty or vice versa remained unknown, although many authors implicitly assumed a reciprocal relationship.

We conclude that there is agreement that frailty should be considered as a condition of vulnerability for adverse health outcomes, but controversy remains about how frailty should be exactly defined and operationalized. An important characteristic of broad frailty definitions is its applicability to clinical practice, where most older persons do not present themselves with problems in only one (physical) domain. For general practitioners for instance, it may be very helpful to evaluate vulnerability of older persons by a broad definition. This broader approach forces clinicians to consider not only physical risk factors, but also factors like social support, cognitive functioning and psychopathology as contributing factors to the general condition of an older person. However, it is important to realize that by including many domains, two frail persons may experience very different problems. Moreover, in old age psychiatry it is of little value for a clinician when all patients meet the criteria of frailty, based on their psychiatric disorder.

The lack of articles about the relationship between frailty and psychiatric disorders, and especially depression, shows that frailty has not received a lot of attention within the field of old age psychiatry. A necessary step would be to clearly define and substantiate the choice for the frailty definition that is used. A recent breakthrough in the discussion about the definition of frailty is a consensus paper by an international group of frailty experts. Here it was concluded that physical frailty is an important medical syndrome with multiple causes and contributors.[3] It was also agreed that a number of validated and well-defined models of frailty exist and that the basic criteria of these models should be used to diagnose frailty. For frailty research within a psychiatric setting, a physical frailty definition seems most useful, because broad frailty definitions include psychiatric symptoms or diseases as a component of frailty. Based on these findings, we chose to operationalize frailty according to a purely physical definition when studying associations between frailty and depression in the following chapters.

Prevalence of frailty in the community and in a depressed sample of older persons
Chapter 3 and 4 report on the prevalence of frailty. Although it is generally assumed that the prevalence of frailty increases with age, is higher among women compared to men and more prevalent in the presence of chronic disease,[4-6] no consensus exists about the prevalence rates of frailty. In Chapter 3 we systematically compared these prevalence rates with regard to definition, gender and age groups in community-dwelling older persons aged 65 and over. Subsequently, these prevalence rates were pooled and weighted in order to calculate overall frailty prevalence. The overall weighted prevalence of frailty based on 21 studies, including 61,500 subjects, was 10.7%.

In studies that used a physical frailty definition, frailty prevalence in persons aged ≥65 years ranged from 4.0% to 17.0%, with a pooled prevalence of 9.9%.[7, 8] In studies that used broad definitions or measurement instruments, the prevalence rates varied from 4.2% to 59.1%, with a pooled prevalence rate of 13.6%.[9, 10] Furthermore, we confirmed that frailty prevalence increased with age and was higher in women than in men. These results imply that frailty is common in later life, however differential operationalization of frailty status results in widely different prevalence rates between studies. The smaller range of frailty prevalence rates among studies that used a physical frailty definition, suggests more consensus between researchers studying physical frailty, and probably a less heterogeneous concept.

Future studies should focus on clarifying which frailty characteristics predict particular negative health outcomes most accurately. Therefore, frailty should not only be measured as a summary score or categorical measure that is either present or absent, but its separate components and potentially multidimensional aspects should also be taken into account.

After determining the prevalence of frailty in community-dwelling older persons, we zoomed in on a group of depressed older persons in Chapter 4. In a cohort of older persons with depression according to DSM-IV criteria[11] (NESDO) we assessed the prevalence of physical frailty. We found that the prevalence was significantly higher in the depressed group compared to the non-depressed comparison group (27.2% versus 9.1%) with an odds ratio (OR) of 2.7 (95% confidence interval [CI] 1.6-5.2) when adjusted for age, sex, level of education, somatic comorbidity and cognitive functioning. Frail-depressed older persons were more severely depressed than non-frail-depressed older persons.

Subsequently, we explored whether the hypothesized association between depression and frailty could be explained by shared characteristics, such as exhaustion and weight loss. We repeated the analyses with two uni-dimensional proxies of frailty

(weakness and slowness), and this yielded similar results compared to the formal physical frailty definition we used.

Finally, we performed the analyses with the sum score of an adapted version of the Inventory of Depressive Symptoms (IDS; without overlapping frailty items), and two subscales of the IDS (mood/ cognition subscale and anxiety/ arousal subscale).[12] These analyses showed that frailty was significantly associated with all measures of depressive symptoms in depressed patients, and it is therefore unlikely that the higher severity of depressive symptoms in frail-depressed older persons can be explained by overlapping criteria between frailty and depression.

Depressed patients therefore, should not be excluded a priori in (community) studies of frailty, as has been done in the hallmark study of Fried et al.[4] In 2001, Fried and colleagues[4] validated physical frailty in the Cardiovascular Health Study as a constellation of elements of which the presence of a critical subset of these components indicates the presence of frailty. The elements were chosen for their predictive value towards adverse health outcomes. Adding together these elements would increase the predictive value even more than just the sum of these elements. Negative health outcomes were defined as major geriatric outcomes and operationalized as: falls, disability, hospitalizations and death. Remarkable in the light of findings presented in this thesis, is that participants that used antidepressants were excluded from the study, as the authors were concerned that a depressed participant could potentially present with frailty as a consequence of a single disease (in this case depression). We showed that within a sample of depressed older persons three quarters are not frail. So, although frailty prevalence is undoubtedly higher in depressed older persons than in community-dwelling older persons, the presence of depression does not make a person meet the criteria of physical frailty. In this light, the importance of studying associations between frailty and depression is emphasized. Previous research already showed that frailty prevalence is higher in patients suffering from chronic somatic disease than in community-dwelling older persons,[13, 14] and now we showed that this applies to depressed patients as well.

Furthermore, recent empirical data confirm that frailty and late-life depression are overlapping,[15] but distinct syndromes rather than a single construct.[16] Based on these findings from literature and the findings from this thesis, it is recommended that when studying frailty or depression in association with adverse health outcomes, both constructs should be treated as determinants of one another in the analyses.

Late-life depression, somatic comorbidity, inflammation and frailty
Depression and frailty are well-established risk factors for somatic diseases,[4, 17] but

they have hardly been examined in concert. Both frailty and depression may share underlying mechanisms or pathways towards somatic diseases, including inflammation.[17, 18] In order to prevent somatic morbidity, knowledge of the interplay between depression and physical frailty is crucial. We therefore conducted the study that is described in Chapter 5. Based on existing literature[19, 20] we hypothesized that somatic diseases are more prevalent among depressed patients than among healthy controls. Second, we examined whether physical frailty is an explanatory factor of the association between depression and somatic diseases. Finally, we explored the moderating effect of frailty in the association between depression and somatic diseases. This study was conducted within a cohort of older persons with depression according to DSM-IV criteria[11] (NESDO).

The study showed that depressed patients suffered from more somatic diseases than the non-depressed comparison group. We also zoomed in on types of diseases (lung disease, stroke and gastro-intestinal disease; retrieved from univariate analyses of nine separate diseases), and showed that depression was only associated with stroke, in the fully adjusted model. Furthermore, depression and frailty remained associated with the number of somatic diseases, independent of each other and frailty partly explained the association that was found between depression and somatic diseases. This implies that depression and frailty not only have shared relations with somatic diseases but also unique relations. No high-risk group could be identified, as frailty did not moderate the relation between depression and somatic diseases.
In geriatric medicine there is a growing consensus that frailty and multimorbidity are distinct clinical entities that are causally interrelated.[21] The relations between depression and somatic diseases are complex, and analogue to the impact of frailty on the course of somatic diseases,[22, 23] the presence of frailty probably also complicates the course and treatment of late-life depression.

After examining the role of frailty in the association between depression and somatic diseases, we wanted to learn more about the possible mechanisms underlying frailty and depression. Both depression and frailty are associated with low-grade inflammation.[17, 18, 24, 25] Hence, in Chapter 6 we examined whether low-grade inflammation in late-life depression is conditional on the level of frailty. We first assessed the associations between inflammatory markers and physical frailty in a sample of depressed older persons (NESDO). Next, we examined which frailty components contribute to the association between frailty and inflammation. We found that physical frailty was not associated with increased levels of inflammatory markers in depressed older persons. When studying the individual components of frailty, we found that weakness (handgrip strength) and slowness (walking speed) were associated with markers of low-grade inflammation.

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Principal component analysis showed that the frailty components that do not overlap with the criteria of depression represent one dimension of the construct of frailty (performance-based dimension: consisting of weakness, slowness and low activity level). Only this dimension is associated with low-grade inflammation. The other dimension consisted of the frailty items weight loss and exhaustion and was labelled the vitality-based dimension. These findings imply that physical frailty is not a uni-dimensional construct within a depressed population.

Our findings suggest differential patterns between specific inflammatory markers and specific frailty components. However, all inflammatory markers were associated with the performance-based physical frailty dimension. Low-grade inflammation may thus be a general underlying mechanism of the shared variance by the three individual frailty components compiling performance-based physical frailty.

Does frailty predict the incidence and course of depression?
To better understand the findings from the cross-sectional data we need a cause and consequence approach. Hitherto, the impact of physical frailty on depression has been examined only twice using a prospective study design. Both studies identified physical frailty as an independent predictor of incident depressive symptoms according to a depression scale.[26, 27] Although a cutoff of a depression severity scale cannot be extrapolated to a depressive disorder,[28] it is still of interest as clinically relevant depressive symptoms have high impact on well-being, disability and utilization of health care services.[29] Generalization to a Western society, however, may be limited because both studies were conducted in an Asian population. Moreover, one of these studies had a follow-up duration of only 15 months.[27] Therefore, we conducted two longitudinal studies, one within a sample of community-dwelling older persons and focusing on clinically relevant depressive symptoms (InCHIANTI; Chapter 7), and one within a sample of older persons with depression according to DSM-IV criteria[11] (NESDO; Chapter 8).

In the first study, we assessed whether physical frailty predicts a higher incidence of depressed mood in non-depressed community-dwelling older persons. We also assessed whether physical frailty decreases the chance on remission of depressed mood in persons with depressed mood at baseline. We found that physical frailty predicts onset and non-remission of depressed mood. When frailty was decomposed into components, only low physical activity level increased the risk of incident depressed mood and non-remission of depressed mood.

These findings are in line with findings from the two longitudinal studies described earlier.[26, 27] Both studies also found a longitudinal association between frailty and depressive symptoms. Separate frailty components were also analyzed in the study

by Feng et al.[26] and it was concluded that exhaustion, weakness, slowness and low physical activity level were predictive of onset and persistence of depressive symptoms. Our study confirms these findings in a Western society, but also extends these findings by determining the contribution of frailty to remission of depressed mood. In addition, the risk of depression in the case of frailty is also confirmed for a relatively long follow-up period (nine years).

Our study differed from the study by Feng and colleagues[26] in the level of correction for possible confounders of the association between frailty and depressive symptoms, since we did not correct for activities of daily living (ADL) and instrumental activities of daily living (IADL) dependency in our analyses. Our multicollinearity tests showed high correlations between frailty, ADL and IADL dependency (all >0.6) and therefore we decided not to include these potential confounders in our model. However, to confirm that our results are independent of functional status we repeated the analyses with correction for ADL, IADL and WHO level of disability status for this chapter. The analyses showed that frailty remained an independent predictor of depressed mood and lack of frailty predicted remission of depressed mood, even after correction for various measures of functional status (all P values <.026).

A recent literature review on the relation between frailty and depression also showed that frailty, its components and functional impairments are risk factors for depression.[30] However, none of the studies in this review used a formal definition of frailty. Instead, ADL indices were used as a measure of frailty.

In Chapter 7, physical frailty consistently predicted depressed mood. Results with respect to individual frailty components also seem quite consistent. This may be an indicator of unequivocal validity of physical frailty as a uni-dimensional concept in the general population with respect to its association with late-life depressed mood.

Whether physical frailty predicts the course of not only depressive symptoms, but also of depressive disorder, was examined in Chapter 8. Additionally, we focused on depressive symptoms subscales representing symptom clusters. Recent research by Hegeman and colleagues with the NESDO data revealed three IDS subscales; a mood subscale, a somatic subscale, and a motivational subscale.[31] We showed that physical frailty was associated with depression diagnosis after two years (statistically significant in the unadjusted model and a trend towards significance in the fully adjusted model). With respect to frailty components, both exhaustion and low physical activity level were associated with a depression diagnosis two years later. Furthermore, we confirmed that a higher level of physical frailty was associated with a higher severity of

depressive symptoms (IDS) over time. Despite a higher decline in depression symptom severity over time, depression with comorbid frailty is less likely to resolve.

The analyses of the depressive symptoms subscales showed that motivational and somatic symptoms of depression improve faster with increasing frailty, an effect not found with respect to the mood symptoms of depression. However, despite this improvement, the motivational and somatic symptoms of depression remained inflated over the two years, as frailty scores increased. This finding has clinical relevance, since these remaining symptoms will often be regarded as residual depressive symptoms that need further psychiatric treatment. However, these symptoms might also be accounted to frailty and in that case, frail older persons might be classified as still being depressed while their depression has already improved. This may place them at risk for psychiatric overtreatment (and associated side-effects).

These findings support conclusions that were drawn from earlier studies about overlap between physical frailty and depression,[16, 33] since the somatic and motivational subscales show overlap with frailty components. This is also in line with findings from a recent study that finds that the severity of depression may be overestimated in the presence of somatic comorbidity, but only with respect to somatic and motivational symptoms.[34]

Overall conclusions

All in all, the physical frailty phenotype[4] appears to be a relevant operationalization of frailty for research in old age psychiatry. In community-dwelling older persons, one out of every ten persons is frail and frailty predicts the incidence of depressed mood, as well as chronicity of depressed mood. In older persons that suffer from depression according to DSM-IV criteria,[11] over a quarter is also physically frail. Furthermore, in these clinically depressed older persons frailty partly explains the associations between depression and somatic diseases, and inflammatory makers are associated with the performance-based components of frailty. Finally, physical frailty predicts an adverse course of depression over two years.

These results are indicative of intertwined relations between frailty and late-life depression, and may suggest the existence of a specific subtype of late-life depression, which might be labeled as a frail-depression. Although this depressive subtype is associated with non-remission, the implications of this thesis are positive as well. As both depression and frailty are essentially treatable conditions, the comorbidity between both conditions argues for the development of multimodal treatment strategies focusing on both mental and physical health. Future studies in this particular group

of depressed older persons should teach us whether the prognosis of frail-depression can indeed be improved.

Methodological considerations

Strengths and limitations of the individual studies have already been discussed in the previous chapters. Below, some overarching considerations will be discussed.

Study type

The middle part of this thesis was based on cross-sectional findings; the baseline NESDO data. No causal relations can be drawn from these studies, as it cannot be determined which of the factors occurred first. In addition, the comparison group of NESDO was recruited among non-depressed general practitioner visitors, who can be assumed to have more illnesses and medical complaints than community-dwelling elderly. Therefore, the differences we found between the depressed group and the comparison group are probably conservative and may represent an underestimation of the actual associations addressed in Chapter 4 and 5.

In Chapter 7 and 8 we used longitudinal data of respectively the InCHIANTI study and NESDO, in order to draw cause and consequence conclusions. InCHIANTI consists of a large community-dwelling sample with a long follow-up period (nine years) with selective dropout during follow-up; persons that dropped out were more often frail than persons who stayed in the study, biasing the results towards an underestimation of the associations that were found between frailty and depressed mood.

A limitation of the longitudinal NESDO data is the naturalistic aspect of the study, with no detailed information about the type of treatment and whether the treatment that depressed persons underwent was the most appropriate treatment available.

Frailty definition

As shown in Chapter 2, many definitions of frailty are available. We concluded that for research in a psychiatric population, a physical definition of frailty is most applicable. Although this definition showed some overlap with depression symptoms, the broad definitions show even more overlap with depression, by including depressed mood as a component of the frailty definition.

In all chapters we addressed the potential overlap between frailty and depression and attempted to control for this overlap by repeating the analyses with an adapted IDS sum score (overlapping items were removed) and using proxies of frailty.

Frailty was used as a dichotomous variable (present yes/no) in Chapter 4. In Chapter 5 we also assessed frailty as a continuous variable and examined separate components of frailty. We kept this approach throughout the subsequent chapters, as it turned out that dimensional frailty was more informative that a dichotomized frailty measure.

Depressive symptoms versus depressive disorder
Depressive symptoms are generally considered on a continuum with depressive disorder, and they also have a high impact on quality of life.[29] When possible we examined both depressive disorder according to DSM-IV criteria[11] and depressive symptoms in addition to each other. Only the InCHIANTI data did not provide the opportunity for that, since no information about depression diagnosis was available (Chapter 7). In 2013 DSM-5 came out as a successor of DSM-IV. With regard to diagnosing depression no significant alterations have been made, implying that the findings from this thesis hold true in the light of the DSM-5.

Confounding
Both NESDO and InCHIANTI provide the opportunity for adequate control of potential confounders. However, it cannot be ruled out that the associations that were studied were confounded by some unknown variables.

Implications for clinical practice and recommendations for future studies

An important step is to translate the findings from this thesis to clinical practice. Frailty is relatively unknown and unrecognized in daily clinical practice of old age psychiatry. However, this thesis will hopefully add to the growing sense of importance of frailty, in order to provide the complex care that frail-depressed older persons need.

Frailty can be a useful construct to detect a particularly vulnerable group within depressed older persons that are at risk of a more chronic course of late-life depression. We showed that physical frailty predicts the onset of depressed mood, as well as lower remission rates of depressed mood. In a clinically depressed sample we confirmed the adverse course of depression in the presence of frailty.

Since frailty is a potentially reversible condition that can be targeted with specific interventions such as exercise, vitamin D supplementation and reduction of polyphar-macy[3], it can guide treatment. Therefore screening for frailty deserves a prominent place in the treatment of late-life depression. Besides screening for frailty, monitoring is also an important element. Nurses and clinicians should keep themselves informed about the frailty status of a person in order to help determine whether a symptom

should be accounted to depression, to frailty of perhaps another phenomenon that is highly prevalent in old age, such as somatic diseases. This makes the treatment of late-life depression complicated, and we therefore advocate disentangling depressive symptoms in future studies.

In Chapter 8 we unraveled depressive symptoms into three subscales and concluded that depressed mood improves similarly in both frail and non-frail depressed persons. Motivational and somatic complaints show more improvement with increasing frailty status, although the overall level of these complaints remained higher over time. This is a finding with high clinical relevance, as it changes the perspective on the course of late-life depression. It should be assessed whether these remaining symptoms are part of the depressive disorder, or whether they are part of frailty. In the first case, psychiatric treatment may be intensified. When these symptoms are accounted to frailty, a psychiatric treatment setting is no longer indicated and interventions targeting frailty are more appropriate.

From a clinical point of view, we could argue that physical frailty and depression are intertwined and that frailty contributes to a chronic, more severely depressed subtype. This asks for a treatment of late-life depression in which screening and monitoring of frailty are embedded. Interventions that reduce frailty may also be beneficial for depressive complaints, but this should be examined in future intervention studies.

Not only intervention studies are needed, also more longitudinal research that specifically studies the (reciprocal) associations between frailty and depressive disorder over a longer period are needed. In addition, future studies should pay attention to the relationship between adverse health outcomes and the individual components of frailty in order to determine the validity of the concept of frailty with regard to various health outcomes.

Back to the case-report
How can we use the findings from this thesis in the case of ms E that was described in Chapter 1? An important element in treatment of late-life depression is the disentangling of (depressive) symptoms. Late-life depression is a heterogeneous disorder and therefore, for each symptom it should be assessed whether it can be accounted to the depressive disorder, or to frailty. With this in mind, we will discuss the case of ms E.

"I am 70 years old, but I look and feel like I am 85 years", said ms E with a gloomy voice. Glancing at ms E while she shared this with me, I could only agree with her. I wondered, where does this discrepancy between her presentation and her real age come from? Why does her neighbor that has the same age still babysits her grandchildren and has an independent life, while ms E is obviously struggling with active aging? Should we consider ms E both frail and depressed?

When examined in more depth, ms E may meet the criteria for, major depressive disorder (or at least minor depression) and physical frailty. Frailty may be an explanation for the prolonged admission of ms E, as compared to previous admissions to the psychiatric ward for depression treatment. Furthermore, the chronic character of her depressive complaints may be partly accounted to the presence of frailty. It is striking that ms E's mood improved, but wearily and exhaustion symptoms remained present. It should be carefully considered whether these remaining symptoms are abiding depressive symptoms that need continuation, or even intensifying of psychiatric treatment, or whether ms E may have been frail before she was admitted to the psychiatric ward with depression and these symptoms should be accounted to frailty. The latter is the most likely explanation, since the information that was provided by ms E's daughter also points to the presence of frailty characteristics before she became depressed. If this is indeed the case, interventions that target frailty are in place, besides the continuation of the antidepressant treatment.

All in all, the case of ms E demonstrates the complexity of treating late-life depression in the presence of frailty. In old age psychiatry, persons often present with comorbid somatic diseases and frailty that in a bad case scenario may culminate in a vicious cycle that ultimately leads towards adverse health outcomes and loss of independence. However, the good news is that when nurses and clinicians take the approach of unravelling symptoms, this may guide them in their choice for appropriate interventions that are beneficial for this vulnerable group of older persons.

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Chapter 10

Samenvatting (Summary in Dutch)

Introductie

Depressie op latere leeftijd is een ernstige psychiatrische ziekte met grote gevolgen voor de persoon zelf en de omgeving.[1] Dit is voor een groot deel te wijten aan het vaak chronische beloop van depressie en de hoge mate van terugval.[2-5] Lichamelijke ziektes en cognitieve beperkingen komen bij depressieve ouderen vaker voor dan bij niet-depressieve ouderen.[6-9] Dit suggereert een invloed van verouderingsmechanismen op het ontstaan of beloop van de ouderdomsdepressie. Normale veroudering wordt gekenmerkt door lichamelijke en functionele achteruitgang met de leeftijd, zoals botontkalking, vermindering van gezichtsvermogen, gehoor en spiermassa. Bij sommige mensen echter, zijn deze veranderingen nadrukkelijker aanwezig en leidt dit tot een verminderd welzijn en vatbaarheid voor ziektes en beperkingen.[10] Frailty is een toestand waarbij een persoon extra kwetsbaar is voor het optreden van complicaties door een afname van de reservecapaciteit van het lichaam.[10] Hierdoor kan zelfs een relatief kleine stressor ernstige gevolgen voor de gezondheid hebben.

Het doen van onderzoek bij ouderen is complex door de verwevenheid verschillende begrippen zoals depressie, lichamelijke ziektes, invaliditeit en frailty. Soms worden deze begrippen zelfs uitwisselbaar gebruikt. In dit proefschrift worden twee van deze begrippen nader bekeken in relatie tot elkaar, namelijk frailty en depressie.

Dit proefschrift bestaat uit drie delen, waarbij in het eerste deel ingegaan wordt op frailty als concept en op de prevalentie van frailty. In deel twee wordt gekeken naar het verband tussen frailty en depressie op latere leeftijd. Tenslotte wordt in deel drie de invloed van frailty op het beloop van depressie op latere leeftijd onderzocht. In **hoofdstuk 1** staan de achtergronden en doelen van dit proefschrift beschreven. Ook wordt in dit hoofdstuk een gevalsbeschrijving gepresenteerd om de klinische relevantie van het onderwerp te illustreren.

We formuleerden de volgende onderzoeksvragen (de nummers van de vragen corresponderen met hoofdstuknummers in dit proefschrift):

Deel I:
2. Welke operationalisaties van het concept frailty bestaan er en hoe verhoudt frailty zich tot psychopathologie?
3. Wat is de prevalentie van frailty bij ouderen in de algemene bevolking?

Deel II:
4. Wat is de prevalentie van frailty bij depressieve ouderen? Kan een eventueel verhoogde prevalentie onder depressieve ouderen verklaard worden door symptoomoverlap tussen frailty en depressie?

5. Hoe verhouden depressie op latere leeftijd en frailty zich tot lichamelijke comorbiditeit?
6. Bestaat er een verband tussen inflammatie (ontstekingsactiviteit in het bloed) en frailty bij depressieve ouderen?

Deel III:
7. Voorspelt frailty zowel het ontstaan als voortbestaan van depressieve klachten bij ouderen in de algemene bevolking?
8. Voorspelt frailty het niet in remissie zijn van depressie na twee jaar? Heeft frailty bij depressieve ouderen invloed op het beloop van (specifieke) depressieve symptomen over de tijd?

Deel I: Frailty

Leeftijd is een belangrijke voorspeller voor het optreden van allerlei negatieve gezondheidsaspecten. Echter, met het stijgen van de levensverwachting in de laatste helft van de twintigste eeuw, kwam naar voren dat ook onder ouderen het risico op negatieve gezondheidsuitkomsten sterk verschilde. Dit heeft geleid tot de introductie van het begrip frailty om de meest kwetsbare ouderen met het grootste risico op slechte gezondheidsuitkomsten en verlies van zelfstandigheid te identificeren. Het gebruik van frailty in de klinische praktijk en in onderzoek wordt beperkt door een tot op heden voortdurende discussie omtrent de conceptualisatie en operationalisatie van het begrip frailty. Deze discussie wordt gedomineerd door twee onderzoeksgroepen. Hierbij definieert de ene groep frailty op basis van enkel lichamelijke kenmerken (fysieke frailty), terwijl de andere groep een brede definitie van frailty aanhangt waarbij ook psychosociale componenten opgenomen worden in de definitie.

Ondanks dit gebrek aan overeenstemming over de definitie van frailty, is frailty een belangrijk concept gebleken in de zorg voor patiënten met een lichamelijke ziekten, waarbij een groep extra kwetsbare patiënten kan worden geselecteerd voor specifieke interventies om het risico op complicaties door de onderliggende kwetsbaarheid te verlagen. Het is onduidelijk of frailty ook op deze manier kan fungeren in de psychiatrie.

In **hoofdstuk 2** wordt een bijdrage geleverd aan de hierboven beschreven discussie door een overzicht te geven van de bestaande frailty definities en de bijbehorende operationalisaties. Verder wordt de relatie tussen frailty en psychiatrische ziektes beschreven. Dit wordt gedaan middels een systematisch literatuuronderzoek. In totaal worden 35 operationalisaties van frailty gevonden. Hiervan gebruikten vier studies een enkele meting als schatting van frailty, achttien studies gebruikten een syndroom diagnose

van frailty en dertien studies gebruikten een score op een meetinstrument voor frailty.

Op basis van de gevonden studies kan worden geconcludeerd dat er impliciete overeenstemming is over *wat* frailty is; namelijk een toestand van verhoogde kwetsbaarheid voor het optreden van negatieve gezondheidsuitkomsten. *Hoe* frailty wordt geoperationaliseerd loopt sterk uiteen. Een belangrijk kenmerk van de brede definities van frailty is de compatibiliteit met de klinische praktijk, waarin de meeste ouderen problemen ervaren in verschillende domeinen, en niet alleen lichamelijke problemen hebben. Een nadeel hiervan is echter dat door het includeren van zoveel domeinen in de frailty definitie, twee personen die beide frail zijn, totaal verschillende problemen kunnen ervaren.

Slechts zes studies werden gevonden die de relatie tussen frailty en psychiatrische ziektes beschreven. In deze studies werd een verband gevonden tussen frailty en psychopathologie, in het bijzonder depressie. Of depressie en frailty dezelfde onderliggende pathofysiologische mechanismen delen, en of depressie leidt tot frailty of andersom, blijft onbeschreven. Het gebrek aan artikelen over frailty en psychopathologie illustreert dat frailty nauwelijks aandacht krijgt in de psychiatrie. Voor dit type onderzoek is een fysieke frailty definitie het best toepasbaar, omdat de brede frailty definities psychiatrische ziektes of symptomen hiervan opnemen als onderdeel van de definitie.

In **hoofdstuk 3** wordt het voorkomen van frailty in de bevolking onderzocht met behulp van een systematische literatuurstudie. Hierbij werd rekening gehouden met het type definitie van frailty, alsmede met de leeftijd en het geslacht van de deelnemers.

De gewogen prevalentie van frailty was 10.7%, gebaseerd op 21 studies met 61,500 deelnemers in totaal. Wanneer gekeken werd naar de studies die een fysieke definitie van frailty gebruikten was deze prevalentie iets lager, namelijk 9.9%. Bij de bredere definities kwam de prevalentie hoger uit, namelijk 13.6%. Opvallend was het verschil in variatie binnen de prevalentiecijfers die gevonden werden, tussen de studies die fysieke (4.0%-17.0%) dan wel brede frailty definities (4.2%-59.1%) gebruikten. Hiernaast werd bevestigd dat de prevalentie van frailty stijgt met het oplopen van de leeftijd en hoger is bij vrouwen dan bij mannen.
Dit betekent dat frailty veelvoorkomend is op latere leeftijd en dat de prevalentie hierbij sterk afhankelijk is van definitie van frailty die wordt gebruikt. De smallere reikwijdte van de prevalentiecijfers van frailty bij fysieke frailty definities, suggereert meer overeenstemming tussen onderzoekers die een fysieke frailty definitie gebruiken en naar alle waarschijnlijkheid een minder heterogeen begrip. In dit proefschrift gebruiken we dan ook de fysieke definitie van frailty van Fried en collega's,[10] waarbij

frailty wordt gedefinieerd als de aanwezigheid van minimaal drie van de volgende vijf kenmerken: gewichtsverlies, lage loopsnelheid, spierzwakte, uitputting en een verlaagd activiteitenniveau.

Deel II: Frailty en depressie

In de voorgaande hoofdstukken werd geconcludeerd dat er een gebrek is aan onderzoek naar frailty en depressie. Daarom hebben we in **hoofdstuk 4** in een cohort depressieve ouderen gekeken wat de prevalentie van frailty is. Deze bleek aanzienlijk hoger dan de prevalentie die eerder vastgesteld werd in de algemene bevolking in hoofdstuk 3. Van de depressieve ouderen bleek 27.2% frail te zijn. Ook bleek dat depressieve ouderen met frailty een ernstiger depressie hadden dan de depressieve ouderen zonder frailty. Bovendien lieten de analyses zien dat er zelfs een verband is tussen frailty en depressie na verwijdering van overlappende items uit de depressie schaal.

Omdat zowel depressie als frailty bekende risicofactoren zijn voor het optreden van lichamelijke ziektes,[10, 11] wordt in **hoofdstuk 5** beschreven of frailty een verklarende factor is in het verband tussen depressie en lichamelijke ziektes. Ook deze studie werd gedaan bij depressieve ouderen. Aangetoond werd dat depressieve ouderen meer lichamelijke ziektes hadden dan de niet-depressieve ouderen in de controlegroep. Wanneer we keken naar individuele ziekten in plaats van naar de optelsom van het aantal ziektes, vonden we alleen een verband tussen depressie en beroerte.

Frailty bleek een gedeelte van de gevonden relatie tussen depressie en lichamelijke ziektes te verklaren. Dit suggereert dat frailty en depressie gedeelde verbanden met lichamelijke ziekten hebben, maar ook unieke, aan het eigen concept toebehorende verbanden.

Na de verbanden tussen frailty, depressie en lichamelijke ziekten bestudeerd te hebben, wilden we meer weten over de rol van mogelijke onderliggende mechanismen van frailty bij depressieve ouderen. Met de leeftijd neemt ook de mate van ontstekingsactiviteit toe in het lichaam. Nu blijkt dat zowel bij ouderen met frailty als bij depressieve ouderen, verhoogde ontstekingswaardes zijn gevonden, al zijn de bevindingen bij depressieve ouderen minder eenduidig.[12, 13] In **hoofdstuk 6** wordt beschreven of er een verband is tussen deze ontstekingsactiviteit en frailty bij depressieve ouderen. Het bleek dat dit niet het geval is. Wel werd er een verband gevonden tussen de frailty kenmerken spierzwakte en lage loopsnelheid en ontstekingsactiviteit. Een principale componenten analyse liet zien dat frailty in een groep depressieve ouderen bestaat uit twee dimensies; de *lichamelijke prestatie-dimensie* (bestaande uit spierzwakte,

lage loopsnelheid en verlaagd activiteitenniveau) en de *vitaliteits-dimensie* (bestaande uit gewichtsverlies en uitputting). Tussen ontstekingsactiviteit en de lichamelijke prestatie-dimensie bleek een verband te bestaan.

Deel III: Frailty en het beloop van depressie

De beschreven hoofdstukken roepen vragen op over de gevolgen van frailty voor het beloop van depressie. Daarom beschrijven we in **hoofdstuk 7** de invloed van frailty op het ontstaan en op het negen-jaars beloop van depressieve stemming op latere leeftijd in de algemene bevolking. We vonden dat frailty zowel de incidentie van depressieve stemming voorspelt, als het niet in remissie gaan van depressieve stemming. Ook hier hebben we gekeken naar de invloed van de losse componenten van frailty. Hier bleek alleen verlaagd activiteitenniveau de incidentie van depressieve stemming en het niet in remissie gaan van depressieve stemming te voorspellen.

Wanneer we kijken naar wat deze bevindingen betekenen voor frailty als uni-dimensioneel concept in relatie tot depressie, komen we tot een andere conclusie dan in hoofdstuk 6. De componenten van frailty laten namelijk consistente resultaten zien met betrekking tot het voorspellen van de incidentie en het beloop van depressieve stemming. Dit wijst op samenhang tussen de componenten van frailty in de bevolking met betrekking tot het ontstaan en beloop van depressieve klachten.

Na vastgesteld te hebben dat frailty het beloop van depressieve klachten in de bevolking beïnvloedt, hebben we in **hoofdstuk 8** gekeken of dit ook geldt voor een klinische depressie diagnose in een cohort depressieve ouderen over twee jaar. Bovendien hebben we in dit hoofdstuk ingezoomd op subschalen van een meetinstrument dat de ernst van depressie meet, zodat we dieper in konden gaan op het verband tussen frailty en het beloop van depressie op latere leeftijd. Dit meetinstrument heeft drie subschalen; één subschaal meet de ernst van de stemmingsklachten, de tweede meet de ernst van de lichamelijke depressieklachten en de derde de ernst van de motivationele depressieklachten.

We vonden een verband tussen frailty en het niet in remissie zijn van depressie na twee jaar. Wanneer de individuele componenten van frailty werden geanalyseerd, vonden we een verband tussen zowel uitputting, als een verlaagd activiteitenniveau en depressie na twee jaar.
Betreffende de subschalen zagen we dat de lichamelijke en motivationele depressieklachten sterker afnamen bij toenemende frailty. Dit kan verklaard worden doordat depressieve ouderen met frailty meer ruimte hadden voor verbetering. Voor de stemmingsklachten gold dit niet. Ondanks de sterkere verbetering van lichamelijke

en motivationele depressiesymptomen, bleven deze klachten bij mensen met frailty ernstiger. Dit kan dus ook betekenen dat het niet herstellen van de depressie verward wordt met frailty. Juist dit punt verdient nader onderzoek.

Conclusies

Voor het doen van onderzoek naar frailty in de ouderenpsychiatrie is fysieke frailty een relevant en bruikbaar begrip. In de *algemene bevolking* is één op de tien ouderen frail en voorspelt frailty zowel de incidentie als het aanhouden van depressieve stemming. Van de *ouderen met een klinische depressie* diagnose is ruim een kwart frail. Bovendien verklaart de aanwezigheid van frailty gedeeltelijk het bestaande verband tussen depressie en lichamelijke ziektes en vinden we een verband tussen ontstekingsactiviteit en de lichamelijke prestatie-dimensie van frailty. Verder voorspelt de aanwezigheid van frailty een slechter beloop van depressie over twee jaar. Hoewel de lichamelijke en motivationele depressiesymptomen meer verbeteren bij toenemende frailty, houden deze mensen toch nog meer lichamelijke en motivationele depressieklachten.

De bevindingen uit dit proefschrift wijzen op een verwevenheid van frailty en depressie op latere leeftijd en zouden kunnen duiden op een specifiek frail-depressief subtype van depressie wanneer er ook sprake van frailty is. Hoewel dit subtype sterke verbanden heeft met een chronisch beloop van depressie, is er ook goed nieuws. Aangezien er zowel voor frailty als depressie behandelmogelijkheden zijn, biedt dit kansen voor de ontwikkeling van speciale interventies die gericht zijn op de fysieke en de psychische gezondheid. Toekomstig onderzoek zal moeten uitwijzen of deze interventies de prognose van deze bijzonder kwetsbare groep ouderen kunnen verbeteren.

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About the author

Rose Milou Collard was born on August 29th, 1978 in Nijmegen, The Netherlands. She grew up in Gennep, a small town in the North of Limburg. She graduated from high school (HAVO) in 1995 at the Merletcollege in Cuijk. After this, she studied Nursing at the HAN University of Applied Sciences in Nijmegen. Next to her study, she worked as a nursing assistant in nursing home Malderburch in Malden. In 2000 she graduated and then her clinical career started at a psychiatric nursing ward at ProPersona in Nijmegen.

Because of her growing interest in research, in 2005 she started to work as a research-nurse at the Psychiatry department of the Radboud university medical center in Nijmegen. During her work at this department, she started her Masters in Clinical Health Sciences, Nursing Science in 2008 at the University of Utrecht, which she completed in 2010 (cum laude). Her master thesis was the basis of the research proposal she wrote for her PhD, which she started at the beginning of 2011. As the Netherlands Study of Depression in Older persons is an ongoing study, she assessed all the participants from Nijmegen during the (several) measurements as a part of her PhD project.

In the future she will remain active in both research and nursing. An important topic for her is to integrate research and practice, and to translate findings from research to practice and vice versa. Furthermore, she hopes to contribute to the professionalization of the nursing discipline and to improve care for patients.

Rose lives in Nijmegen with her family: her husband Chris Geelen, and her three children Sam (2000), Sofie (2003) and Lune (2013).

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Mijn allerliefste Chris, wat ben ik blij dat wij elkaar gevonden hebben. Mijn leven met jou te delen is voor mij het mooiste wat er is!

Rose

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