FRAIL OLDER PEOPLE: WHO ARE THEY?

Frailty screening and profiles

Linda Op het Veld

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The research presented in this dissertation was conducted at:
CAPHRI Care and Public Health Research Institute, Department of Family Medicine and Health Services Research, of Maastricht University. CAPHRI participates in the Netherlands School of Public Health and Care Research CaRe

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CHAPTER 1

General Introduction

Aging society

People worldwide are living longer and the pace of population aging is increasing.[1] This also leads to increasing numbers of older people who are frail. Estimates show that the number of frail older people (65+ years) in the Netherlands will increase from approximately 700,000 in 2010 to 1,000,000 in 2030, which is about 25% of all older people.[2] Many frail people suffer from numerous health problems; they have, for example, an increased risk of mortality, falls, hospitalizations, and (worsening) disability.[3,4] Treatment and support should be targeted at those in need of such care. If people are incorrectly identified as not being frail, they will fail to receive the care they need. Conversely, those incorrectly identified as frail will receive treatment they do not need, the effect of which will likely be minimal meaning that healthcare costs will rise unnecessarily. Unnecessary treatments on the one hand, and the increasing number of frail people suffering adverse outcomes on the other, impose a great burden on the healthcare system.[5] From a policy perspective, in order to reduce the high costs of institutionalization older people are encouraged to age in place.[6] At the same time, aging in place is the wish of most older people.[7] This adds to the importance of identifying frailty in them. In the past decades, research on frailty has rapidly increased.[8,9] Its focus has been on concepts and definitions, instruments for measuring frailty, and interventions for frail older people. However, consensus on the conceptualization of frailty and the pathway from frailty to adverse outcomes is still lacking; furthermore, it remains unclear which instrument is best able to identify frail people who are at risk for adverse outcomes.

Frailty concept

Although the term 'frailty' is used frequently, it has been conceptualized in numerous ways.[10,11] There is no consensus as yet on its nature or concepts.[12] Broadly, three approaches to conceptualizing frailty emerge from the literature. The first states that frailty comprises solely physical factors. The frailty phenotype, as described by Fried and colleagues, is an example of this approach and is the one used most often for research purposes.[13] It considers frailty to be "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes."[14] Both the second and third approaches consider frailty to be a multidimensional concept. Supporters of these approaches believe that frailty comprises factors from more domains (e.g. social and/or psychological) than solely the physical one. The difference between the second and

third approach is the choice of specific domains. In the second approach, the domains are pre-defined and consist of a fixed set of items per domain. An example of this approach is that described by Gobbens and colleagues: "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."[11] These authors developed the Tilburg Frailty Indicator (TFI), which comprises questions in the physical (eight items), psychological (four items) and social (three items) domains.[15] The third approach requires the inclusion of multiple domains without defining which domains and items should be included. The so-called Frailty Index (FI) can be used in this approach and will be explained later in this chapter. This broader approach also makes it possible to include a variety of items, such as nutritional status, smoking status, or lab results. It was proposed by Rockwood and colleagues, who consider frailty as "A combination of aging, disease, and other factors (e.g. fitness, nutritional status) that make some people vulnerable."[16]

Profiles of people with different levels of frailty

In general, compared with non-frail persons frail older people tend to be older and female, have a low income and low education level, and live alone.[17-19] These characteristics are independent of the frailty conceptualization used. Nevertheless, there is still a debate on whether to include one (i.e. physical) or multiple domains in the conceptualization and measurement of frailty. It is not known whether people with different levels of frailty show different profiles in terms of levels of functioning in various domains (e.g. physical, social, psychological). More insight into this topic could help to untangle the complex concept of frailty. Therefore, expanding our knowledge of the profiles of people with different levels of frailty in terms of levels of functioning in multiple domains is one of the aims of this dissertation.

Resources influencing the pathway from frailty to adverse outcomes

Knowledge about the pathway from frailty to adverse outcomes is still lacking. Previous research has clearly demonstrated that frail people are at higher risk for adverse outcomes such as death, disability, institutionalization, hospitalization, and falls.[20] Nevertheless, not all persons who are frail experience these adverse outcomes, and

vice versa: there are non-frail persons who experience problems even though they do not appear to be at risk. This suggests that there are factors that can influence the pathway from frailty to adverse outcomes: some of these can have detrimental moderating effects, such as a poor sense of control resulting in an increase in mortality within 12 months;[21] others, such as educational level and living situation, can have beneficial moderating effects on self-perceived health.[22] Such factors, or resources, can be used to develop intervention programs. Therefore, another aim of this dissertation is to examine which resources are able to influence the pathway from frailty to adverse outcomes.

Psychometric properties of frequently used frailty instruments

Many instruments for identifying frailty in older people have been developed. In the Netherlands, the Frailty Phenotype (FP)[14], Tilburg Frailty Indicator (TFI)[15], Groningen Frailty Indicator (GFI)[23], and Frailty Index (FI)[24,25] are frequently used to detect frailty in community-dwelling older people.

Researchers and healthcare professionals who support the physical concept of frailty most often use the frailty criteria described by Fried and colleagues.[14] This FP consists of five items: weight loss, exhaustion, low physical activity, slowness, and weakness. The first three items are self-report questions and the last two are performance-based tests. For every item that is present, a score of 1 is assigned. Sum scores classify people as non-frail (score 0), pre-frail (score 1-2) or frail (score 3-5). When the FP is used in large-scale studies, the performance-based tests are often substituted by (self-report) questions because the latter are much easier and faster (and thus cheaper) to administer. However, researchers use a variety of self-report questions, which influences the results of the studies and hampers comparison between them.[26,27] It is therefore important to study the substitution of the performance-based measures of the FP with self-report questions, in order to increase uniformity in the use of the self-report FP in future studies.

For the second, multidimensional, approach described above, questionnaires with pre-defined sets of questions in at least two domains are used. The TFI is an example of such a measure.[15] It is a 15-item questionnaire with questions across the physical (eight items), social (three items), and psychological (four items) domains. Theoretical scores range from 0 (no frailty) to 15, where persons with a score of ≥5 are considered frail.[15] Another example is the GFI, developed by Steverink and colleagues.[23] This questionnaire also comprises 15 pre-defined questions, focusing on multiple, pre-

defined domains: physical (nine items), cognitive (one item), social (three items), and psychological (two items). Sum scores range from 0 (no frailty) to 15, where a person is considered frail with a score of ≥4.[28]

The third approach to conceptualizing frailty, which also includes multiple domains, is the FI and was proposed by Mitnitski and Rockwood.[24,25] The unique feature of this measure is that the user can decide which questions or parameters (so-called deficits) should be included. Criteria for creating an FI have been described by Searle and colleagues: included variables must be deficits associated with health status, the prevalence of which must increase with age; deficits must not saturate too early; and multiple domains must be included.[29] Items that can be included range from physical functioning and cognition to self-rated health, nutritional status, and even lab results. The ratio of the number of 'deficits' present to the total number of items is the FI score. Although it is suggested that the FI should be used as a continuous scale, with a score of 0 indicating no frailty and 1 maximum frailty, a cut-off value of 0.25 has been proposed.[30] The predictive ability of the FP, TFI, GFI, and FI have been tested,[31-33] but not all the instruments simultaneously, in one large sample, with several outcomes, and with a long follow-up period. This makes it hard to compare the results in order to determine which instrument is better able to predict adverse outcomes and thus best for use in research or daily practice. Therefore, the predictive ability of these four frailty instruments will also be investigated in this dissertation. Additionally, it has been suggested by Cesari and colleagues and Dent and colleagues that the predictive ability might be improved by combining two frailty instruments.[34,35] Combinations of available frailty instruments will therefore also be investigated in this dissertation.

Aims and research questions

Despite large variation in the conceptualization and measurement of frailty, it is still important to focus on identifying frailty in older people. In order to provide the right people with the right treatment and care, more insight into the characteristics of frail older people, the pathway from frailty to adverse outcomes, and the quality of frequently used frailty screening tools is needed.

The aims of this dissertation are therefore threefold: (1) to expand our knowledge about profiles of persons with different levels of frailty in terms of functioning in multiple health domains; (2) to examine which resources influence the pathway from frailty to several adverse outcomes; and (3) to increase our knowledge of the psychometric properties of frequently used frailty instruments. To achieve these aims, the following specific research questions were addressed:

Profiles of frailty

1. What are the profiles of persons at different levels of frailty in terms of levels of functioning in multiple domains?

Pathways of frailty

2. Which resources influence the pathway from frailty to adverse outcomes?

Psychometric properties of frailty instruments

3. Can performance-based frailty criteria be substituted by self-report questions?
4. How well can frequently used frailty instruments predict adverse outcomes?
5. Can the combined use of frailty instruments improve their predictive power?

Frailty in this dissertation

In order to answer these research questions (except number 3), we collaborated with the Community Health Services (CHS) in Limburg in the Netherlands. Every four years the CHS sends out an extensive questionnaire to a large sample of community-dwelling older people (55+ years). It comprises questions about health, lifestyle, and social situation.[36] In the 2012 questionnaire, Fried's frailty criteria were also included.[14] This frailty measure was chosen because it is short and simple and the one used most often by researchers. From the approximately 30,000 respondents out of the 56,000 persons who received the questionnaire, we selected people who were at least 65 years old and gave their informed consent to participate in our study. For research question 1, we

used the data of 8,684 people who met these criteria. Only pre-frail and frail people (n=3,162) were invited to participate in the follow-ups of our study. After gathering additional baseline information, the remaining 2,420 persons formed our study cohort. For a period of two years they received a questionnaire every six months. The questionnaire comprised several frailty instruments and questions about healthcare use and adverse outcomes. This cohort allowed us to investigate resources that might influence the pathway from frailty to adverse outcomes (research question 2) and the performance of several frailty instruments (research questions 4 and 5), simultaneously, in a large sample of community-dwelling older people.

Dissertation outline

In **Chapter 2**, the profiles of older people at different levels of frailty in terms of levels of functioning in multiple domains is investigated. **Chapter 3** examines the potential moderating effect of several resources on the pathway from frailty to adverse outcomes. **Chapters 4, 5, and 6** focus on the psychometric properties of frailty instruments. **Chapter 4** focuses on the Frailty Phenotype where, since they are often used in large-scale research, the performance-based measures of walk-time and handgrip strength are compared with self-report questions on these two items. In **Chapter 5**, the predictive ability of four commonly used frailty instruments in the Netherlands, the Frailty Phenotype, Groningen Frailty Indicator, Tilburg Frailty Indicator, and Frailty Index, is compared in a large prospective cohort study. **Chapter 6** explores the combined (i.e. sequentially and in parallel) use of frailty instruments in order to improve their predictive power. Finally, **Chapter 7** summarizes the main findings of this dissertation, discusses methodological aspects, and considers the lessons learned followed by the implications for research, practice, and education.

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CHAPTER 2

Fried phenotype of frailty: cross-sectional comparison of three frailty stages on various health domains

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Abstract

Background

The population ageing in most Western countries leads to a larger number of frail older people. These frail people are at an increased risk of negative health outcomes, such as functional decline, falls, institutionalisation and mortality**.** Many approaches are available for identifying frailty among older people. Researchers most often use Fried and colleagues' description of the frailty phenotype. The authors describe five physical criteria. Other researchers prefer a combination of measurements in the social, psychological and/or physical domains. The aim of this study is to describe the levels of social, psychological and physical functioning according to Fried's frailty stages using a large cohort of Dutch community-dwelling older people.

Methods

There were 8,684 community-dwelling older people (65+) who participated in this cross-sectional study. Based on the five Fried frailty criteria (weight loss, exhaustion, low physical activity, slowness, weakness), the participants were divided into three stages: non-frail (score 0), pre-frail (score 1-2) and frail (score 3-5). These stages were related to scores in the social (social network type, informal care use, loneliness), psychological (psychological distress, mastery, self-management) and physical (chronic diseases, GARS IADL-disability, OECD disability) domains.

Results

63.2% of the participants was non-frail, 28.1% pre-frail and 8.7% frail. When comparing the three stages of frailty, frail people appeared to be older, were more likely to be female, were more often unmarried or living alone, and had a lower level of education compared to their pre-frail and non-frail counterparts. The difference between the scores in the social, psychological and physical domains were statistically significant between the three frailty stages. The most preferable scores came from the non-frail group, and least preferable scores were from the frail group. For example use of informal care: non-frail 3.9%, pre-frail 23.8%, frail 60.6%, and GARS IADL-disability mean scores: non-frail 9.2, pre-frail 13.0, frail 19.7.

Conclusion

When older people were categorised according to the three frailty stages, as described by Fried and colleagues, there were statistically significant differences in the level of social, psychological and physical functioning between the non-frail, pre-frail and frail persons. Non-frail participants had consistently more preferable scores compared to the frail participants. This indicated that the Fried frailty criteria could help healthcare professionals identify and treat frail older people in an efficient way, and provide indications for problems in other domains.

Background

An ageing society is a common phenomenon. The increasing proportion of older people in most Western countries leads to a larger number of people who are old and frail. These frail older people are at an increased risk of negative health outcomes, such as functional decline, falls, institutionalisation and mortality.[1] Over the last decade, the interest in frailty has grown.[2] The main reason is the belief that early identification of those at risk could help to delay or prevent the adverse outcomes of frailty. Despite considerable research on frailty, there is still debate on the nature, definition, prevalence, and the characteristics of older people in various frailty 'stages'.[1,3]

Three main approaches to conceptualising frailty have been distinguished. One approach considers frailty to be a decline in physical functioning. The frailty phenotype, as described by Fried and colleagues, is based on five pre-defined physical frailty criteria, which are well known and most frequently used by researchers.[4,5] Another approach is to look at frailty as the accumulation of deficits across various domains (e.g. cognition, physical functioning, self-rated health, smoking history, and laboratory results). The Frailty Index, developed by Rockwood and colleagues, is often used for this approach and it is characterised by the use of a non-fixed set of clinical conditions and diseases.[6,7] A third approach also assumes that multiple domains (social, psychological, physical) are involved in the concept of frailty, with researchers using a pre-defined set of questions related to each domain (e.g. Tilburg Frailty Indicator, Groningen Frailty Indicator).[8,9]

Each approach has its advantages and disadvantages. In the present study, we are looking for a brief and simple tool (i.e. a self-report questionnaire with a limited number of items) that is feasible for use in large populations of community-dwelling older people. The Fried frailty criteria seem to reflect such a tool. Although the Fried criteria were originally not developed as a self-report questionnaire, researchers nowadays often use (partly) modified questionnaires that are based on the frailty phenotype (e.g. Barreto and colleagues, Macklai and colleagues).[10,11]

The five frailty criteria are weight loss, exhaustion, low physical activity, slowness and weakness. The sum score of these five criteria classifies people into one of three frailty stages (or groups): not frail (score 0), pre-frail (score 1-2) and frail (score 3-5). Fried and colleagues described the characteristics of these three groups using a cohort of United States citizens. The trend was that frail people were older, more likely to be female, suffered from more diseases (except cancer), reported higher rates of disability, were less educated, had lower income, were in poorer health, had more cognitive impairments and experienced higher levels of depressive symptoms compared to their pre-frail and non-frail counterparts.[5] Results from the pre-frail people were

intermediate, falling between the scores of the frail and non-frail people (except for cancer). In addition, outcomes of the Survey of Health, Aging and Retirement in Europe (SHARE), which also used the Fried criteria to assess frailty in populations from 11 European countries, showed that frail people were more likely to be female and report more disability problems compared to their pre-frail and non-frail counterparts.[11] The particular characteristics of interest in both aforementioned studies were demographics, and aspects in the physical domain, as well as (chronic) diseases. Studies from Bandeen-Roche and colleagues[12], Ble and colleagues[13] and Cawthon and colleagues[14] also used the five Fried frailty criteria to differentiate between groups, focusing on similar characteristics of interest. It is still unclear whether this limited scope is sufficient for identifying different profiles of functioning of frail, pre-frail and non-frail older people. Levels of social and psychological functioning might also, for example, play an important role in the development of frailty.

Additional knowledge regarding whether such social and psychological factors could add to the discriminative power of the three Fried frailty stages will be very useful for both healthcare professionals and researchers. Up until now, the psychological and social factors relative to the frailty stages have not been extensively studied. If these stages also show variations in these domains, this could help healthcare professionals in efficiently identifying and treating frail older people. If a patient is (pre-)frail according to the Fried criteria, it could alert them to the existence of problems in other domains as well. Moreover, as the number of items of the Fried frailty criteria is limited, the use of this short instrument is much more efficient than many other frailty measures.

The aim of this study is to describe the levels of social, psychological and physical functioning according to the three Fried frailty stages using a large cohort of Dutch community-dwelling older people. We also studied possible gender differences in these levels of functioning.

Methods

A cross-sectional study was conducted among community-dwelling older people in Limburg, a province in the southern part of the Netherlands. The medical ethical committee Atrium-Orbis-Zuyd approved this study (12-N-129). Selection of the study population was made from the Health Monitor, an extensive postal general health questionnaire which is sent every four years by the Community Health Service to a large sample of community-dwelling people in the Netherlands.[15]

Study population

For the measurement using the Health Monitor in Limburg, during the fall of 2012, 56,000 people aged 55 years and over were selected. Selection was random for all age groups, except for those over 75 years. This population was overrepresented in the sample in order to obtain sufficient data among the oldest age group living at home. People living in neighbourhoods with a low socioeconomic status were overrepresented as well. Respondents were asked to give their consent for using their data for our study.

The response rate for the Health Monitor was 54% (n=30,130). Of the respondents, 13,521 gave permission for the use of their data in our study. The selection was also restricted to those who were 65 years and older, because this is the age group in which the Fried criteria were originally developed.[5] After excluding the questionnaires that were filled out by a person other than the addressee and those questionnaires with a significant amount of missing data, a total of 8,684 people participated in our study.

Measurements

The Health Monitor is comprised of a broad range of questions. In addition to demographic characteristics (age, gender, marital status and level of education), questions included the Fried frailty criteria, (chronic) diseases, use of healthcare services, use of informal care and items about social, psychological and physical functioning.

Fried frailty criteria

Fried and colleagues developed five criteria (weight loss, exhaustion, low physical activity, slowness and weakness) to be used for identifying frail older people.[5] In contrast with the original criteria, we replaced the two physical measurements of slowness and weakness by questions. *Weight loss* was measured using the question: "In the last year, have you lost more than 4.5 kilograms unintentionally? (i.e. not due to dieting or exercise)". This question is the same as proposed by Fried and colleagues, only pounds were replaced by kilograms. This criterion was met when the participant answered "yes". *Exhaustion* was measured using two questions from the Center for Epidemiologic Studies Depression (CES-D) scale: "How often did you feel that everything you did was an effort? " and "How often did you feel that you could not get going?".[16,17] These questions are the same as proposed by Fried and colleagues. Response options were slightly different: "always, most of the times, sometimes, occasionally, never", compared to "rarely or none of the time (<1 day), some or a little

of the time (1-2 days), a moderate amount of the time (3-4 days), most of the time" in Fried's version. This criterion was met when participants answered: "always or most of the times" to at least one of the two questions. *Low physical activity* was not measured by using the Minnesota Leisure Time Activity Questionnaire, as proposed by Fried and colleagues. Instead, a slightly adjusted version of the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was used.[18] Participants had to answer questions about how many times a week they spent time walking, cycling, gardening, doing odd jobs or exercising/playing sports. For each activity, they had to report how much time they spent engaged in that activity on each occasion. Kilocalories per week were calculated. The results were stratified by gender and compared with the cut-off values as described by Fried and colleagues (men 383 kcal/week, women 270 kcal/week). If a person used fewer kcals per week this criterion was met. *Slowness/walk time* was measured using the question: "Can you reach the other side of the road when the light turns green at a zebra crossing?". We developed this question ourselves. If the participant chose any reply other than "yes, without any trouble", the criterion was met. *Weakness/grip strength* was measured by asking the question: "Do you experience difficulties in daily life because of low grip strength?" This question was derived from the Tilburg Frailty Indicator.[8] If the participant answered "yes", the criterion was met.

The stages of frailty, based on the Fried criteria, were defined as follows: a score of 0 means that a person is robust or not frail. Persons with a score of 1 or 2 are at intermediate risk for adverse outcomes or are considered to be pre-frail. A score of 3-5 indicates that someone is frail.[5]

Perceived health and healthcare use

One question was asked regarding perceived health: "How well is your health in general?". The question could be answered on a 5-point Likert scale with answer choices ranging from "very good" to "very poor". The use of healthcare services was measured by reporting any contact with a general practitioner within the last two months. The participants also had to provide details regarding the healthcare professional they had contacted over the past twelve months. The healthcare providers were already specified: medical specialist, dietician, occupational therapist, physiotherapist, homecare (nursing care and household care) and social worker.

Social domain

Wenger and colleagues developed an 8-item questionnaire regarding social network.[19] The scores divided people into five types of support networks: family dependent, locally integrated, local self-contained, wider community focused, and private

restricted. The family dependent and private restricted support networks are characterised by a limited number of people that could provide support. The locally integrated and wider community-focused support networks are larger networks. Wenger and colleagues found that these network types were consistent with the availability of informal support and the use of healthcare services.[19] In addition, one question was asked about the use of informal care over the past 12 months. Loneliness was measured by using the De Jong-Gierveld Loneliness Scale.[20] This is a 11-item scale, with questions such as "I miss having a really close friend", which allows the participants to choose from three answer choices: "yes", "more or less" or "no". A higher score indicates more feelings of loneliness.

Psychological domain

The 10-item Kessler Psychological Distress Scale (K-10) was used to measure psychological distress.[21] This questionnaire is comprised of questions such as: "During the last four weeks, about how often did you feel depressed?". The five-category response scale ranged from "all of the time" (score 5) to "never" (score 1). A higher total score indicated higher levels of psychological distress. Mastery was assessed by the using Pearlin and Schooler's instrument.[22] Seven statements, such as: "I have little control over the things that happen to me", are answered using a 5-point scale, ranging from "I totally agree" to "I totally disagree". The higher the total score, the more the respondent thinks that life-chances are under one's own control. Self-management was measured using the short version of the Self-Management Ability Scale (SMAS-S).[23] The SMAS-S consists of six three-item subscales (taking initiative, investment behaviour, variety, multifunctionality, self-efficacy and positive frame of mind), which reflect core abilities to form the construct of self-management of well-being.[24] Response options were slightly adjusted so that every question had six possible answers. Therefore, the final scores range from 1 to 6, with a higher score indicating more self-management abilities.

Physical domain

Chronic diseases were measured by asking participants whether or not they suffered from one or more of the following chronic diseases: diabetes, stroke/cerebral haemorrhage/cerebral infarction, myocardial infarction, other cardiac diseases , cancer, asthma, chronic obstructive pulmonary disease (COPD), hip or knee arthrosis, chronic joint inflammation, or back problems (incl. hernia). For cancer and myocardial infarction the participants had to report if they ever had the diseases. For all of the other diseases, they had to report whether they suffered from the disease over the past twelve months.

IADL-disability (Instrumental activities of daily living) was measured using a seven-item subscale from the Groningen Activity Restriction Scale (GARS).[25,26] The subscale is comprised of questions, such as “Can you fully independently prepare dinner?”. The items were answered on a four-point scale, with answers ranging from “Yes, without any difficulty” to “No, only with someone’s help”. Scores range from 7 to 28 points, with a higher score indicating a higher level of IADL-disability. Physical limitations were assessed using the Organization for Economic Cooperation and Development (OECD) long-term disability questionnaire.[27] In this study, we used a six-item version, as used by the Community Health Service. This version is comprised of questions about problems with hearing, vision, bending, and walking 400 metres. The number of items that people indicated as problematic were used for analysis.

Statistical analysis

The central focus of this study was to describe the levels of functioning across various domains. Descriptive statistics were used to present demographic characteristics of the study population and the levels of functioning. Associations between scores in the three health domains and the frailty stages were analysed using Kendall’s tau for nominal and ordinal variables, and analyses of variance (ANOVA) for all other variables ($P < 0.05$).These associations were also studied separately for men and women, as older women are more likely to be frail. Where available, missing data for all of the included instruments were handled as proposed by the original authors. Fried and colleagues excluded people with three or more missing frailty components. Missing data with respect to the Fried criteria in our study were handled more strictly than originally proposed by the authors. To reduce the number of misclassifications, only one missing value was allowed when a person had a valid Fried score of 0-2. If a person had a valid Fried score of 3 points or more, two missing values were allowed, because this would not cause misclassification. The analyses were performed using IBM SPSS Statistics software version 19.

Results

The characteristics of the study population are displayed in Table 2.1. The 8,684 participants were 65 to 98 years of age (mean age 74.2 ± 6.4 yrs.), with slightly more men (53.2%) than women. The majority of the participants (68.8%) were married or living together, and more than half of the population had a lower level of education. Nearly 60% rated their health as very good or good. Almost 51% had visited their general practitioner during the previous two months, and nearly two-thirds visited a medical specialist over the previous twelve months.

Figure 2.1 shows the prevalence of each frailty criterion. In this study, 20% of the participants reported problems with grip strength. Weight loss was reported less often than were the other problems (8%). The total number of frailty components that were present in the study population is shown in Table 2.2. In total, 63.2% of the participants were not frail, 28.1% were pre-frail and 8.7% were frail. There were differences between men and women. Men were more often not frail (72.9% vs. 52.2%) whereas women were more often pre-frail (35.5% vs. 21.6%) or frail (12.3% vs. 5.5%).

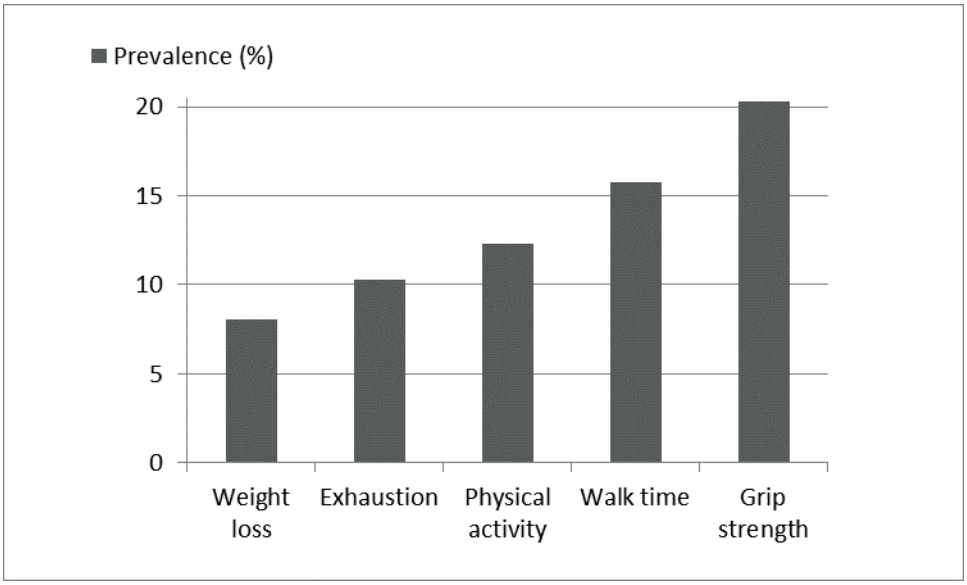

Figure 2.1 Prevalence of each frailty criterion as proposed by Fried and colleagues.

Table 2.1 Demographic characteristics, perceived health and healthcare use according to the three frailty stages.

		All	**Non-frail**	**Pre-frail**	**Frail**	**P-value**
		n = 8684	n = 5488 (63.2%)	n = 2441 (28.1%)	n = 755 (8.7%)	
Age (yrs.) (mean ± SD)		74.2 (±6.4)	72.9 (±5.9)	75.9 (±6.5)	78.2 (±6.8)	<0.001
Age groups	65-74	4510 (51.9%)	3314 (60.4%)	985 (40.4%)	211 (27.9%)	<0.001
	75-84	3597 (41.4%)	1979 (36.1%)	1215 (49.8%)	403 (53.4%)	
	85+	577 (6.6%)	195 (3.6%)	241 (9.9%)	141 (18.7%)	
Gender (male)		4619 (53.2%)	3366 (61.3%)	999 (40.9%)	254 (33.6%)	<0.001
Marital status	married/living together	5837 (68.8%)	4056 (75.2%)	1422 (60.2%)	359 (48.9%)	<0.001
	unmarried/divorced	721 (8.5%)	392 (7.3%)	231 (9.8%)	98 (13.4%)	
	widowed	1931 (22.7%)	943 (17.5%)	711 (30.1%)	277 (37.7%)	
Level of education	low	4903 (58.6%)	2796 (52.2%)	1554 (67.4%)	553 (78.8%)	<0.001
	medium	1783 (21.3%)	1254 (23.4%)	415 (18.0%)	114 (16.2%)	
	high	1681 (20.1%)	1309 (24.4%)	337 (14.6%)	35 (5.0%)	

		All	Non-frail	Pre-frail	Frail	P-value
Perceived health and healthcare use						
Perceived health (%)	very good	7.3	10.5	2.2	0.1	<0.001
	good	50.9	64.4	33.8	6.1	
	fair	35.6	24.4	55.5	53.9	
	poor	5.6	0.7	8.1	34.1	
	very poor	0.6	0.1	0.4	5.8	
Healthcare use (past 12 months) (%)	general practitioner <2 months	50.9	43.3	61.3	74.3	<0.001
	medical specialist	64.2	57.3	73.9	83.5	<0.001
	dietician	9.6	6.9	13.1	19.3	<0.001
	occupational therapist	4.1	1.7	6.2	16.8	<0.001
	physiotherapist	35.7	29.2	45.4	53.0	<0.001
	homecare (nursing care and household care)	19.1	6.4	31.9	68.1	<0.001
	social work	2.4	1.0	3.6	9.4	<0.001

When comparing the three different stages, frail people appeared to be older, were more likely to be female, were more often unmarried or living alone, and had a lower level of education compared to their pre-frail and non-frail counterparts (Table 2.1). Pre-frail participants had intermediate scores between the scores of the frail and non-frail participants. Perceived health was worse when someone was frailer, and frail older people used more health care services. All of the aforementioned differences were statistically significant.

Table 2.2 Distribution of frailty sum scores.

Frailty Components	**Total**	**Men**	**Women**
	n= 8684	n = 4619	n = 4065
0	5488 (63.2%)	3366 (72.9%)	2122 (52.2%)
1	1691 (19.5%)	705 (15.3%)	986 (24.3%)
2	750 (8.6%)	294 (6.4%)	456 (11.2%)
3	468 (5.4%)	154 (3.3%)	314 (7.7%)
4	244 (2.8%)	88 (1.9%)	156 (3.8%)
5	43 (0.5%)	12 (0.3%)	31 (0.8%)

Table 2.3 shows the results of the measurements for the various health domains. Data are presented for the total study population, as well as per frailty stage. The scores of the non-frail people were more favourable than were those of the pre-frail people, and the scores of the pre-frail people were more favourable than were the ones of the frail people.

In the social domain, frail older people more often had a family dependent or a private restricted support network. These network types were characterised by a limited number of people that could offer support. The locally integrated and wider community-focused support networks (both large support networks) were more often present in non-frail older people. A larger proportion of the frail older people used informal care (60.6%) during the past 12 months compared to the pre-frail (23.8%) and non-frail older people (3.9%). They also reported more feelings of loneliness.

Measurements in the psychological domain showed that frail older people experienced more psychological distress (K-10 score 25.3 ± 8.2 than did their pre-frail (18.4 ± 6.6) and non-frail (13.6 ± 4.0) counterparts. They also had a lower sense of mastery and had less self-management abilities.

Measurements in the physical domain illustrated that all chronic diseases were more present among the frail older participants. More than half of the frail older people suffered from three or more chronic diseases. Scores on the GARS indicated that frail older people also had more problems with IADL activities. On the OECD disability

questionnaire, 93.9% of the frail participants reported at least one disability, compared to 49.0% of the pre-frail and 12.0% of the non-frail older people. Analyses showed that the differences for all of the scores across the domains were statistically significant between all three frailty stages.

In addition, the associations, as described in Table 2.3, were studied separately for men and women (Tables 2.4 and 2.5 respectively). All of the results showed the same statistically significant differences that were reported for the total study population, except for social network type (men: P=0.211, women: P=0.111).

Table 2.3 Scores for the total population in the social, psychological and physical domains according to the three frailty stages.

		All	**Non-frail**	**Pre-frail**	**Frail**	**P-value**
		n = 8684	n = 5488	n = 2441	n = 755	
Social domain						
Social network type (%)	family dependent	22.5	21.8	22.7	27.8	0.049
	locally integrated	40.1	42.5	37.0	31.5	
	local self-contained	21.6	20.6	24.0	21.8	
	wider community focused	8.2	9.2	7.4	3.7	
	private restricted	7.6	6.0	8.9	15.2	
Informal care use in past 12 months (%)	yes, and still present	14.3	3.9	23.8	60.6	<0.001
	no	84.3	95.1	74.2	37.7	
Loneliness (De Jong-Gierveld, 0-11)*		3.0 (±3.3)	2.3 (±2.8)	3.8 (±3.5)	5.3 (±3.7)	<0.001
Psychological domain						
Psychological distress (K-10, 10-50)		15.9 (±6.4)	13.6 (±4.0)	18.4 (±6.6)	25.3 (±8.2)	<0.001
Mastery (Pearlin & Schooler, 7-35)		25.8 (±5.6)	27.3 (±4.8)	24.1 (±5.6)	19.2 (±5.6)	<0.001
Self-management (SMAS-S, 1-6)		4.1 (±0.7)	4.2 (±0.6)	3.9 (±0.7)	3.4 (±0.8)	<0.001

		All	Non-frail	Pre-frail	Frail	P-value
Physical domain						
Chronic diseases (%)	diabetes	16.8	12.5	22.0	31.8	<0.001
	stroke/cerebral haemorrhage or infarction (past 12 months)	1.7	0.9	2.5	4.9	<0.001
	myocardial infarction (ever)	12.6	9.8	15.2	25.0	<0.001
	other heart conditions (CHF or AP) (past 12 months)	8.0	4.6	12.4	19.2	<0.001
	cancer (ever)	18.8	16.8	21.3	25.9	<0.001
	asthma or COPD (past 12 months)	15.5	11.1	21.0	28.5	<0.001
	hip or knee arthrosis (past 12 months)	41.2	30.2	56.2	69.1	<0.001
	chronic joint inflammation (past 12 months)	15.2	7.3	24.8	40.0	<0.001
	back problems (incl. hernia) (past 12 months)	21.3	14.1	29.3	44.7	<0.001
Number of chronic diseases (%)	0	29.0	38.3	15.6	5.0	<0.001
	1	32.1	36.0	27.6	18.3	
	2	19.8	16.9	25.4	22.8	
	≥3	19.1	8.8	31.4	53.9	
GARS IADL-disability (7-28)		11.2 (±5.2)	9.2 (±3.3)	13.0 (±5.4)	19.7 (±5.4)	<0.001
OECD disability	1 or more disabilities (%)	29.4	12.0	49.0	93.9	<0.001

* Preferable score is underlined.

Table 2.4 Scores for men in the social, psychological and physical domains according to the three frailty stages.

		All n = 4619	**Non-frail** n = 3366	**Pre-frail** n = 999	**Frail** n = 254	**P-value**
Social domain						
Social network type (%)	family dependent	22.0	21.1	23.3	28.4	0.211
	locally integrated	41.1	43.5	36.0	28.9	
	local self-contained	21.1	19.9	24.4	23.7	
	wider community focused	8.1	8.9	6.2	3.9	
	private restricted	7.8	6.6	10.1	15.1	
Informal care use in past 12 months (%)	yes, and still present	10.6	3.2	23.6	59.4	<0.001
	no	88.7	96.2	75.6	40.2	
Loneliness (De Jong-Gierveld, 0-11)*		2.8 (±3.1)	2.3 (±2.8)	3.9 (±3.5)	5.1 (±3.7)	<0.001
Psychological domain						
Psychological distress (K-10, 10-50)		15.0 (±6.0)	13.2 (±3.8)	18.5 (±7.0)	25.3 (±8.4)	<0.001
Mastery (Pearlin & Schooler, 7-35)		26.4 (±5.5)	27.6 (±4.7)	23.9 (±5.8)	18.6 (±5.4)	<0.001
Self-management (SMAS-S, 1-6)		4.1 (±0.7)	4.2 (±0.6)	3.8 (±0.7)	3.3 (±0.8)	<0.001

		All	Non-frail	Pre-frail	Frail	P-value
Physical domain						
Chronic diseases (%)	diabetes	17.0	13.8	24.6	30.6	<0.001
	stroke/cerebral haemorrhage or infarction (past 12 months)	1.8	1.0	3.3	7.5	<0.001
	myocardial infarction (ever)	17.1	13.7	23.9	36.4	<0.001
	other heart conditions (CHF or AP) (past 12 months)	8.0	5.1	14.4	21.5	<0.001
	cancer (ever)	19.0	17.1	22.9	29.0	<0.001
	asthma or COPD (past 12 months)	15.2	11.0	24.5	32.4	<0.001
	hip or knee arthrosis (past 12 months)	31.7	25.8	44.8	56.2	<0.001
	chronic joint inflammation (past 12 months)	10.9	7.0	18.8	32.2	<0.001
	back problems (incl. hernia) (past 12 months)	18.8	14.3	28.4	39.8	<0.001
Number of chronic diseases (%)	0	31.0	38.0	14.0	5.5	<0.001
	1	33.2	35.2	29.6	21.7	
	2	18.8	17.2	23.4	21.7	
	≥3	17.0	9.6	33.0	51.2	
GARS IADL-disability (7-28)		11.4 (±5.2)	9.9 (±3.7)	14.3 (±5.8)	20.8 (±5.6)	<0.001
OECD disability	1 or more disabilities (%)	23.8	11.7	47.6	92.4	<0.001

* Preferable score is underlined.

Table 2.5 Scores for women in the social, psychological and physical domains according to the three frailty stages.

		All	**Non-frail**	**Pre-frail**	**Frail**	**P-value**
		n = 4065	n = 2122	n = 1442	n = 501	
Social domain						
Social network type (%)	family dependent	23.2	22.9	22.2	27.5	0.111
	locally integrated	38.8	41.0	37.7	32.9	
	local self-contained	22.3	21.6	23.7	20.8	
	wider community focused	8.4	9.6	8.3	3.6	
	private restricted	7.3	5.0	8.0	15.2	
Informal care use in past 12 months (%)	yes, and still present	18.7	5.1	23.9	61.2	<0.001
	no	79.2	93.2	73.2	36.5	
Loneliness (De Jong-Gierveld, 0-11)*		3.2 (±3.4)	2.3 (±2.9)	3.8 (±3.6)	5.5 (±3.8)	<0.001
Psychological domain						
Psychological distress (K-10, 10-50)		17.0 (±6.7)	14.2 (±4.3)	18.3 (±6.2)	25.4 (±8.1)	<0.001
Mastery (Pearlin & Schooler, 7-35)		25.0 (±5.7)	26.9 (±4.8)	24.2 (±5.5)	19.5 (±5.7)	<0.001
Self-management (SMAS-S, 1-6)		4.1 (±0.7)	4.3 (±0.6)	4.0 (±0.7)	3.5 (±0.8)	<0.001

		All	Non-frail	Pre-frail	Frail	P-value
Physical domain						
Chronic diseases (%)	diabetes	16.5	10.4	20.2	32.5	<0.001
	stroke/cerebral haemorrhage or infarction (past 12 months)	1.6	0.8	2.0	3.5	<0.001
	myocardial infarction (ever)	7.3	3.5	8.9	19.1	<0.001
	other heart conditions (CHF or AP) (past 12 months)	8.1	3.9	11.0	18.1	<0.001
	cancer (ever)	18.7	16.4	20.1	24.4	<0.001
	asthma or COPD (past 12 months)	15.9	11.3	18.6	26.6	<0.001
	hip or knee arthrosis (past 12 months)	52.0	37.3	64.0	75.5	<0.001
	chronic joint inflammation (past 12 months)	20.1	7.8	29.0	44.0	<0.001
	back problems (incl. hernia) (past 12 months)	24.0	13.9	30.0	47.1	<0.001
Number of chronic diseases (%)	0	26.7	38.6	16.7	4.8	<0.001
	1	30.9	37.4	26.2	16.6	
	2	21.0	16.5	26.8	23.4	
	≥3	21.5	7.5	30.3	55.3	
GARS IADL-disability (7-28)		10.9 (±5.2)	8.1 (±2.2)	12.1 (±4.9)	19.1 (±5.2)	<0.001
OECD disability	1 or more disabilities (%)	35.8	12.4	50.0	94.6	<0.001

* Preferable score is underlined.

Discussion

The aim of this study was to describe the levels of physical, psychological and social functioning according to the three Fried frailty stages using a large cohort of Dutch community-dwelling older people. The results demonstrated consistent differences across all three domains between the non-frail, pre-frail and frail older people. Frail people had poorer scores than did their pre-frail and non-frail counterparts, and older people that were pre-frail had intermediate scores that fell between the scores of frail and non-frail older people.

Social domain

A family dependent or a private restricted support network was more present among the frail older participants. People in the first network type focused on close family relationships and having few good friends. People in the second network type hardly had any contact with family members (except for sometimes a spouse), minimal contact with neighbours or friends, and a lack of wider community contacts or involvement.[19] This makes people in these network types more vulnerable compared to the ones in a locally integrated or wider community focused network. The latter networks result in having more people to depend on in case of need, and people in these larger networks are considered to be more robust.[28] In addition, the non-frail older people in our study more often had a locally integrated or wider community focused network.

When these analyses were conducted stratified for gender, social network type appeared to be the only characteristic that was not statistically significant different between the frailty subgroups, both in men and in women. There does seem to be a trend in the total and the gender subgroup populations, in which there is a shift from broader to smaller network types when people are more frail. The fact that this difference is not statistically significant is probably due to the local self-contained network type, which appears to be rather stable between the frailty stages. However, because of the cross-sectional nature of the data it is unclear what can be considered cause and effect regarding the changes mentioned previously. One can image that reduced physical abilities (i.e. a higher frailty state) may cause people to stay at home more often, leading to a more restricted network. On the other hand, it cannot be excluded that a decrease in social support leads to a decrease in physical abilities.

Frail older people reported higher levels of loneliness compared to non-frail older people. These results were similar to Ní Mhaoláin and colleagues' findings.[29]

Psychological domain

Cramm and colleagues showed that people in poor health were more often frail and had less self-management abilities than their counterparts in good health (SMAS-S mean score 3.5 vs. 4.1).[30] These results were in line with our study: non-frail participants scored 4.2, pre-frail ones 3.9, and frail persons scored 3.4. Andrew and colleagues also found an association between frailty and psychological well-being.[31] However, this was also a cross-sectional study and the direction of the association is, as in our study, uncertain. We agree with their interpretation that it is most likely that there is a bi-directional relationship: a decline in physical functioning (i.e. increasing frailty) may cause a decline in psychological well-being and vice versa.

Physical domain

Scores on the measurements in the physical domain were most favourable for the non-frail older people, and worst for the frail people. Because the phenotype of frailty consists of physical measures, we expected the other measurements in the physical domain to show similar characteristics. Pre-frail participants in our study showed an increased number of chronic diseases compared to their non-frail counterparts. The number of chronic diseases was even higher among the frail people. These results were comparable to those in Fried and colleagues' study.[5] In Fried's study, cancer was the only chronic condition that was not significantly different between the frailty stages. In our study, there were differences between stages. This supports Fried's suggestion that non-significance was due to the exclusion of patients under active treatment for cancer.[5] The more frail the participant was, the higher the GARS-score was, indicating more IADL-disability. Cawthon and colleagues also showed that a larger proportion of frail people had at least one IADL limitation compared to pre-frail or non-frail ones.[14]

Prevalence of frailty criteria

The prevalence estimates of the frailty criteria 'weight loss' and 'grip strength' in our study were about the same as those found by Fried and colleagues (8 vs. 6% and 20 vs. 20% respectively)[5]. The prevalence of other components was lower in our study. Drey and colleagues compared four large epidemiologic studies where the Fried criteria were applied.[32] They showed that the percentages of frail, pre-frail and non-frail people differ between studies. Our study has the highest prevalence of non-frail, the lowest prevalence of pre-frail and a moderate level of frail older people, compared to other studies among community dwelling older people.[5,12-14,33] This variation between studies was probably due to several reasons. First, different measurements were used to

determine each criterion. For example, 'exhaustion' was measured with different questions in the studies, with the prevalence varying from 8% to 30%. Furthermore, 'hand grip strength' should have ideally been determined by a physical test. In our study, a self-reported question was used instead. Nevertheless, the prevalence in our study was the same as Fried and colleagues.[5] This could be chance or it might be possible to measure this criterion correctly by using our question instead of a physical test.[34] Slowness/walk time was also not measured by a physical test. The question we used is probably not a perfect measure of walking speed, because there is some variability in the speed of the lights turning red/green at a zebra crossing. In other studies self-report questions on walking capability are often used, for example in the study of Woods and colleagues.[35] They used the Rand-36 physical function scale which does not include specific questions on walking speed. More research is therefore needed on optimal self-report questions to replace the physical measurement of slowness/walk time. Overall, the validity of our Fried operationalizations is supported by the dose response association between our Fried scores and those on the functional status scores (GARS IADL and OECD disability, see Table 2.3).

Second, an important factor involved differences in the inclusion of persons in the study population. Fried and colleagues, for example, excluded patients under active treatment for cancer. Also, more men than women were present in our study, where usually it is vice versa. The study sample was randomly selected, pre-stratified for age and socioeconomic status. As we have no indications for specific reasons for this 'imbalance', we think the overrepresentation of men is a coincidence. Third, we handled missing values for the Fried criteria more strictly than did the original authors.

Strengths and limitations

The strength of the present study is that we included a large cohort from the general population. Many questions were asked across various domains and all questions were answered at the same time. Throughout the three health domains, a clear and consistent trend was found, indicating more preferable scores for the non-frail population compared to the frail older population. The pre-frail older people had an intermediate score that was between the scores of the other two populations. This trend remained clear when stratifying for gender (except for social network). Although statistical corrections are often made for gender, age and other factors that vary between different stages of frailty, one can argue whether that is necessary from a clinical point of view. Higher levels of physical disfunctioning are associated with higher levels of social and psychological disfunctioning. In practice, impairments in physical functioning can be used by healthcare professionals to detect impairments in other

domains. For that aim no adjustments are needed and therefore we did not use multivariate analyses in our study.

Our study had some limitations as well. First, the overrepresentation of people living in a neighbourhood with a low socioeconomic status and people aged 75 years and over may cause differences in frailty prevalence estimates when our results are compared with those in other studies. Nevertheless, it does not influence comparisons between the frailty stages, which was the main focus of this study. Second, the response rate was 54%. There is no information available on the characteristics of the non-responders. Therefore, it is not fully clear to what extend the results from our sample can be generalised to other community-dwelling populations. Suijker and colleagues[36] and Van Dalen and colleagues'[37] studies investigated the differences between respondents and non-respondents in a population of community-dwelling older people (≥ 70 years). They found that non-respondents more often had ADL dependency, cognitive impairment, a lower socioeconomic status and received more home visits from their general practitioner.[36,37] Third, as previously stated, the frailty criteria were not all measured exactly as proposed by Fried and colleagues.[5] Another limitation of this study is the cross-sectional design, as it hampers to determine the direction of the associations that were found. Increasing physical frailty could lead to problems in all described domains. However, problems in these other domains might be factors that cause people to become physical frail. For that reason, all results should be interpreted with caution. Longitudinal studies are necessary to gain more insight in the direction of the associations.

Implications

All of the results across all domains showed the same trend, indicating more preferable scores for non-frail compared to frail older people, with intermediate scores for the pre-frail people.

The five Fried frailty criteria could help healthcare professionals efficiently identify and treat frail older people, and providing indications for problems in other domains. So, for (first step) screening purposes one might restrict the screening to the five physical Fried criteria and not use a more elaborated (multidimensional) tool. In subsequent assessment of problems and risks one needs a more multidimensional approach, as our data show that often problems in various health domains co-exist. Further longitudinal research is needed to obtain a better view of which factors predict the negative consequences of frailty.

Conclusions

When older people are categorised according to the three frailty stages, as described by Fried and colleagues, differences in the level of social, psychological and physical functioning can be found between the non-frail, pre-frail and frail persons. Non-frail participants had consistently more preferable scores compared to frail participants, and pre-frail participants had intermediate scores.

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CHAPTER 3

Can resources moderate the impact of levels of frailty on adverse outcomes among (pre-) frail older people? A longitudinal study

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Abstract

Background

Higher levels of frailty result in higher risks of adverse frailty outcomes such as hospitalisation and mortality. There are, however, indications that more factors than solely frailty play a role in the development of these outcomes. The presence of resources, e.g. sufficient income and good self-management abilities, might slow down the pathway from level of frailty to adverse outcomes (e.g. mortality). In the present paper we studied whether resources (i.e. educational level, income, availability of informal care, living situation, sense of mastery and self-management abilities) moderate the impact of the level of frailty on the adverse outcomes mortality, hospitalisation and the development of disability over a two-year period.

Methods

Longitudinal data on a sample of 2,420 community-dwelling pre-frail and frail older people were collected. Participants filled out a questionnaire every six months, including measures of frailty, resources and outcomes. To study the moderating effects of the selected resources their interaction effects with levels of frailty on outcomes were studied by means of multiple logistics and linear regression models.

Results

Frail older participants had increased odds of mortality and hospitalisation, and had more deteriorating disability scores compared to their pre-frail counterparts. No moderating effects of the studied resources were found for the outcomes mortality and hospitalisation. Only for the outcome disability statistically significant moderating effects were present for the resources income and living situation, yet these effects were in the opposite direction to what we expected. Overall, the studied resources showed hardly any statistically significant moderating effects and the directions of the trends were inconsistent.

Conclusions

Frail participants were more at risk of mortality, hospitalisation, and an increase in disability. However, we were unable to demonstrate a clear moderating effect of the studied resources on the adverse outcomes associated with frailty (among pre-frail and frail participants). More research is needed to increase insight into the role of moderating factors. Other resources or outcome measures should be considered.

Background

In societies with growing numbers of older people, the numbers of frail older people are increasing as well, which imposes a burden on the healthcare system.[1] Despite the frequent use of the frailty concept, there is a lack of consensus regarding its nature and definition. Roughly, three approaches to conceptualise frailty emerge from the literature. One approach considers frailty to be a decline in physiological aspects of functioning. This phenotype of frailty, as described by Fried and colleagues, comprises five predefined physical frailty criteria and distinguishes between non-frail, pre-frail and frail persons.[2] A second approach considers frailty to be the accumulation of deficits across various domains (e.g. comorbidities, psychological functioning and physical functioning). Rockwood et al. proposed a Frailty Index which is often used for this approach. It is characterised by the use of a non-fixed set of clinical conditions and diseases.[3,4] Similar to the second one, a third approach also considers frailty to be a multidimensional concept. In contrast with the accumulation of deficits approach, this third approach includes a pre-defined set of physical, social and psychological questions (e.g. Tilburg Frailty Indicator (TFI)).[5]

The variety in definitions of frailty has resulted in an abundant number of screening instruments.[6,7] Irrespective of the instrument used, however, researchers agree that higher levels of frailty result in higher risks of adverse outcomes of frailty. For example, Fried and colleagues have shown that mortality was over threefold higher over a seven-year period for people who were frail at baseline compared to non-frail people (43% vs. 12%).[2] The same holds for hospitalisation (96% vs 79%) and disability (63% vs 23%). There are however indications that more factors than solely frailty play a role in the development of adverse outcomes. Verbrugge and Jette proposed, in their process of disablement, a pathway that links pathology through impairments and functional limitations to disability. However, this pathway is supposed to be influenced by risk factors and particularly moderated by intra- and extra-individual factors[8] of which the latter two can be considered as resources that alleviate the impact of, for example, impairments and functional limitations on disability. Similarly, the associations between the levels of frailty and adverse outcomes may also be moderated by different resources individuals may have. In frail older people, characteristics such as low income, low educational level, and living alone status, intra-individual factors (e.g. sense of mastery, self-management abilities) and extra-individual factors (e.g. availability of informal care) may moderate the impact of frailty on the development of adverse outcomes. Although prior studies have shown that several of these factors are related to frailty,[9,10] studies on potential moderating effects of these factors (resources)

between frailty level and adverse outcomes are scarce. For example, Dent and colleagues found that hospitalized frail older people with a low sense of control had an increased likelihood of 12-month mortality compared to frail people with a good sense of control.[11] Ament and colleagues showed that the impact of personal deficits, as an indicator of frailty, on receiving professional care and self-perceived health is moderated by educational level and living alone status, although the latter was only found in women.[12]

Previous research often used cross-sectional data and mainly focused on just one domain of moderating factors (e.g. environmental factors or psychological factors). The present study was designed to examine whether resources (i.e. educational level, income, availability of informal care, living situation, sense of mastery and self-management abilities) moderate the impact of frailty level on the adverse outcomes mortality, hospitalisation and the development of disability over a two-year period. As Fried's frailty criteria are most frequently used by researchers to identify frail older people, we use them in the present study as well.[6] We focused on community-dwelling pre-frail and frail persons as they have an increased risk of suffering from adverse outcomes. We hypothesised that more favourable resources (i.e. higher educational level, higher income, availability of informal care, living with someone, higher sense of mastery and better self-management abilities) slow down the pathway from level of frailty to adverse outcomes.

Methods

A longitudinal study with a two-year follow-up period was conducted. The study was approved by the medical ethical committee of Zuyderland and Zuyd University of Applied Sciences (METC Z, 12-N-129).

Procedure and participants

Every four years, the Community Health Services in the Netherlands send an extensive general health questionnaire to a large sample of community-dwelling people. People are questioned about their health, social situation and lifestyle.[13] A total of 56,000 people (55+ years) living in Limburg, a province in the southern part of The Netherlands, received this questionnaire in the autumn of 2012. In total, 30,130 persons returned it of whom 13,521 gave permission to potentially participate in further research. Persons younger than 65 years and not frail according to Fried's frailty

criteria (see below)[2] were excluded. Questionnaires completed by the wrong person or with a significant number of missing values were also excluded. Eventually, a total of 3,162 persons were eligible for the present study and received a shorter questionnaire to obtain relevant additional baseline data. Those who responded to this additional questionnaire and gave written informed consent, were included in the present study (n=2,420). After 6, 12, 18 and 24 months the participants received additional questionnaires comprising questions about their level of frailty, the availability of several resources, and outcome measures. People who died, moved to a nursing home or explicitly stated that they did not want to participate anymore were considered as drop-out during the study.

Fried frailty criteria

The five frailty criteria as described by Fried and colleagues (weight loss, exhaustion, low physical activity, slowness and weakness) were used to classify the participants into non-frail, pre-frail or frail.[2] Weight loss was measured as proposed by Fried et al., with pounds being replaced by kilograms: 'In the last year, have you lost more than 4.5 kilograms unintentionally? (i.e. not due to dieting or exercise)'. When someone answered 'yes', this criterion was met. As proposed by Fried et al., two questions from the Center for Epidemiologic Studies Depression (CES-D) scale were used to measure exhaustion: 'How often did you feel that everything you did was an effort? ' and 'How often did you feel that you could not get going?'.[14,15] Instead of the original response options 'rarely or none of the time (<1 day)', 'some or a little of the time (1-2 days)', 'a moderate amount of the time (3-4 days)', 'most of the time', the answer options 'always', 'most of the time', 'sometimes', 'occasionally', 'never' were used in our study. When participants answered 'always' or 'most of the time' to at least one of the two questions this criterion was met. The criterion of physical activity was measured with a slightly adjusted version of the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH).[16] Persons were asked how many times a week they spent time walking, cycling, gardening, doing odd jobs or exercising, and how much time they spent on each activity on each occasion. Kilocalories per week were calculated and compared to the cut-off values as proposed by Fried and colleagues. The criterion slowness was assessed by asking the question: 'Can you reach the other side of the road when the light turns green at a zebra crossing?'. If the participant answered other than 'yes, without any trouble', this criterion was met. The criterion of weakness was assessed by asking the question: 'Do you experience difficulties in daily life because of low grip strength?'. This is the same question as used in the TFI.[5] If the participant answered 'yes', this criterion was met. Based on the sum score of these five criteria

(range 0-5) people were divided into three categories: non-frail (score 0), pre-frail (score 1-2) and frail (score 3-5). To investigate possible moderating effects of resources, persons who are pre-frail or frail are a relevant population, as they are at increased risk of adverse outcomes. Therefore, only pre-frail and frail people were asked to participate in the follow-up measurements of the present study.

Resources

Resources tested for having a moderating effect on the adverse outcomes of frailty included: educational level, income, availability of informal care, living situation, sense of mastery and self-management abilities. Educational level was divided into two categories. The lower category comprises no education, completion of primary school or pre-vocational secondary education. All other levels of completed education are included in the higher category. Statistics Netherlands, an organisation that compiles statistics and publishes information about topics directly affecting the lives of Dutch citizens (such as economic growth, consumer prices and crime)[17], provided information about disposable income per person, adjusted for differences in family composition of the household. Persons were, by Statistics Netherlands, categorised into one of five groups ranging from a low to a high income. For the present study these categories were dichotomised into two, approximately equally sized, groups: low income and high income (cut-off 19,400 euro). Availability of informal care was determined using the question 'Suppose you got the flu and you had to stay in bed for a couple of days. Is there someone who could take care of you?'.[18] Results were dichotomised into 'yes' and 'no'. Living situation was measured by asking participants how many people were present in their household. The results were dichotomised into 'living alone' and 'not living alone'. Sense of mastery was measured by using the instrument developed by Pearlin and Schooler.[19] It comprises seven statements, such as 'There is really no way I can solve some of the problems I have'. Five-point answering options range from 'I totally agree' to 'I totally disagree'. Theoretical scores ranged from 7 to 35 with higher scores indicating a higher sense of mastery. Self-management abilities were measured with the short version of the Self-Management Ability Scale (SMAS-S).[20] It consists of six three-item subscales that reflect core abilities to form the construct of self-management of well-being. It comprises statements and questions such as 'Are you able to have friendly contacts with others?'. Final self-management scores theoretically ranged from one to six. Higher scores indicate more self-management abilities.

Outcome measures

Mortality, hospitalisation, and (Instrumental) Activities of Daily Living ((I)ADL) disability were used as adverse outcome measures. Mortality data (yes or no) at two-year follow-up were obtained from Statistics Netherlands. Data on hospital admission and (I)ADL disability were obtained from the self-report questionnaires. For hospital admission, respondents were asked at each of the follow-up measurements whether they had been admitted to a hospital in the previous six months. Outpatient clinic visits or emergency department visits were not included. Two groups were created: persons who reported at least one admission and those who did not. The Groningen Activity Restriction Scale was used to determine the level of (I)ADL disability and was measured at baseline and after two years.[21] This questionnaire comprises 18 items, such as 'Can you, fully independently, wash and dry your whole body?'. There are four possible answering options ranging from 'Yes, I can do it fully independently without any difficulty' to 'No, I can do it only with someone's help'. Theoretical scores range from 18 to 72. Higher scores indicate a higher level of (I)ADL disability.

Statistical Analysis

First, descriptive statistics were computed to provide an overview of the baseline characteristics of the total study population and pre-frail and frail persons separately. Second, analyses were performed to study the main effects between levels of frailty (pre-frail used as reference standard) and the adverse outcomes adjusted for age and gender, but without taking the potential moderating effect of resources into account. Logistic regression analyses were performed for the outcomes hospitalisation and mortality. An independent samples t-test was conducted to compare the change scores between pre-frail and frail persons for the outcome disability. The third step in the analyses was to study the potential moderating effects of the resources. This was done by adding an interaction term of frailty with the specific resource in logistic (for the outcomes hospitalisation and mortality) and linear (for the outcome disability) regression models. Subsequently, regression analyses were performed for the outcomes hospitalisation and mortality with results split by resource (e.g. low and high income) to show possible differences in Odds Ratio (OR). For the outcome measure disability (at two-year follow-up) baseline disability was included as a covariate in all models. Mean change scores including standard deviations of disability were calculated to compare pre-frail and frail persons, and results were again split by resource. Scores of mastery and self-management were dichotomised, based on median values, as suggested in previous research.[22] Age and gender were added to all regression models

as covariates. P values < 0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics for Windows version 22.

Results

A total of 2,420 persons participated in our study. Their baseline characteristics are displayed in Table 3.1. Mean age was 76.3 ± 6.6 years and there were more female participants (60.5%) compared to males. Frailty was present in 22.2% of the study population, 77.8% were pre-frail. Pre-frail and frail participants differed statically significant in all characteristics, except for the availability of informal care (p = 0.185). Frail participants had worse baseline disability scores ((I)ADL disability 43.0 ± 11.8 vs 28.6 ± 10.0) and less potentially beneficial resources compared to pre-frail participants (e.g. high educational level 21.4% vs 33.9%).

During the two-year follow-up 182 participants (7.5%) died and 836 participants(34.5%) were admitted to a hospital at least once. Mean disability score at two-year follow-up was 32.9 ± 12.5, while for these persons the disability score at baseline was 29.9 ± 11.0 (p < 0.001).

Table 3.2 presents the results of logistic regression analyses for mortality and hospitalisation, presenting the relation with frailty (the OR of frail versus pre-frail participants) for each level of the resources studied, including the p values of the interaction terms. Results for disability are presented in Table 3.3, displaying mean change scores of disability for pre-frail and frail participants within the resource categories, and p values of the interaction terms. Both in Table 3.2 and 3.3 the first level of each resource presented is considered to be disadvantageous, the second to be beneficial.

Overall, frail participants had a threefold increased risk of mortality (OR = 2.99, 95% CI = 2.17-4.13) and an over twofold increased risk of hospitalisation (OR = 2.21, 95% CI = 1.73-2.82) compared to pre-frail participants. They also deteriorated significantly faster on disability: on average 3.93 (± 8.26) points versus 2.82 (± 6.78) points for the pre-frail participants over the two-year period (p = 0.022).

None of the interaction terms were statistically significant for the outcomes mortality and hospitalisation, indicating no moderating effect for any of the resources, even though OR estimates sometimes differed substantially. For example, among

participants with *no* availability of informal care frail participants had a threefold risk (OR 3.18, 95% CI = 1.42-7.12) of hospitalisation compared to pre-frail ones. For participants *with* informal care available, the frail ones had a twofold higher risk of hospital admission compared to their pre-frail counterparts (OR 2.15, 95% CI = 1.66-2.78). This indicates a buffering effect of availability of informal care, however the difference was not statistically significant (p = 0.299). Regarding mortality, the data showed contradictory results: the availability of informal care is associated with an increased mortality risk for frail participants (OR 3.12, 95% CI = 2.23-4.37) compared to pre-frail participants, while this risk is only slightly higher for frail participants with no availability of informal care (OR 1.17, 95% CI = 0.29-4.74). Again this difference was not statistically significant (p = 0.278). Thus, in addition to the fact that none of the moderating effects were statistically significant, trends were inconsistent. Similar unexpected or inconsistent trends were found regarding educational level, sense mastery and self-management abilities.

For the outcome disability, two resources, income and living situation, showed a statistically significant interaction with frailty. However, the direction of these two moderating effects was opposite to that hypothesised. Among participants with a high income frail participants deteriorated more (Δ = 5.18 ± 7.88) than their pre-fail counterparts (Δ = 2.71 ± 6.39), while among those with a low income the changes in levels of disability were fairly similar between pre-frail and frail participants (about 3.0 points). Among those who were not living alone the mean change score was larger for frail than pre-frail participants (Δ = 4.72 ± 8.08 versus Δ = 2.64 ± 6.59 respectively). No large differences over time were detected between pre-frail and frail participants who were living alone (Δ = 3.16 ± 7.04 and Δ = 3.40 ± 7.96 respectively). The interacting effects of the other resources were not significant.

Results of all analyses were based on valid cases. For mortality, complete data were available. For hospitalisation, results were based on 1803 valid cases. Of the total number of missing cases (n=617, 25% of the population) about one third can be explained by participants who were admitted to a nursing home (n=53) or had died during follow-up (n=132). The group with valid data was compared with the group with missing data on baseline characteristics using chi-square and Mann-Whitney tests. Participants in the group with missing data were significantly older, more often frail, less educated, more often living alone, had a lower sense of mastery, less self-management abilities and more (I)ADL disability at baseline. Similar patterns were found for the outcome disability (1883 valid cases); participants with missing data (n=537) had less favourable baseline scores compared to valid cases.

Table 3.1 Baseline descriptive characteristics of the total study population, and pre-frail and frail participants separately.

		Total group	**Pre-frail**	**Frail**	**P value**
		n=2420	n=1883 (77.8%)	n=537 (22.2%)	
Age (mean ± SD)		76.3 ±6.6	75.8 ± 6.5	78.0 ± 6.8	P < 0.001[A]
Male gender		957 (39.5%)	767 (40.7%)	190 (35.4%)	P = 0.025[B]
(I)ADL disability (18-72)[D] (mean ± SD)		31.8 ± 12.0	28.6 ± 10.0	43.0 ± 11.8	P < 0.001[A]
Resources					
Level of education					
	low	1579 (68.9%)	1182 (66.1%)	397 (78.6%)	P < 0.001[B]
	high	714 (31.1%)	606 (33.9%)	108 (21.4%)	
Income					
	low	1145 (47.4%)	830 (44.1%)	315 (58.8%)	P < 0.001[B]
	high	1272 (52.6%)	1051 (55.9%)	221 (41.2%)	
Informal care					
	not available	224 (9.4%)	167 (8.9%)	57 (10.9%)	P = 0.185[B]
	available	2167 (90.6%)	1699 (91.1%)	468 (89.1%)	
Living situation					
	living alone	906 (39.2%)	668 (37.0%)	238 (46.9%)	P < 0.001[B]
	not living alone	1404 (60.8%)	1135 (63.0%)	269 (53.1%)	
Mastery (7-35)[D] (mean ± SD)		23.1 ± 5.9	24.2 ± 5.6	19.5 ± 5.5	P < 0.001[A]
	low	1093 (49.9%)	726 (42.5%)	367 (75.8%)	P < 0.001[B]
	high	1098 (50.1%)	981 (57.5%)	117 (24.2%)	

		Total group	Pre-frail	Frail	P value
Self-management (1-6)[D] (mean ± SD)		3.8 ± 0.7	3.9 ± 0.7	3.5 ± 0.8	P < 0.001[C]
	low	1045 (47.1%)	713 (41.3%)	332 (66.9%)	P < 0.001[B]
	high	1176 (52.9%)	1012 (58.7%)	164 (33.1%)	

All results are presented as number of cases (percentage) unless stated differently
[A] Mann-Whitney U test, [B] Chi-square, [C] Independent samples t-test, [D] Preferable score is underlined

Table 3.2 Association between frailty and outcome variables mortality and hospitalisation, within each level of the resources.

		Mortality	**Hospitalisation**
		OR of frailty (95% CI)[A]	OR of frailty (95% CI)[A]
Frailty (frail vs. pre-frail)		2.99 (2.17-4.13)	2.21 (1.73-2.82)
Resources			
Level of education			
	low	2.80 (1.85-4.25)	1.98 (1.49-2.65)
	high	3.48 (1.98-6.10)	3.04 (1.80-5.13)
	interaction (p value)	0.616	0.148
Income			
	low	3.48 (2.20-5.51)	2.55 (1.81-3.58)
	high	2.62 (1.64-4.21)	1.70 (1.18-2.44)
	interaction (p value)	0.394	0.138
Informal care			
	not available	1.17 (0.29-4.74)	3.18 (1.42-7.12)
	available	3.12 (2.23-4.37)	2.15 (1.66-2.78)
	interaction (p value)	0.278	0.299
Living situation			
	living alone	3.08 (1.85-5.14)	2.60 (1.75-3.88)
	not living alone	2.86 (1.84-4.44)	2.06 (1.49-2.85)
	interaction (p value)	0.958	0.290
Mastery			
	low	3.04 (1.96-4.73)	2.15 (1.56-2.96)
	high	3.33 (1.79-6.18)	1.81 (1.10-2.97)
	interaction (p value)	0.689	0.723
Self-management			
	low	2.24 (1.47-3.42)	2.41 (1.72-3.39)
	high	3.75 (2.14-6.58)	1.84 (1.22-2.78)
	interaction (p value)	0.151	0.329

All models are adjusted for age and gender
The first level of each resource is considered disadvantageous, the second beneficial
[A]OR (95% confidence interval)

Table 3.3 Mean change in disability scores for pre-fail and frail participants, within each level of resources.

		Disability	
		mean Δ disability (SD)[A]	
		pre-frail	frail
Frailty		2.82 (6.78)	3.93 (8.26)
Resources			
Level of education			
	low	3.01 (6.94)	4.00 (8.11)
	high	2.43 (6.38)	4.10 (7.16)
	interaction (p value)	0.486	
Income			
	low	3.01 (7.14)	2.99 (8.43)
	high	2.71 (6.39)	5.18 (7.88)
	interaction (p value)	0.002	
Informal care			
	not available	3.77 (7.31)	3.48 (11.35)
	available	2.68 (6.66)	3.95 (7.86)
	interaction (p value)	0.110	
Living situation			
	living alone	3.16 (7.04)	3.40 (7.96)
	not living alone	2.64 (6.59)	4.72 (8.08)
	interaction (p value)	0.011	
Mastery			
	low	3.74 (7.40)	4.28 (8.36)
	high	2.36 (6.03)	1.78 (6.38)
	interaction (p value)	0.222	
Self-management			
	low	3.24 (7.03)	4.26 (8.73)
	high	2.53 (6.46)	2.91 (6.59)
	interaction (p value)	0.666	

All models are adjusted for age and gender
The first level of each resource is considered disadvantageous, the second beneficial
[A]Mean change in disability score (two year follow-up –baseline) (standard deviation)

Discussion

The aim of the present study was to investigate whether specific resources moderate the impact of frailty level on adverse outcomes over a two-year period. Results show that frail older participants, compared to those who are pre-frail, have increased odds of mortality and hospitalisation, and deteriorate more on disability scores. This is in line with previous research.[2,23] The resources studied have no moderating effects for the outcomes mortality and hospitalisation. Moreover, the directions of trends were inconsistent. Only for disability statistically significant moderating effects were found for the resources income and living situation. However, the direction of these results contradicted our expectations. Overall, we may conclude that the selected resources hardly seem to moderate the effects of the level of frailty on the adverse outcomes in our study.

Although previous research showed relationships between the resources we investigated and frailty[24], the resources were scarcely studied as moderating factors in the pathway from frailty to its adverse outcomes. Hoogendijk and colleagues investigated whether psychosocial resources (such as mastery and self-efficacy) moderate the effect of frailty on functional decline and mortality among community-dwelling older people.[22] They found no moderating effects of the resources they studied, including mastery, which is similar to the results of our study. In contrast, Dent et al. reported several moderating effects of psychosocial factors, including sense of control (mastery).[11] This might be due to differences between the populations studied; Dent et al.'s study had a (smaller) hospital-based population including non-frail persons and had a larger proportion of frail people. Ament and colleagues found that educational level moderated the effect of difficulty in performing ADLs on self-perceived health in males and it moderated the effect of psychological distress on self-perceived health in women.[12] In our study no significant moderating effect of educational level was found. Ament et al. also found that living alone status (in women) significantly moderated the effect of difficulty in performing ADLs on receiving professional care. In their study, female participants who live with someone received less professional care, which is considered to be beneficial. We found that living with someone else leads to significantly more deteriorating disability scores compared to living alone, which is considered to be disadvantageous. Ament and colleagues defined frailty in a different way and used different outcome variables compared to our study, which might be reasons why the results seem to contradict. For all resources we found results which contradicted our expectations on one or more outcome measures. The

effects of frailty status on the outcomes measures might be so dominant , that the moderating effects are being overshadowed.

The strength of the present study is that it is one of the first to investigate the moderating effect of several resources using longitudinal data of a large sample of community-dwelling pre-frail and frail older people. However, a relatively large proportion of outcome data were missing regarding hospitalisation and (I)ADL disability. As those with missing data had worse baseline scores, results of the present study should be interpreted with caution. Also, selective mortality or admission to a nursing home might have influenced the results, as the most severely frail participants dropped out for these reasons. It is uncertain to what extend and in which direction the missing data influenced the results.

So far, research on the moderating effect of resources is scarce and results vary between studies. In order to gain more insight into the role of resources in the pathway from frailty level to adverse outcomes, future research should try to include the frailest cases that were missed or had dropped-out in previous studies. Also, non-frail persons could be included as resources might have a beneficial effect especially in the early onset of frailty and less in the phases of pre-frailty and frailty. A follow-up period longer than two years might therefore also be necessary in order to find possible moderating effects. However, if moderating factors take many years to have beneficial effects, it is questionable if it is useful in daily practice to intervene in them, as frail people are already at risk of adverse outcomes. Furthermore, both the frailty criteria and the adverse outcomes (partially) that were used in this study have a physical nature. Their coherence is therefore fairly strong. Consequently, non-physical resources may not have a moderating effect. Given the latter two remarks, the focus of future research might be on (1) finding other moderating factors that are easy to intervene in and/or require less time to moderate, and hence are more useful in daily practice, and/or (2) choosing other (non-physical) outcome measures to study possible moderating effects of the resources.

Conclusions

Results of the present study showed that frail older participants had increased odds of mortality and hospitalisation, and deteriorated more on disability scores, compared to those who were pre-frail. However, no clear moderating effects of the studied resources on the adverse outcomes associated with frailty were found among pre-frail and frail participants.

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CHAPTER 4

Substitution of Fried's performance-based physical frailty criteria with self-report questions

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Abstract

Objective

To identify self-report questions that can substitute Fried's performance-based frailty measures for use in large-scale studies and daily practice.

Methods

A cross-sectional study was conducted among community dwelling older people (65+). Based on a literature search and interviews with older people and experts, 11 questions concerning walk time and 10 on handgrip strength were selected. All participants completed these sets of self-report questions as well as the original Fried criteria (including performance-based tests). Regression analyses were performed to find the questions that best substituted the performance-based tests.

Results

In total, 135 individuals (mean age 73.8 ± 7.0, 58.5% female) in different stages of frailty (non-frail 38.5%, pre-frail 40.7%, frail 20.7%) were included. Regression analyses revealed four questions for walk time and two for handgrip strength. Cut-off values of three for walk time (range 0-5) and one for handgrip strength (range 0-3) seem most optimal. This resulted in a sensitivity of 69.2%, 86.1% specificity and 79.4% agreement for walk time and a sensitivity of 73.2%, 71.3% specificity and 71.9% agreement for handgrip strength. The comparison of frailty stages using frailty criteria including the performance-based measures and scores based solely on self-report questions, resulted in an observed agreement of 71.1% (kappa value =0.55).

Conclusions

Considering the agreement between the questions and the performance-based tests, these two sets of questions might be used in settings where the performance-based tests of walk time and handgrip strength are unfeasible, such as in daily practice and large-scale research.

Introduction

There is ongoing debate concerning the nature and definition of frailty, and consequently many instruments for identifying frail older people have been developed.[1,2] Research into the psychometric quality of most of these instruments is limited.[3,4] The "frailty phenotype" as described by Fried and colleagues is the measure most frequently used.[2,5] The phenotype uses five criteria to determine the level of frailty: weight loss, exhaustion, low physical activity, slowness, and weakness. The first three criteria are measured with self-report questions, while slowness and weakness are assessed with the performance-based measures of walk time and handgrip strength. A recent review by Theou et al. showed a large variation in how these criteria are assessed between studies.[6] These differences cause variations in frailty prevalence estimates and predictive ability.[6,7]

When screening large populations, performance-based measures can be difficult to conduct because they are time consuming and costly, and often require well-trained assessors.[8] Therefore, many researchers use questionnaires or a single question instead of performance-based measures. These substitutions are also often used for the two performance-based measures of the Fried frailty criteria.[6,9,10] In previous frailty studies, handgrip strength and walk time have been measured by questions such as: "Because of health problems, do you have difficulty walking 100 m, or climbing one flight of stairs without resting?" or "In the past 4 weeks, how satisfied have you been with your overall muscle strength?".[11,12] In most studies the validity of these questions has not been tested, or at least not reported. Therefore, it is unclear which question (or set of questions) can adequately substitute the performance-based measures of the Fried frailty phenotype in the identification of frail older people.

Cong and colleagues substituted the measurement of gait speed with self-report questions.[13] Although they used the same performance test as described by Fried and colleagues, they employed different cut-off values. Simard and colleagues tried to identify questions concerning tasks and activities done with the hands that could estimate the objectively measured handgrip strength on a continuous scale.[14] The average age of the participants was 66.1 (±12.6) years and the majority considered themselves to be active. The characteristics of frail older people are different; they are mostly older and less active, leading to reduced grip strength. It is thus uncertain whether the questions these researchers proposed can be applied in research among frail older people. Therefore, the aim of this study was to investigate whether the performance-based measures of walk time and handgrip strength, as described by Fried and colleagues, could each be substituted by self-report questions in a population of non-frail, pre-frail and frail older people.

Methods

Recruitment and selection of participants

A cross-sectional study was conducted among older people in different stages of frailty: non-frail, pre-frail, and frail. To include such a heterogeneous group, participants were recruited from different settings: a community center for older people, clients of a physical therapy practice, people admitted to a hospital, and people attending day care facilities. We aimed to include 50 persons per frailty stage. People were invited to participate in the study if they were 65 years or older and physically and cognitively able to complete the performance-based tests and complete the questionnaires. They also had to be community-dwelling. Potential candidates received written and verbal information on the study, and had to give their written informed consent. This study was approved by the medical ethics committee Atrium-Orbis-Zuyd (13-N-176).

Measurements

The Fried criteria (with performance-based measures) were used to determine the level of frailty. Weight and height were also measured, and Body Mass Index (BMI) was calculated, as these measures were needed to determine the cut-off values for some of the Fried criteria. Eleven questions on walk time and ten questions on handgrip strength were asked as potential substitutes for the performance-based tests. Trained assessors conducted data collection to minimize intra- and inter-assessor variability.

Fried Frailty Criteria

The five Fried frailty criteria are weight loss, exhaustion, low physical activity, slowness, and weakness.[5] The first three criteria were measured with questions. *Weight loss* and *exhaustion* were measured as proposed by Fried and colleagues. *Low physical activity* was measured using a slightly adjusted version of the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH).[15] Details of the measurement of these three criteria can be found elsewhere.[16]

The other two frailty criteria, slowness and weakness, are performance-based measures. *Slowness (walk time)* was determined by measuring the time participants needed to walk 4.57 m (15 ft) at a normal pace with a standing start. Instructions were standardized. No encouragement was given by the assessor as this would presumably increase the pace of the participant. A walking aid was permitted if necessary. The test was performed three times and average values were used for the analyses. *Weakness (handgrip strength)* was measured using a Saehan hand dynamometer (Saehan Corporation, South Korea). As the measurement protocol was not stated by Fried et al.

and considerable variation exists in methods for assessing grip strength,[17] the following protocol was used: Participants were seated upright on a chair without armrests, the shoulder and forearm in neutral and the elbow in 90° flexion. The handle position of the dynamometer was determined in such a way that the intermediate phalanges were on the front side of the handle. Three measurements per hand were conducted alternately with a minimum of 30s rest between each attempt. All participants received standardized instructions and were verbally encouraged. The results of the measurements per hand were averaged and the highest average score, i.e. either left or right hand, was used for analyses. Cut-off values for both performance-based measures were used as described by Fried and colleagues.[5]

The result of each frailty criterion is dichotomous: frail (score 1) or not frail (score 0). The final frailty sum scores range from 0 to 5 and classify persons into non-frail (score 0), pre-frail (score 1-2) or frail (score 3-5).

Questions on Walk Time and Handgrip Strength

Questions on walk time and handgrip strength were derived from various sources. First, multiple databases were searched using terms related to frailty, grip strength, and walk time. Only questionnaires in English or Dutch were included. This resulted in 11 questionnaires with potential useful questions, including the Dutch version of the 36-Item Short-Form Health Survey (SF-36) and the Disability Rating Index.[18, 19] These questionnaires were screened for questions that were specifically related to walk time or handgrip strength. In addition, community-dwelling older people and experts (scientists and physical therapists, all working with frail older people) were interviewed. Based on face validity and consultation with the aforementioned experts, final sets of 11 questions for walk time and 10 questions for handgrip strength were composed (Table 4.2). The response options for all questions were “Yes” or “No”.

Statistical analysis

Descriptive statistics were used to describe the study population. To get a first impression of the data, Cronbach’s α of all questions on walk time and all questions on handgrip strength were calculated followed by the value of α if the item is removed. This gives an idea of how the different items in the scales performed in terms of measuring the traits they set out to measure. Logistic regression analyses with backward stepwise elimination were performed to find the optimal set of questions as a substitute for the performance-based measures. The performance of the model was quantified as the area under the receiver operating characteristic curve (AUC).

Bootstrap-validation was then performed to calculate the optimism in the estimation of the AUC (i.e. the likely decrease in AUC when applied with future patients).[20]
The regression coefficients of the questions in the final regression model determined the degree to which each question contributed to the total questionnaire score. The coefficients were converted into simple integers (i.e. one and two), which are easy to use in future research and clinical applications. Next, the summed scores of the questionnaire were calculated for all participants. Then, cut-off values were determined by calculating the sensitivity, specificity and percentage observed agreement for all possible cut-off scores in the sets of questions. The best combination of sensitivity and specificity determined the optimal cut-off score. Finally, the frailty stages were recalculated based on these cut-off scores and compared (percentage agreement and Cohen's kappa) with the frailty stages based on the scores of the performance measures.
All analyses were performed using SPSS 22 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY) and R version 3.1.3 (R Foundation for Statistical Computing, R Core Team, Vienna, Austria).

Results

In total, 135 persons (41.5% men) with an average age of 73.8 years (SD = 7.0) participated in this study. The characteristics of the total study population and for men and women separately are described in Table 4.1 There were fewer frail participants (20.7%) compared to non-frail (38.5%) and pre-frail (40.7%) participants. Men were taller, heavier and had greater grip strength compared to women. No significant differences between men and women were found for the other variables.

An overall Cronbach's α of 0.84 was found for walk time and 0.88 for handgrip strength (Table 4.2). Deletion of any item did not improve the α.

Table 4.1 Characteristics of the total study population (n=135) and for men and women separately.

Characteristic	Total	Male	Female	P value
N	135	56 (41.5%)	79 (58.5%)	
Age (yr)[a]	73.8 ± 7.0 (65-93)	73.2 ± 6.5 (65-93)	74.2 ± 7.4 (65-93)	P=0.608[c]
Fried score				
0	52 (38.5%)	22 (39.3%)	30 (38.0%)	P=0.527[c]
1	28 (20.7%)	11 (19.6%)	17 (21.5%)	
2	27 (20.0%)	16 (28.6%)	11 (13.9%)	
3	16 (11.9%)	4 (7.1%)	12 (15.2%)	
4	10 (7.4%)	2 (3.6%)	8 (10.1%)	
5	2 (1.5%)	1 (1.8%)	1 (1.3%)	
Frailty stage				
non frail	52 (38.5%)	22 (39.3%)	30 (38.0%)	P=0.303[c]
pre-frail	55 (40.7%)	27 (48.2%)	28 (35.4%)	
frail	28 (20.7%)	7 (12.5%)	21 (26.6%)	
Height (cm)[a]	166.0 ± 9.3 (143.0-188.0)	173.6 ± 6.6 (158.0-188.0)	160.6 ± 6.7 (143.0-176.0)	P<0.001[b]
Weight (kg)[a]	75.3 ± 14.6 (42.1-129.0)	82.5 ± 11.1 (56.0-106.0)	70.2 ± 14.6 (42.1-129.0)	P<0.001[c]
Body Mass Index (kg/m^2)[a]	27.3 ± 4.8 (18.4-49.2)	27.4 ± 3.5 (20.0-37.3)	27.2 ± 5.5 (18.4-49.2)	P=0.353[c]
Walk time (s)[a]	7.2 ± 4.5 (3.3-33.3)	6.3 ± 2.7 (3.3-18.5)	7.8 ± 5.3 (3.4-33.3)	P=0.180[c]
Handgrip strength (kg)[a]	27.2 ± 10.3 (2.8-54.0)	35.8 ± 8.3 (18.7-54.0)	21.1 ± 6.5 (2.8-37.0)	P<0.001[c]

[a]Mean ± standard deviation (range)
[b]independent samples t-test
[c]Mann-Whitney *U* test

Table 4.2 Cronbach's α for all questions together and the value of α if the item is deleted.

Number	Question	Cronbach's α	Cronbach's α if item deleted
	Walk time	0.84	
1	When the doorbell rings, do you usually get there in time to open the door?		0.84
2	When the phone rings, do you usually get there in time to answer it?		0.84
3	Do you feel like you walk more slowly than other people your age?		0.81
4	Do you walk more slowly than you'd like?		0.82
5	When walking with other people your age, do you struggle to keep up?		0.82
6	Do other people your age regularly pass you when you're walking?		0.82
7	Do you have enough time to cross the street on foot when the traffic light turns green?		0.83
8	Do you take approximately two steps per second when walking?		0.82
9	Do you encounter problems in daily life due to walking difficulties?		0.81
10	Do you encounter problems in daily life due to poor balance?		0.83
11	Do you have enough time to cross the street at a pedestrian crossing when the light turns green?		0.81

Number	Question	Cronbach's α	Cronbach's α if item deleted
	Handgrip strength	0.88	
1	Do you have trouble opening a jar that has already been opened?		0.87
2	Do you have trouble opening a jar that has not yet been opened?		0.87
3	Do you require assistance and/or a device to open the lid of a jar?		0.87
4	Do you have trouble watering plants with a spray bottle?		0.88
5	Do you have trouble wringing out a facecloth/dishrag?		0.88
6	Do you have trouble opening a drinks bottle or a carton of milk that has not yet been opened?		0.86
7	Do you have trouble turning on a tap that has been tightly closed?		0.86
8	Do you find it difficult or painful to give a firm handshake?		0.87
9	Do you encounter problems in daily life due to lack of hand strength?		0.86
10	Do you feel like you have less hand strength than other people your age?		0.87

The final regression model included four questions for walk time (questions 1, 4, 7, and 10) and two for handgrip strength (questions 4 and 10). The model was robust as bootstrap analyses showed no evidence of optimism in the estimation of the AUC.

Inspection of the regression coefficients of the final regression models showed that question 4 for walk time and question 4 for handgrip strength contributed substantially more to the total score than any of the other questions. Therefore, they were assigned a score of two, while the other questions were given a score of one. Subsequently, summed scores were calculated for each participant. The results of the performance-based tests and summed questionnaire scores are displayed in Table 4.3, as well as the sensitivity, specificity, and percentages of observed agreement for each possible cut-off value. For walk time, the best combination of sensitivity and specificity (69.2% and 86.1%, respectively), and the highest percentage agreement (79.4%) were found for a cut-off value of 3 (a score of 3-5 classifies someone as frail). For handgrip strength, the best combination of sensitivity and specificity was found when a cut-off value of 1 was applied, while the percentage observed agreement was highest for a cut-off value of 2 or 3 (agreement for both cut-off values = 78.5%). As the sensitivity drops considerably when applying a cut-off of 2 or 3, we recommend a cut-off score of 1 (a score of 1-3 classifies someone as frail).

Table 4.3 Distribution of scores for the performance-based tests and questionnaires, and sensitivity, specificity and percentage observed agreement for each cut-off point.

	Walk time (n = 131)					**Handgrip strength (n = 135)**				
Measurement method	**Score**	**No.**	**Se (%)**	**Sp (%)**	**Ag (%)**	**Score**	**No.**	**Se (%)**	**Sp (%)**	**Ag (%)**
Performance	0	79				0	94			
	1	52				1	41			
Questionnaire	0	36				0	78			
			96.2	43.0	64.1			73.2	71.3	71.9
	1	8				1	39			
			92.3	50.6	67.2			36.6	96.8	78.5
	2	40				2	2			
			69.2	86.1	79.4			34.1	97.9	78.5
	3	28				3	16			
			36.5	100.0	74.8					
	4	11								
			15.4	100.0	66.4					
	5	8								

No. number of participants, *Se* sensitivity, *Sp* specificity, *Ag* agreement

Finally, the Fried frailty scores were recalculated based on the questions instead of the performance-based measures and persons were again classified as non-frail, pre-frail and frail. This resulted in an observed agreement of 71.1% with a Cohen´s kappa of 0.55.

Discussion

We aimed to identify self-report questions that can substitute the performance-based tests of walk time and handgrip strength in Fried and colleagues' frailty phenotype measure. The final regression models revealed a set of four questions for walk time and two questions for handgrip strength. Cut-off values of 3 for the walk time questionnaire and 1 for the handgrip strength questionnaire seem to be most optimal. When the frailty stages of all participants based on the frailty criteria including the performance-based measures were compared to the scores based solely on self-report questions, this resulted in an observed agreement of 71.1% (Cohen's kappa = 0.55).

So far, little research has been reported on the substitution of Fried's performance-based measures with questions. Johansen and colleagues studied this substitution among patients receiving maintenance hemodialysis.[21] They used the Physical Function scale of the SF-36 as a substitution for the two performance-based measures together. This scale measures limitations in performing 10 activities, such as lifting or carrying groceries, and walking one block. Although they did not replace each performance-based test separately and the questions were not specifically related to handgrip strength or walking speed, they found an overall agreement of 72.5%. This is a fairly reasonable result and comparable to our study. Prior studies (not specifically related to frailty) have reported on discrepancies between self-report measures and performance-based tests. Factors such as the level of cognitive functioning, personality, affective functioning, perceived physical competence, mastery and depressive symptomatology can influence the association between such measures.[22,23]

The coefficients of the regression models determined the degree to which each question contributed to the total questionnaire score. For handgrip strength, one question was assigned a score of 2 and all others a score of 1. The results show an optimal cut-off value of 1, indicating frailty when someone answers "Yes" to any of the questions. Consequently, the weighted scores of the handgrip strength questions have no impact on the classification. For easy use in future research or in practice, a score of 1 for each of the handgrip strength questions can be used.

The strength of this study is that the primary goal was to substitute the Fried frailty criteria of walk time and handgrip strength using specific questions. We also included persons in all stages of frailty, which makes the questions useful for all community-dwelling older people, provided that they are cognitively able to complete a questionnaire. The performance-based measurements in our study were carried out under strict protocol, nevertheless some errors may have occurred. The Saehan dynamometer was previously marketed under the trade name Jamar, which is regarded as the "gold standard" in measurements of handgrip strength.[24] However, Fried and colleagues did not describe the protocols for their performance-based tests in detail. Protocols can differ greatly between studies leading to different results.[17,25,26] Because of the uncertainty concerning whether Fried's protocols match ours, the results of the performance-based measures might be slightly different. As our study population was small we were unable to conduct gender-stratified analyses, which limits the generalizability of the results. Our questions should be further validated in other (international) cohorts. Cultural differences should also be investigated as, for example, not all countries have traffic lights for pedestrians that turn green as in the Netherlands, and the use of plant spray bottles may not be very common in other countries. Furthermore, it is important to investigate whether self-report questions (such as the ones we suggested) and performance-based tests are equally capable of predicting adverse outcomes of frailty, or that one of these measurement types is superior. Papachristou and colleagues reported that substituting Fried's criteria by self-reported items provided a better predictive ability for incident disability, falls, and all-cause mortality in a population of 1198 British older men.[27] Nevertheless, the self-report questions in their study differed from the ones we used, so future research should provide insight in the predictive ability of the questions that we proposed.

Despite some limitations of our study, the advantages of using the questions are that they are easy to answer and administer compared to performance-based measures, requiring no specially trained assessors or special equipment. This makes them highly suitable for use in daily practice and large-scale research.[8] The cut-off values that we propose are based on a combination in which both sensitivity and specificity are (equally) important. However, we have presented the results for all possible cut-off values. This provides the opportunity for other users to choose their own cut-off values depending on their (research) goal. For example, if one is interested in screening older people for intervention purposes, a high specificity seems favorable, implying higher cut-off values.

In conclusion, this study provides two, brief sets of questions that might be used to substitute the performance -based test of walk time and handgrip strength of the Fried frailty criteria when performance-based tests are unfeasible. The questions can be specifically useful for screening for frailty among older people in clinical practice and large-scale research. Cultural differences and the predictive validity of these questions should be further investigated.

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CHAPTER 5

The ability of four frailty screening instruments to predict mortality, hospitalization and dependency in (instrumental) activities of daily living

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Abstract

The aim of this study was to assess the predictive ability of the Frailty Phenotype (FP), Groningen Frailty Indicator (GFI), Tilburg Frailty Indicator (TFI) and Frailty Index (FI) for the outcomes mortality, hospitalization and increase in dependency in (instrumental) activities of daily living ((I)ADL) among older persons.

This prospective cohort study with two-year follow-up included 2420 Dutch community-dwelling older people (65+, mean age 76.3 ± 6.6 years, 39.5% male) who were pre-frail or frail according to the FP. Mortality data were obtained from Statistics Netherlands. All other data were self-reported. Area under the receiver operating characteristic curves (AUC) was calculated for each frailty instrument and outcome measure. The prevalence of frailty, sensitivity and specificity were calculated using cutoff values proposed by the developers and cutoff values one above and one below the proposed ones (0.05 for FI). All frailty instruments poorly predicted mortality, hospitalization and (I)ADL dependency (AUCs between 0.62-0.65, 0.59-0.63 and 0.60-0.64, respectively). Prevalence estimates of frailty in this population varied between 22.2% (FP) and 64.8% (TFI). The FP and FI showed higher levels of specificity, whereas sensitivity was higher for the GFI and TFI. Using a different cutoff point considerably changed the prevalence, sensitivity and specificity. In conclusion, the predictive ability of the FP, GFI, TFI and FI was poor for all outcomes in a population of pre-frail and frail community-dwelling older people. The FP and the FI showed higher values of specificity, whereas sensitivity was higher for the GFI and TFI.

Introduction

Over the past decades, many instruments have been developed to identify frail older people.[1] Since consensus on a frailty definition is still lacking, these instruments are based on different concepts. For example, Fried and colleagues proposed an instrument based on (five) solely physical measures, the Frailty Phenotype (FP).[2] Others prefer a broader concept and also include other, predefined domains, such as social or psychological domains, in their frailty instrument. An example of the latter is the Tilburg Frailty Indicator (TFI), developed by Gobbens and colleagues.[3] Rockwood and Mitnitski[4] also proposed a multi-domain concept with their Frailty Index (FI). In contrast to the frailty measures with predefined domains, the FI is characterized by a non-fixed set of items of so-called deficits. The common factor of all of these instruments, irrespective of the frailty definition used, is that when a person is classified as frail, there is an increased risk of adverse outcomes, such as mortality, disability, institutionalization, and hospitalization.[5]

A fair amount of research has been conducted on the predictive validity of frailty instruments.[6,7] Nevertheless, much variation exists, for instance in study setting (community-dwelling, assisted living, hospitalized)[8-10], outcomes (e.g. death, disability, institutionalization, hospitalization, falls)[5], follow-up period (ranging from a few weeks to several years)[2,11], ethnicities (e.g. African American, Mexican American)[12,13], and gender (males, females or both).[5,14] If only one instrument is included in a study, the aforementioned variation makes it difficult to compare the predictive accuracy of different frailty instruments. Several studies have examined two or more instruments in one population. For example, Theou and colleagues[15] compared eight different frailty instruments with regard to their ability to predict all-cause mortality.

Two instruments that are frequently used worldwide are the FP and the FI. In the Netherlands and other European countries, the multi-dimensional Groningen Frailty Indicator (GFI) and TFI with fixed sets of questions are often used in particular. However, the predictive ability of these instruments has not been thoroughly tested before in one population with the same, multiple outcomes and within the same timeframe.[15]

The aim of this study was to investigate and compare the predictive ability of the four aforementioned frailty instruments for the outcomes mortality, hospitalization and increase in (I)ADL dependency, in a large sample of community-dwelling older people in the Netherlands.

Methods

A prospective cohort study with a two-year follow-up period was conducted.[16] The study was approved by the medical ethical committee of Zuyderland and Zuyd University of Applied Sciences (METC Z, 12-N-129).

Selection of Participants

The Dutch Community Health Services sent out an extensive general health questionnaire to 56,000 people aged 55 years and over in the province of Limburg, a southern region of The Netherlands in 2012. Of the respondents to this questionnaire, pre-frail or frail individuals (according to Fried's frailty criteria) who were at least 65 years old were asked to participate in our study. The selection of this cohort is described in detail elsewhere.[17] In total, 2420 persons gave their informed consent and participated in our study.

Data collection

Demographic data (i.e. gender, age) were collected at baseline, along with four frailty measures. The occurrence of three different outcome measures was determined at 2-year follow-up.

Frailty Measures

Four frailty instruments were investigated in this study. The FP, GFI, and TFI all have been validated among community-dwelling older people.[2,3,18] The FI that we developed has not been validated yet; however, FI's in general have shown to be a valid frailty instrument among community-dwelling older people.[19,20]

Frailty Phenotype (FP)

Fried and colleagues described five physical criteria (weight loss, exhaustion, physical activity, walk time and handgrip strength) for the identification of frail older people.[2] Weight loss, exhaustion and physical activity are self-report questions, whereas walk time and handgrip strength are originally performance-based measures. A partially modified version of these criteria was used in this study. In short, physical activity was measured with a slightly adjusted version of the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH).[21] The performance-based measures were unfeasible in this large-scale study, and therefore substituted by self-report questions.

More details of the self-report measurement of these criteria are described elsewhere.[22] Theoretical scores range from 0 to 5, classifying individuals as non-frail (score 0), pre-frail (score 1-2) or frail (score 3-5). Only pre-frail and frail persons were included in this study (see above).

Groningen Frailty Indicator (GFI)

The GFI, developed by Steverink and colleagues,[23] is a frailty screening instrument consisting of fifteen self-report questions focusing on multiple domains of functioning: physical (9 items), cognitive (1 item), social (3 items) and psychological (2 items). Theoretical scores range from 0 (no frailty) to 15 where persons with a score ≥4 are considered frail.[24]

Tilburg Frailty Indicator (TFI)

The TFI was developed by Gobbens and colleagues.[3] It consists of two parts: Part A comprises determinants of frailty, such as socio-demographic data and data about chronic diseases, while Part B, which determines the level of frailty, is used in the present study and comprises a total of 15 questions on multiple domains: physical (8 items), psychological (4 items) and social (3 items). Theoretical scores derived from Part B range from 0 (no frailty) to 15. A person is considered frail with a score of ≥ 5.[3]

Frailty Index (FI)

The Frailty Index is characterized by a non-fixed set of 'deficits'.[4] To create a frailty index, we used the guidelines described by Searle and colleagues.[25] Sixty-one potential items were selected from the extensive questionnaire sent by the Dutch Community Health Services. All items were dichotomized, where a score of '0' indicated the absence and a score of '1' the presence of the deficit. Next, all items with a prevalence of less than five percent were excluded, as proposed in a previous study.[20] The final Frailty Index consisted of 53 items, covering several topics, such as (chronic) diseases, loneliness, physical limitations and psychological distress. A cutoff value of 0.25 (which is equal to a positive score on 25% of the total number of items), as proposed by the original authors, was used to distinguish between frail and non-frail individuals.[26]

Outcome Measures

Outcome measures were mortality, hospitalization, and an increase in (I)ADL dependency. Statistics Netherlands provided mortality data (deceased yes/no) at the 2-year follow-up.

Self-report follow-up questionnaires were used to gather information about hospitalization (every 6 months) and (I)ADL dependency (at 2-year follow-up). For hospitalization, every 6 months the study participants were asked whether they had been admitted to hospital in the previous 6 months. Participants were divided into two groups: those who reported a hospital admission at least once and those who reported no hospital admission at any of the time points during the 2-year observation period. To determine the level of (I)ADL dependency, the Groningen Activity Restriction Scale (GARS)[27] was measured at baseline and after 2 years. The GARS comprises 18 questions about the degree to which someone is able to perform ADL and IADL activities independently. The four response options are: 'Yes, I can do it fully independently without any difficulty', 'Yes, I can do it fully independently but with some difficulty', 'Yes, I can do it fully independently but with great difficulty', 'No, I cannot do it fully independently, I can only do it with someone's help'. Results were first dichotomized into being independent (the first three options) or dependent (the fourth option) regarding the performance of activities, as described in the GARS manual.[28] We chose this way of analyzing because losing one's independency is particularly critical and has a higher impact on people's lives than having difficulties (without dependency) in performing (I)ADL. Then, changes over time per item were analyzed. When someone changed from independent to dependent more often than from dependent to independent, a positive score was assigned to the outcome (I)ADL dependency. This means that someone experienced a higher level of dependency in performing (I)ADL activities over the 2-year observation period.

Statistical Analysis

Descriptive statistics were computed to provide an overview of the study population.

As proposed in previous research, one missing value of the FP was allowed when a person had a valid score of 0-2 and two missing values were allowed if the FP score was ≥3.[22] As suggested by Metzelthin and colleagues,[29] missing items of the GFI and TFI were imputed by means of case mean substitution, if less than 25% of all items were missing. Case mean substitution was applied for the GARS if less than 50% of the total number of items were missing.[27] Missing values for each item of the FI were imputed using the non-missing population mean of that item, as proposed by the developers.[30]

Per screening tool, we created receiver operating characteristic (ROC) curves based on the continuous scores of the instrument and calculated the area under the ROC curve (AUC) per outcome measure to assess the predictive validity. We consider an AUC of 0.90-1 being excellent, 0.80-0.90 being good, 0.70-0.80 being fair, 0.60-0.70 being poor, and 0.50-0.60 non-informative. Next, the prevalence of frailty, sensitivity and specificity were calculated for each frailty instrument and for each outcome measure, using the cutoff values as proposed by the developers and for the cutoff values one above and one below the proposed values (0.05 for the FI). All statistical analyses were performed using IBM SPSS Statistics for Windows version 22.

Results

A total of 2420 persons (mean age 76.3 ± 6.6 years, 39.5% male), who were pre-frail or frail according to Fried's frailty score, participated in this study. Characteristics of the study population are described in Table 5.1.

Table 5.1 Characteristics of the study population at baseline (n=2420).

Variable	Value	Observed range
Gender (male, %)	957 (39.5%)	
Age (mean ± SD)	76.3 ± 6.6	65-97
FP (n, %)		
1	1317 (54.4%)	
2	566 (23.4%)	
3	358 (14.8%)	
4	153 (6.3%)	
5	26 (1.1%)	
GFI (**0**-15)[a] (mean ± SD)	4.58 ± 2.97	0-14
TFI (**0**-15)[a] (mean ± SD)	5.97 ± 3.31	0-15
FI (**0**-1)[a] (mean ± SD)	0.20 ± 0.12	0-0.76

FP Frailty Phenotype, *GFI* Groningen Frailty Indicator,
TFI Tilburg Frailty Indicator, *FI* Frailty Index, *SD* standard deviation
[a] Theoretical range, preferable score is bolded

After 2 years, 182 (7.5%) participants had died, about one third (n=836) had been admitted to a hospital at least once, and 668 participants had experienced a higher level of (I)ADL dependency.

First, to assess the predictive ability of the frailty instruments, ROC curves were plotted (Figure 5.1) and the areas under these curves were calculated (Table 5.2) for each instrument and each outcome measure. Per outcome measure, the AUCs of all instruments were fairly similar; the AUCs of all four frailty instruments for the prediction of mortality, hospitalization and (I)ADL dependency were poor (AUCs between 0.62-0.65, 0.59-0.63 and 0.60-0.64, respectively).

Table 5.2 Area under the ROC curve per frailty instrument and for each outcome measure.

Frailty instrument	Mortality[a]	Hospitalization[a]	(I)ADL dependency[a]
FP	0.65 (0.61 - 0.69)	0.59 (0.56 - 0.61)	0.60 (0.57 - 0.63)
GFI	0.64 (0.60 - 0.68)	0.61 (0.58 - 0.64)	0.63 (0.60 - 0.65)
TFI	0.62 (0.58 - 0.66)	0.61 (0.58 - 0.63)	0.64 (0.61 - 0.66)
FI	0.64 (0.60 - 0.68)	0.63 (0.60 - 0.65)	0.64 (0.61 - 0.66)

(I)ADL (instrumental) activities of daily living, *FP* Frailty Phenotype, *GFI* Groningen Frailty Indicator, *TFI* Tilburg Frailty Indicator, *FI* Frailty Index
[a]Area Under the Curve (95% Confidence Interval)

Next, based on the cutoff value proposed by the developers, the prevalence of frail participants was calculated for each frailty instrument, as well as the associated sensitivity and specificity for each outcome measure (Table 5.3). The prevalence of frail participants in this population (pre-frail and frail individuals according to the FP) varied from 22.2% (FP) to 64.8% (TFI). Regarding the proposed cut-offs, the FP and the FI showed higher levels of specificity compared to sensitivity for all outcome measures. Specificity was fairly similar for both instruments (FP range 79.6%-86.2%, FI 71.4%-79.6%). In contrast, the GFI and TFI had higher levels of sensitivity compared to specificity for all outcome measures. The sensitivity of these two frailty instruments varied more between outcome measures than specificity for the FP and FI. Sensitivity of the GFI and TFI were 76.2% and 80.6%, respectively, for mortality, lower for (I)ADL dependency (GFI 66.0%, TFI 72.7%), and lowest for hospitalization (GFI 63.9%, TFI 70.5%).

The same analyses were conducted with the cutoff value one point above or below the proposed cut-off value (0.05 for the FI) (Table 5.3). Using a lower or higher cutoff value than that proposed by the original authors considerably changes the sensitivity and specificity of each frailty instrument.

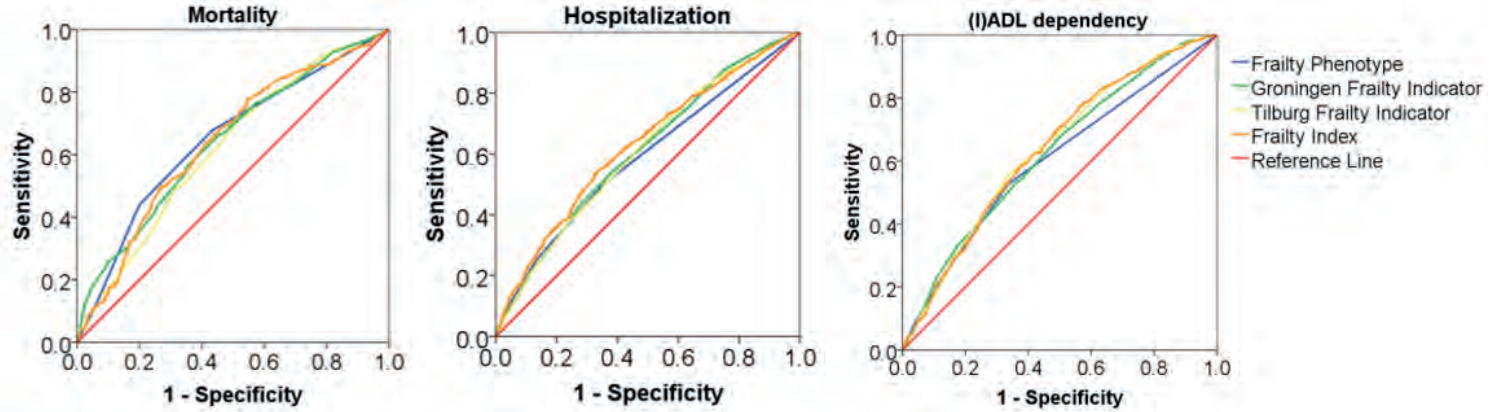

Figure 5.1 Receiver operating characteristic (ROC) curves for all frailty instruments and per outcome measure.

Table 5.3 Prevalence, sensitivity and specificity for different cut-offs of FP, GFI, TFI and FI for mortality, hospitalization and (I)ADL dependency among pre-frail and frail older people.

Frailty instrument	Cut-off	Frail (n)	Frail (%)	Mortality		Hospitalization		(I)ADL dependency	
				Sens[a]	Spec[b]	Sens[a]	Spec[b]	Sens[a]	Spec[b]
FP	≥ 2	1103	45.6	68.1	56.3	50.2	64.0	52.8	66.0
	≥ 3	**537**	**22.2**	**44.5**	**79.6**	**25.6**	**86.2**	**24.7**	**86.2**
	≥ 4	179	7.4	13.7	93.1	8.7	96.4	8.5	96.2
GFI	≥ 3	1697	70.7	82.3	30.3	75.2	37.1	77.5	37.9
	≥ 4	**1424**	**59.3**	**76.2**	**42.1**	**63.9**	**50.3**	**66.0**	**51.1**
	≥ 5	1150	47.9	66.3	53.6	53.5	62.9	53.8	63.1
TFI	≥ 4	1743	73.5	86.1	27.5	79.6	34.7	82.2	36.3
	≥ 5	**1536**	**64.8**	**80.6**	**36.5**	**70.5**	**44.1**	**72.7**	**45.7**
	≥ 6	1280	54.0	72.2	47.5	59.7	54.8	62.8	57.6
FI	≥ 0.20	1079	44.6	64.8	57.0	52.3	67.4	51.8	67.4
	≥ 0.25	**730**	**30.2**	**49.5**	**71.4**	**35.9**	**79.6**	**34.3**	**79.2**
	≥ 0.30	484	20.0	32.6	81.0	24.8	87.7	23.4	87.1

Cut-off values as proposed by the original authors are highlighted in bold.
(I)ADL (instrumental) activities of daily living, *FP* Frailty Phenotype, *GFI* Groningen Frailty Indicator, *TFI* Tilburg Frailty Indicator, *FI* Frailty Index
[a] Sensitivity (%)
[b] Specificity (%)

Discussion

The aim of this study was to investigate the ability of four frailty instruments to predict mortality, hospitalization and an increase in (I)ADL dependency over a 2-year time period among pre-frail and frail community-dwelling older people. The predictive ability of all included frailty instruments was poor for the outcomes mortality, hospitalization and (I)ADL dependency (AUCs between 0.59 and 0.65). The Frailty Phenotype and the Frailty Index showed higher values for specificity, while the Groningen Frailty Indicator and Tilburg Frailty Indicator had higher values for sensitivity. This indicates that the GFI and TFI are more able to correctly identify frail people as frail, whereas the FP and FI seem to be better at identifying non-frail people as such.

The AUCs in our study are low, and whether they can be considered clinically meaningful can be argued. Nevertheless, despite the fact that we used a study population with only pre-frail and frail individuals, our results are fairly in line with previous research. For example, Daniëls and colleagues[11] investigated the GFI and TFI in a 1-year follow-up study and found AUCs of 0.64 and 0.64, respectively, for mortality, 0.54 and 0.60 for hospitalization and 0.67 and 0.66 for the development of disabilities. Also Widagdo and colleagues[31] found comparable values for the FP in predicting mortality (AUC 0.57) and hospitalization (AUC 0.52) and for the FI in predicting mortality (AUC 0.60) and hospitalization (0.56). Theou and colleagues[15] reported higher values of all four frailty instruments for the prediction of mortality at 2-year follow-up (AUCs between 0.72 and 0.77). Their population was younger (50+, mean age 65.3 ± 10.5 years) and also included non-frail persons. The FP, GFI and TFI that they used were modified versions with data derived from one questionnaire. However, it is not known to what extent this could explain the differences in AUC. In our study, all instruments were least able to predict hospitalization, which is in line with other studies.[11,31] Admission to a hospital depends on more factors than only frailty, such as availability of (informal) care, distance to healthcare facilities et cetera.

Although the AUC per outcome measure was fairly comparable between instruments, differences were found in the values of sensitivity and specificity. The GFI and TFI had higher values of sensitivity, which indicates that they are more able to correctly classify frail participants as being frail. These results are not fully in line with the study of Daniels and colleagues.[11] They found values of sensitivity and specificity that were closer to each other (i.e. no high sensitivity with a low specificity or vice versa) than in our study. Also, for hospitalization, a higher specificity was reported compared to sensitivity for both the GFI and TFI, as well as a higher specificity for the TFI with regard

to the development of disabilities. Gobbens and colleagues[32] also investigated the predictive ability of the TFI for the outcome hospitalization over a 2-year period. They found higher specificity values, whereas we found higher values for sensitivity. Contradictory to the GFI and TFI in our study, the FP and FI had higher values of specificity, which indicates that they are more able to correctly classify non-frail participants as such. Similarly, Widagdo and colleagues[31] found higher levels of specificity for the FP and FI in the prediction of mortality and hospitalization. In general, the results that we presented in Table 5.3 show that using different conceptualizations of frailty by the four screening instruments and the associated outcome measures, results in a large variation regarding prevalence rates and predictive values, which has also been demonstrated by previous research on frailty.[11,33]

Considering the fact that none of the instruments in our study had both high sensitivity and specificity, nor when the cutoff values were increased or decreased, choosing an instrument for use in research or daily practice depends on the goals that one aims to achieve. For example, if one wants to include frail persons into an intervention program, a highly specific test should be used. False-positive rates will be low, however, some frail persons will be missed (false-negative). A highly sensitive test has few false-negative results and should be chosen when one does not want to miss any frail person, but such an instrument also includes more non-frail persons (false-positive). When even higher values of either sensitivity or specificity are required, the used cutoff point of a specific instrument can be changed. Another point of consideration when choosing an instrument is the time that is needed for filling out the questionnaire. Most questionnaires are relatively short, however, the FI comprises many items and might therefore seem less suitable. Nevertheless, often a FI can be (automatically) calculated using readily available information from patients records from, for example, general practices or hospitals. Then, the FI can be easily used as a screening instrument.

The strength of the present study is that it was conducted in a large, well-defined sample of community-dwelling older people. Moreover, four instruments were analyzed using the same population with three outcome measures and within the same timeframe of 2 years. It should be noted that the FP was partially modified, which might have influenced the results. Only pre-frail and frail individuals were included in this study. Our target population was a population at risk. In daily practice, frailty instruments are most often applied by healthcare professionals. People that already make use of healthcare services are more likely to be (pre-)frail[22] and therefore at risk. Hence, the inclusion of pre-frail and frail persons in our study makes our population more reflective of the persons for whom frailty measures are useful, than for a large

sample of the general population. Consequently, prevalence rates in our study might differ from the ones found in studies that included samples from a general older population. Also, sensitivity, specificity and AUC might be somewhat smaller due to the choice of a more challenging, yet we think more adequate, population. The AUC of the GFI for the outcome (I)ADL dependency was, at least to some extent, overestimated because four items of the GFI resembled items included in the GARS, the latter which was used as the (I)ADL dependency measure. The same holds for the results of the FI for the outcome (I)ADL dependency, since six out of the 53 items were similar to GARS items. Another factor that could possibly have affected the results of the study is that, except for mortality, all data are based on self-report questionnaires. We cannot rule out recall bias (e.g. with respect to hospitalization in the last 6 months) or bias due to cognitive limitations.

The four studied frailty instruments only poorly predicted mortality, hospitalization and an increase in (I)ADL dependency. As more people become frail and suffer from adverse outcomes, the need for intervention programs is increasing. In order to be able to include or exclude the right target group in these intervention programs, it is important to screen effectively. Previous studies suggested the combined use of frailty measures; for instance, a combination of the Frailty Phenotype and the Frailty Index.[34,35] Our study shows that these instruments both have higher specificity rates. It might be suggested that the combination of an instrument with a high specificity (FI or FP) and one with a high sensitivity (GFI or TFI) would result in a better identification of frail older people and a better prediction of adverse outcomes. Future research could be aimed at investigating the use of several combinations of existing frailty instruments. Another option is to combine individual items of (two or more) existing questionnaires and use this as a starting point for the creation of a new frailty instrument, with preference for items with the highest predictive ability for serious outcomes. Also a different use of instruments, such as the frailty subtypes derived from the FP that were described by Liu and colleagues[36], might increase the predictive ability.

In conclusion, the predictive ability of the FP, GFI, TFI and FI was poor for the outcomes mortality, hospitalization and increase in (I)ADL dependency in a population of pre-frail and frail community-dwelling older people. The FP and the FI showed higher values of specificity, whereas the GFI and TFI had higher values of sensitivity.

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CHAPTER 6

Can the combined use of two screening instruments improve the predictive power of dependency in (instrumental) activities of daily living, mortality and hospitalization in old age?

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Abstract

Background

Due to differences in the definition of frailty, many different screening instruments have been developed. However, the predictive validity of these instruments among community-dwelling older people remains uncertain.

Objective

To investigate whether combined (i.e. sequential or parallel) use of available frailty instruments improves the predictive power of dependency in (instrumental) activities of daily living ((I)ADL), mortality and hospitalization.

Design, setting and participants

A prospective cohort study with two-year follow-up was conducted among pre-frail and frail community-dwelling older people in the Netherlands.

Measurements

Four combinations of two highly specific frailty instruments (Frailty Phenotype, Frailty Index) and two highly sensitive instruments (Tilburg Frailty Indicator, Groningen Frailty Indicator) were investigated. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for all single instruments as well as for the four combinations, sequential and parallel.

Results

2,420 individuals participated (mean age 76.3 ± 6.6 years, 60.5% female) in our study. Sequential use increased the levels of specificity, as expected, whereas the PPV hardly increased. Parallel use increased the levels of sensitivity, although the NPV hardly increased.

Conclusions

Applying two frailty instruments sequential or parallel might not be a solution for achieving better predictions of frailty in community-dwelling older people. Our results show that the combination of different screening instruments does not improve predictive validity. However, as this is one of the first studies to investigate the combined use of screening instruments, we recommend further exploration of other combinations of instruments among other study populations.

Introduction

Life expectancy is increasing in most Western countries, resulting in larger populations of older and frail older people.[1] Although the debate concerning the conceptualization of frailty is ongoing, there is consensus that being frail increases the risk of adverse outcomes, such as mortality, hospitalization and functional decline.[2] The variety in definitions has led to the development and use of many different instruments to identify frail community-dwelling older people; however, the predictive validity of these instruments is generally limited.[3]

In a recent study, Op het Veld and colleagues investigated the ability of various indices to predict mortality, hospitalization and dependency in (instrumental) activities of daily living ((I)ADL), namely: the Frailty Phenotype (FP), the Groningen Frailty Indicator (GFI), the Tilburg Frailty Indicator (TFI) and the Frailty Index (FI).[4] All frailty instruments performed poorly in predicting mortality, hospitalization and (I)ADL dependency (area under the receiver operating characteristic curve [AUC] 0.62–0.65, 0.59–0.63 and 0.60–0.64, respectively). Several other studies have demonstrated somewhat more positive outcomes. A study of Gobbens and colleagues showed one of the highest AUCs: 0.80-0.83 for the TFI in predicting (I)ADL disability over a one- and two-year period.[5] Nevertheless the AUCs of frailty instruments are generally not very convincing.[6]

It has been suggested that the combined use of two frailty screening measures could provide complementary information and might increase the predictive power.[7,8] Instruments can be applied sequentially or in parallel. Sequential use means that the second instrument is only applied when the first instrument gives a positive result. When used in parallel, both instruments are applied at the same time. Sequential use maximizes specificity and the positive predictive value, i.e. the probability that a person with positive test results is indeed frail.[9] Starting with the test with the highest specificity is most efficient, as it requires fewer persons to undergo both screening measures. In contrast, parallel use maximizes sensitivity and the negative predictive value. By applying the two instruments at the same time, frailty will be less likely to be missed and the results are more rapidly available.

The aim of our study was to investigate whether the combined use of available frailty screening instruments, sequential and parallel, would result in a better prediction of frailty in terms of (I)ADL dependency, mortality and hospitalization compared to the use of a single frailty instrument.

Methods

We conducted a prospective cohort study with a two-year follow-up. The study was approved by the medical ethical committee of Zuyderland and Zuyd University of Applied Sciences in the Netherlands (METC Z, 12-N-129).

Participants

A detailed description of the selection of participants is provided elsewhere.[10] Briefly, 56,000 people aged 55 years and over, living in the province of Limburg, a southern region of the Netherlands, received first an extensive general health questionnaire sent out by the Dutch Community Health Services. The respondents, who were at least 65 years old and pre-frail or frail, according to Fried's frailty criteria, were then asked to participate in our study. In total, 2,420 persons gave informed consent and participated in the baseline of the present study. Gender, age, living situation and educational level were assessed at baseline.

Frailty instruments

For the combined use of the two frailty instruments, combinations of four different frailty screening instruments were tested. Instruments with high specificity values (Frailty Phenotype [FP], Frailty Index [FI]), as presented in previous research[4], were combined with instruments with high levels of sensitivity (Tilburg Frailty Indicator [TFI], Groningen Frailty Indicator [GFI]), resulting in four combinations that were investigated: FP-TFI, FP-GFI, FI-TFI and FI-GFI.

The FP, as described by Fried and colleagues, includes five criteria (weight loss, exhaustion, physical activity, walk time and handgrip strength) for the identification of physical frailty among older people.[11] Questions about weight loss and exhaustion were asked as proposed by Fried and colleagues. The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was used to determine the physical activity criterion.[12] Walk time and handgrip strength were measured with the self-report questions 'Can you reach the other side of the road when the light turns green at a zebra crossing?' and 'Do you experience difficulties in daily life because of low grip strength?' respectively, rather than using a performance based measure. A detailed description of the self-report measures for these criteria can be found elsewhere.[13] Theoretical scores range from 0 to 5 and classify individuals into non-frail (score 0), pre-frail (score 1–2) or frail (score 3–5). As mentioned previously, only pre-frail and frail persons were included in the baseline assessment of the present study.

The FI, developed by Rockwood and Mitnitski, is characterized by a non-fixed set of so-called 'deficits'.[14] We created an FI using the guidelines provided by Searle and colleagues.[15] First, we chose all available items from the questionnaire sent by the Dutch Community Health Services, that were presumably related to frailty. We selected 61 potential items that covered several topics, such as (chronic) diseases, loneliness, physical limitations and psychological distress. All items were then dichotomized into the presence '1' or absence '0' of the item. Next, items with a prevalence of less than five percent were excluded, as proposed by Drubbel and colleagues.[16] Finally, we ended up with an FI that consisted of 53 items. The final score of the FI can be calculated by dividing the number of deficits present by the total number of deficits that are measured. Theoretical scores range from 0 to 1, with higher scores indicating a higher level of frailty. A cut-off value of 0.25 was used to distinguish between frail and non-frail individuals.[17]

The TFI was developed by Gobbens and colleagues.[18] This 15-item questionnaire comprises items in the physical (8 items), psychological (4 items) and social (3 items) domains. Theoretical scores range from 0 to 15, with higher scores indicating a higher level of frailty. A person is considered frail with a score of ≥ 5.[18]

The GFI was developed by Steverink and colleagues.[19] This 15-item questionnaire comprises items in the physical (9 items), cognitive (1 item), social (3 items) and psychological (2 items) domains. Theoretical scores range from 0 to 15, with higher scores indicating a higher level of frailty. Persons with a score ≥ 4 are considered frail.[20]

Outcome measures

The outcome measure (I)ADL dependency was defined as an increase in having to depend on someone else when performing (instrumental) activities of daily living, which was determined by the Groningen Activity Restriction Scale (GARS)[21] at baseline and after two years. The GARS is composed of 18 questions about the degree to which someone is able to perform ADL and IADL activities independently. The four response options for each activity are: 1. 'Yes, I can do it fully independently without any difficulty', 2. 'Yes, I can do it fully independently but with some difficulty', 3. 'Yes, I can do it fully independently but with great difficulty', 4. 'No, I cannot do it fully independently, I can only do it with someone's help'. For each question, the results were dichotomized into being independent (options 1–3) or dependent (option 4), as described in the GARS manual.[22] Changes over time per item were then analysed. An increase in dependency was defined as more changes from independent to dependent than vice versa over the two-year observation period.

Data on mortality (deceased yes/no) at two-year follow-up were provided by Statistics Netherlands. The outcome hospitalization was dichotomized into 'Yes' when someone was admitted at least once to a hospital during the study period, or 'No' when no hospital admission had taken place.

Statistical analysis

Missing values were handled as proposed in prior research. Case mean substitution was applied when missing items were less than 25% for the TFI and GFI[23] and 50% for the GARS.[21] On the FP, one missing value was allowed when a person had a valid score of 0–2 and two missing values were allowed if the total score was ≥3.[13] For the FI, the non-missing population mean of an item was imputed for each missing item.[24]

Descriptive statistics were computed to provide information on the characteristics of the study population. Cut-off values for frailty were used as proposed by the developers of the instruments. Analyses regarding the sequential use of instruments were conducted as follows: first, participants were selected who were frail according to a specific frailty instrument; second, of these frail participants, only those who were also frail based on a sensitive frailty instrument were finally classified as frail. All others were considered non-frail. For analyses regarding the parallel use of instruments, participants were considered frail when at least one of the two instruments classified them as frail. Participants were only considered non-frail when they were non-frail according to both frailty instruments. Sensitivity, specificity, positive and negative predictive values were then calculated for each single instrument and for the combined instruments (both sequential and parallel), for all three outcome measures.

All analyses were performed using SPSS 22 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY).

Results

In total, 2,420 persons participated in the study. Their mean age was 76.3 ± 6.6 years and 60.5% were females. Additional baseline characteristics are presented in Table 6.1. At the two-year follow-up, data on changes in (I)ADL dependency were available for 1,872 individuals of whom 35.7% experienced an increase in dependency. Hospitalization was reported by 836 participants (46.4% of 1,803 valid cases) and 182 participants (7.5% of 2,420 valid cases) died during the study period.

Missing data for the outcomes (I)ADL dependency and hospitalization were partly due to mortality (n = 182) and admission to a long-term care facility (n = 53). The remaining participants were lost to follow-up for other (unknown) reasons (n = 313 for (I)ADL dependency and n = 382 for hospitalization).

Table 6.1 Baseline characteristics of the study population.

		Value
n		2420
Age	mean ± SD	76.3 ± 6.6
Female	n (%)	1463 (60.5)
Living situation		
Living alone	n (%)	906 (39.2)
Not living alone	n (%)	1404 (60.8)
Educational level*		
Low	n (%)	1579 (68.9)
High	n (%)	714 (31.1)
FP		
Score	mean ± SD	1.8 ± 1.0
Frail	%	22.2
FI		
Score	mean ± SD	0.20 ± 0.12
Frail	%	30.2
TFI		
Score	mean ± SD	6.0 ± 3.3
Frail	%	64.8
GFI		
Score	mean ± SD	4.6 ± 3.0
Frail	%	59.3
Dependent on at least 1 GARS item	n (%)	1472 (61)

FP Frailty Phenotype, *FI* Frailty Index, *TFI* Tilburg Frailty Indicator, *GFI* Groningen Frailty Indicator, *GARS* Groningen Activity Restriction Scale, *SD* Standard deviation

* Low educational level = no education, completion of primary school or pre-vocational secondary education; high educational level = higher than primary school or pre-vocational secondary education

The sequential use of two frailty instruments is presented in Figure 6.1. Graph A displays the distribution of all participants (n = 1,872) who did and did not experience an increase in (I)ADL dependency on the FI, the specific instrument. Only those classified as frail (n = 480) are included in graph B, which shows the distribution of persons who did and did not experience an increase in (I)ADL dependency on the TFI, the sensitive instrument. Similar results were found for the other sequential combinations of frailty instruments.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the single and the combined instruments for (I)ADL dependency are presented in Table 6.2. For the single instruments, the FP and FI showed higher values of specificity, whereas the TFI and GFI had higher values of sensitivity. As expected, the sequential use of two frailty instruments resulted in lower levels of sensitivity and NPV, together with higher levels of specificity and PPV. However, the degree of change for the PPV and NPV was slight. The parallel use of the two frailty instruments, in general, resulted in high levels of sensitivity and NPV, together with lower levels of specificity and PPV. The PPV and NPV again changed only slightly, as in the other combination. Comparable results were found for the outcomes hospitalization and mortality (see Supplement S6.1).

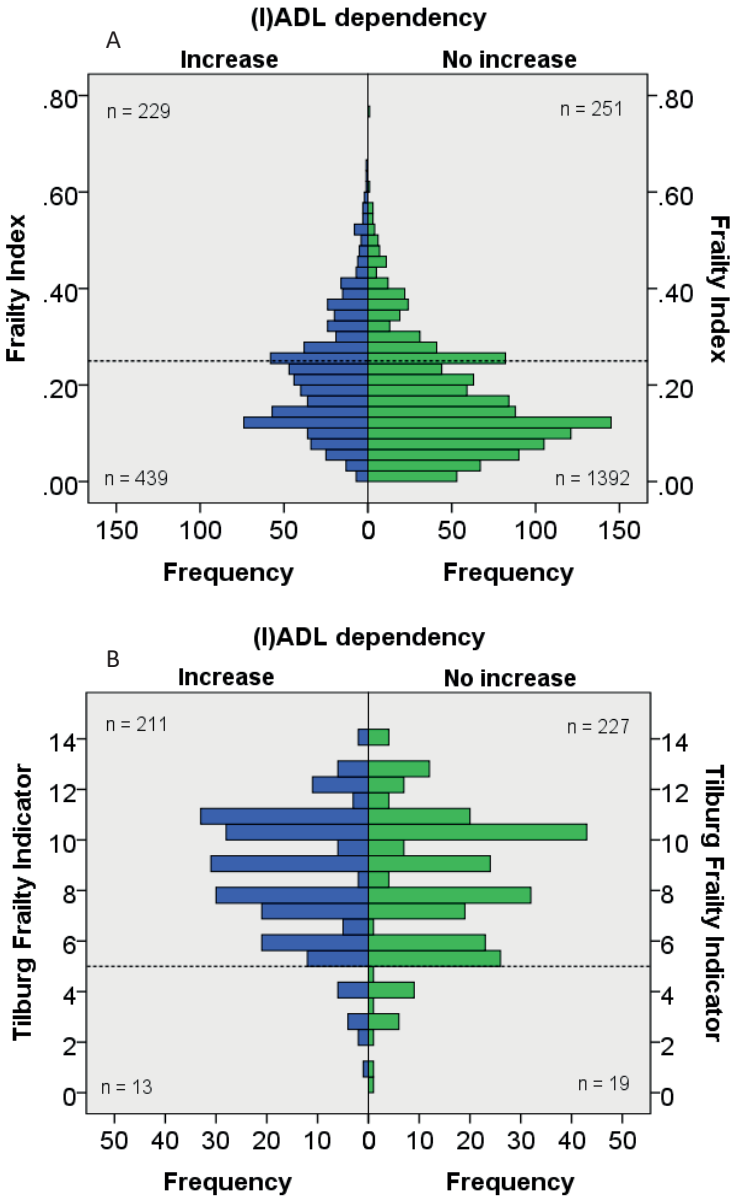

Figure 6.1 Sequential use of the Frailty Index (FI) and the Tilburg Frailty Indicator (TFI) for the outcome increase in dependency in (instrumental) activities of daily living ((I)ADL). A) Distribution of all participants who did and did not experience an increase in (I)ADL dependency on the FI. B) Distribution of individuals, who were frail on the FI, who did or did not experience an increase in (I)ADL dependency on the TFI. Cut-off values are presented as dotted lines.

Table 6.2 The number of frail persons at baseline and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the four single frailty instruments and the combined frailty instruments (sequential and parallel) for the outcome (I)ADL dependency at two-year follow-up.

	Frail according to instruments (n, baseline)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Single instrument					
FP	537	24.7	86.2	49.8	67.4
FI	730	34.3	79.2	47.7	68.5
TFI	1536	72.7	45.7	42.6	75.2
GFI	1424	66.0	51.1	42.8	73.1
Sequential					
FP & TFI	485	23.1	87.9	51.3	67.4
FP & GFI	464	21.6	88.5	51.1	67.0
FI & TFI	663	31.8	81.1	48.2	68.3
FI & GFI	651	30.6	81.4	47.8	67.9
Parallel					
FP & TFI	1567	73.8	44.4	42.3	75.4
FP & GFI	1490	69.0	49.0	42.8	74.1
FI & TFI	1580	74.7	44.1	42.5	75.9
FI & GFI	1495	69.6	49.0	43.0	74.5

FP Frailty Phenotype, *FI* Frailty Index, *TFI* Tilburg Frailty Indicator, *GFI* Groningen Frailty Indicator

Discussion

The aim of our study was to investigate whether the combined use of frailty instruments, either sequential or parallel, would result in a better prediction of (I)ADL dependency, mortality and hospitalization, compared to the use of a single frailty instrument. In our study, we were unable to demonstrate a clear beneficial effect of using either combination of frailty instruments. As expected, specificity levels increased when applying the instruments sequentially; however, the PPV hardly increased. The parallel use of two instruments increased sensitivity; however, the NPV hardly increased.

To the best of our knowledge, this is the first study to investigate the possible value of the combined application of two frequently used frailty screening instruments. In some other studies, a frailty instrument has been combined with another measurement. For instance, Kenig and colleagues examined frailty (defined by deficits in two or more

domains of the comprehensive geriatric assessment) and the Surgical Apgar Score.[25] Compared to the individual instruments, the combination did not increase the PPV for 30-day morbidity and only slightly increased the NPV for 30-day mortality among older patients undergoing abdominal cancer surgery. Also, frailty screening can be followed by a more thorough assessment. For example, the 'Prevention of Care' programme comprises screening with the GFI.[26] When someone scores 5 or higher, a multidimensional assessment is conducted by a practice nurse at the patient's home to gain insight into problems in performing daily activities and risk factors for disability. However, the screening instruments used in such approaches often include many false-positive cases, which render them inefficient, and the second steps are often very time consuming. In these cases, the sequential use of two screening instruments might be relevant.

A major strength of this study is the simultaneous assessment of four available frailty instruments in a large cohort of community-dwelling older people, which is the best strategy for comparing the performance of instruments. In particular, PPV and NPV, which are affected by the prevalence of the outcomes, are difficult to compare when the results are obtained from different studies. By applying instruments sequentially, a higher PPV can be achieved.[9] At the same time, it also causes more false-negative cases, indicating that frail persons are missed in screening. One might utilize this strategy, for example, when costly or time-consuming clinical management follows in terms of advanced diagnostics or expensive treatment. On the other hand, while parallel testing increases the NPV, it causes more false-positive cases. This method would be best applied if one desired to include as many frail persons as possible, for research purposes or in daily practice. However, follow-up and interventions would then often be applied to those not needing extensive monitoring.

Our study population consisted of pre-frail and frail patients and did not include non-frail persons. In daily practice, frailty instruments are most often applied by healthcare professionals in persons who are at risk of becoming frail. The inclusion of pre-frail and frail persons makes our population more reflective of the persons for whom frailty measures are useful rather than persons sampled from the general population. Nevertheless, for the selection of the cohort the FP was used, which focusses on the physical aspects of frailty. Persons that were frail in other domains (e.g. psychological or social) might therefore have been excluded, which may have influenced the results.

All frailty instruments were assessed as proposed by the developers, except for the FP, for which we used self-report questions instead of performance-based measures,

potentially having a slight influence on the results.[27] In our study, the FP and FI were handled as specific instruments and the TFI and GFI as sensitive instruments.[4] Some studies, however, show other values of sensitivity and/or specificity.[5,28] The combined use of instruments should therefore be studied further with different instruments (with high levels of sensitivity and/or specificity), in other study populations and/or with different (handling of) outcome measures. One of the instruments that might be interesting to investigate is the Vulnerable Elders Survey (VES)-13.[29] In a recent study of Bongue and colleagues this instrument demonstrated very high levels of sensitivity for various outcome measures.[30] Moreover, this instrument has often been cited over the past years and is thus of interest to many researchers.[31] Regarding the investigation of another study population, the oldest old (80+ years) could be considered. Frailty is more present among people in this age group and older people are more at risk for adverse health outcomes compared to younger ones. An example of a different handling of an outcome measure is the number of hospital admissions. From the participants who reported to be admitted to a hospital in our study, 355 (42%) were admitted once, 196 (23%) twice, and 227 (27%) three times or more (missing values: n = 58 (7%)). Clearly there is a large variation in the number of admissions. Hospital admissions can be caused by factors unrelated to frailty. It is unknown if multiple admissions are more often related to frailty compared to one admission and if combined use of frailty instruments can predict multiple admissions.

Based on our results, we conclude that the combined application of two frailty instruments might not be a solution to achieve a better identification of frailty in community-dwelling older people. However, as this is one of the first studies to investigate the combined use of screening instruments, we recommend further exploration of other combinations of instruments in various study populations.

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Supplement S6.1

The number of frail persons at baseline and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the four single frailty instruments and the combined frailty instruments (sequential and parallel) for the outcomes mortality and hospitalization at two-year follow-up.

Mortality

	Frail according to instruments (n, baseline)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Single instrument					
FP	537	44.5	79.6	15.1	94.6
FI	730	49.5	71.4	12.3	94.6
TFI	1536	80.6	36.5	9.4	95.8
GFI	1424	76.2	42.1	9.7	95.6
Sequential					
FP &TFI	485	42.8	81.6	15.9	94.6
FP & GFI	464	39.8	82.4	15.5	94.4
FI & TFI	663	46.7	73.9	12.8	94.4
FI & GFI	651	46.2	74.6	12.9	94.4
Parallel					
FP &TFI	1567	81.7	35.2	9.4	95.9
FP & GFI	1490	80.7	39.5	9.8	96.2
FI & TFI	1580	83.3	34.7	9.5	96.2
FI & GFI	1495	79.6	39.1	9.6	95.9

FP Frailty Phenotype, *FI* Frailty Index, *TFI* Tilburg Frailty Indicator, *GFI* Groningen Frailty Indicator

Hospitalization

	Frail according to instruments (n, baseline)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Single instrument					
FP	537	25.6	86.2	61.7	57.3
FI	730	35.9	79.6	60.4	59.0
TFI	1536	70.5	44.1	51.8	63.7
GFI	1424	63.9	50.3	52.6	61.7
Sequential					
FP &TFI	485	23.5	87.6	61.9	57.1
FP & GFI	464	23.1	88.6	63.7	57.1
FI & TFI	663	32.9	81.2	60.1	58.5
FI & GFI	651	32.7	82.2	61.3	58.5
Parallel					
FP &TFI	1567	72.0	43.1	51.9	64.3
FP & GFI	1490	66.3	48.1	52.4	62.3
FI & TFI	1580	73.0	42.8	52.1	65.0
FI & GFI	1495	67.1	48.0	52.7	62.8

FP Frailty Phenotype, *FI* Frailty Index, *TFI* Tilburg Frailty Indicator, *GFI* Groningen Frailty Indicator

CHAPTER 7

General Discussion

Introduction

This dissertation is about the detection of frailty in older people and the prediction of its adverse outcomes. Frailty is a complex concept and consensus on its definition is lacking. Nevertheless, various studies confirm that frail older people are at higher risk for adverse health outcomes. Therefore, in this dissertation, we aimed: (1) to expand our knowledge about profiles of persons with different levels of frailty in terms of functioning in multiple health domains; (2) to examine which resources influence the pathway from frailty to several adverse outcomes; and (3) to increase our knowledge of the psychometric properties of frequently used frailty instruments. Hence, the following research questions were addressed:

Profiles of frailty

1. What are the profiles of persons at different levels of frailty in terms of levels of functioning in multiple domains?

Pathways of frailty

2. Which resources influence the pathway from frailty to adverse outcomes?

Psychometric properties of frailty instruments

3. Can performance-based frailty criteria be substituted by self-report questions?
4. How well can frequently used frailty instruments predict adverse outcomes?
5. Can the combined use of frailty instruments improve their predictive power?

This chapter describes the main findings of the dissertation, followed by some methodological considerations. Then, lesson learned are considered and the implications for research, practice and education given.

Main findings

Study populations

For the first research question, regarding profiles of frailty, cross-sectional data from 8,684 community-dwelling older people (65+) in the Netherlands was used. Participants were divided into three levels of frailty (non-frail, pre-frail, frail) based on their scores on the Frailty Phenotype (FP).[1] The FP was developed by Fried and colleagues, comprises five physical criteria (weight loss, exhaustion, low physical activity, slowness, weakness), and is widely used in daily practice and for research purposes.[2] Of these

8,684 persons, only those considered to be at higher risk for adverse health outcomes (i.e. pre-frail and frail persons) were invited to participate in a longitudinal study with 2-year follow-up. In total, prospectively collected data from 2,420 people was available for research questions 2, 4, and 5 (pathways of frailty and predictive ability of frailty instruments). A group of 135 people, across all three levels of frailty, was separately recruited to address research question 3 (substitution of performance-based frailty criteria by self-report questions).

Profiles of frailty

Because of the various conceptualizations of frailty, many instruments have been developed to screen for its incidence in older people. Many researchers use the FP, which comprises criteria in the physical domain only. However, it is unclear whether this limited scope is sufficient for identifying different profiles of functioning in non-frail, pre-frail, and frail older people. An increasing number of researchers support a broader perspective of frailty, preferring to use a multidimensional frailty instrument that includes criteria from, for instance, social or psychological domains as well. Chapter 2 describes the profiles of functioning in multiple domains among older people (65+ years) with different levels of frailty. In total, 8,684 community-dwelling people were divided into the three levels of frailty according to the FP: non-frail, pre-frail, or frail. These levels were related to scores in social (social network type, informal care use, loneliness), psychological (psychological distress, mastery, self-management), and physical (chronic diseases, instrumental activities of daily living (IADL) disability) domains of functioning. The differences in scores for the social, psychological, and physical domains were statistically significant between the three frailty levels. Non-frail participants had consistently more favorable scores compared with those of frail participants, and pre-frail participants had intermediate scores. For example, scores for the use of informal care were as follows: non-frail 3.9%, pre-frail 23.8%, frail 60.6%; and for three or more chronic diseases: non-frail 8.8%, pre-frail 31.4%, frail 53.9%.

Pathways of frailty

Although higher levels of frailty generally result in greater risk for adverse health outcomes, not all frail persons suffer from these adverse outcomes. This suggests that more factors than frailty alone play a role in their development. In Chapter 3 we examined the potentially moderating effect of six resources on the impact of frailty. Level of education, income, availability of informal care, living situation, mastery, and self-management abilities were investigated in terms of their ability to (beneficially)

influence the pathway from frailty to mortality, hospitalization, and disability. The results showed that frail participants had a higher risk for mortality, hospitalization, and disability, compared with those who were pre-frail. In total, 18 potentially moderating effects were investigated (six resources x three outcomes). For the outcome disability only, two significant moderating effects (income and living situation) were found. However, the directions of these effects contradicted our expectations. Among those with a high income or not living alone, the disability scores of frail people worsened more than did those of pre-frail people. Among those with a low income or living alone, changes in disability scores were fairly similar between frail and pre-frail people. Overall, we concluded that for the resources studied no clear pattern of moderating effects on the adverse outcomes associated with frailty was found among pre-frail and frail participants.

Psychometric properties of frailty instruments

Three studies were conducted on the psychometric properties of frailty instruments. The first concerned the five physical criteria of the FP, used by many researchers worldwide. The use of the FP can be problematic because the criteria of slowness and weakness are meant to be measured using the performance-based tests of walk time and handgrip strength, respectively; for obvious reasons, administering such tests may be not feasible in large-scale studies. In Chapter 4 we aimed to identify self-report questions that could be used as a substitute for these performance-based measures. In total, 135 non-frail, pre-frail, and frail older people completed the five original criteria of the FP, including the two performance-based measures. Additionally, they answered several questions relating to walk time and handgrip strength. We were able to produce two brief sets of questions (four questions for walk time, two for handgrip strength) that can be used as substitutes for the performance-based tests of walk time and handgrip strength of the FP when performance-based tests are not feasible.

In Chapter 5 we examined the predictive ability of four frequently used frailty instruments. Although the predictive ability of these instruments has been tested before, it has not been done for all instruments simultaneously, in one large sample, with several outcomes and a 2-year follow-up period. This makes it hard to compare the results of all those studies. With the 2,420 persons in our cohort we tested how well the FP, Groningen Frailty Indicator (GFI)[3], Tilburg Frailty Indicator (TFI),[4] and Frailty Index (FI)[5] were able to predict mortality, hospitalization, and increasing dependency in (I)ADL. In all four cases, the instruments were barely able to predict these adverse outcomes: the area under the receiver operating characteristic curves (AUCs) was

around 0.6 for all instruments and all outcomes, indicating poor predictive ability. The FP and FI showed higher values of specificity, whereas sensitivity was higher for the GFI and TFI. Because of these differences in sensitivity and specificity values, we explored whether combining instruments could increase their predictive ability. In Chapter 6 we combined higher specificity instruments (FP, FI) with higher sensitive ones (GFI, TFI) and tested whether their predictive values increased. The same study population and same outcome measures as described above were used. The positive and negative predictive values barely changed when combinations of specific and sensitive instruments were tested. On the basis of these results, we concluded that combining two existing frailty instruments does not appear to be a solution to achieving better predictions of frailty in older people.

Methodological considerations

In this section, several methodological considerations are discussed regarding the correct use of frailty instruments, the selection of the study population, response rates and missing values, and follow-up.

Correct use of frailty instruments

Most chapters in this dissertation report on prospectively collected data from a large cohort with a follow-up period of two years. In that cohort, the primary goal was to investigate several frailty instruments and their ability to predict adverse outcomes related to frailty. Therefore, the instruments used were all administered in accordance with the directions of their developers, except for the performance-based measures of the FP. Because of the size of our study population (>3,000 at the start of the study period), the geographical spread of participants (max ≈ 100 km apart), the frequency of measurement (every six months) and the costs, it was not feasible to include performance-based tests in our cohort. Instead, we used self-report questions as a substitute for these tests. In a subsequent study, described in Chapter 4, we present an optimal set of questions for this substitution. Unfortunately, the questions that we used in our cohort to determine scores on the FP, appeared not to be the best ones. Thus, the assignment of participants to the different levels of frailty on this basis may have led to some misclassifications. As a consequence, the actual results of the studies in this dissertation that used the cohort might be slightly better than the scores observed indicate. However, it is not known to what extent the results were affected by this misclassification. Despite the fact that these two criteria were not measured as

originally intended, most items of the FP and the other questionnaires were, in the same large prospective cohort study, which is a strong point of our studies. In other studies, researchers have used retrospective data from studies that were not primarily focused on frailty or specific frailty instruments.[6-8] Hence, the frailty instruments included in those studies are often not measured using the specific items of the frailty instruments originally proposed by their developers, which can influence the scores and hence the interpretation of the results.[9]

Selection of the study population

An important point to consider is that in this cohort only pre-frail and frail persons were included. We purposely selected this sample because we wanted to focus on a population at risk. In daily practice, frailty instruments are most commonly used by healthcare professionals when screening older people whom they believe are at risk. People who make use of healthcare services are more likely to be (pre-) frail.[10] By including only pre-frail and frail persons, our study population specifically reflects people for whom frailty measures are more useful rather than the general population. Obviously, the prevalence of frailty here may therefore differ from that for the general population. Our choice of sample also has consequences for comparing our results on the predictive ability of instruments with studies using a general population sample. The frailty instrument that is best at distinguishing between non-frail and frail persons is not necessarily the best for distinguishing between pre-frail and frail persons. For the latter, the instruments need to contain items that will be answered differently by people with high and low degrees of frailty, and thus should be sensitive to differences in this particular region of the frailty scale. Therefore, comparison between our results and those of studies on other populations should be made with caution.

Response rate and missing values

Of the 8,684 persons who participated in our first cross-sectional study, 3,162 pre-frail or frail persons were invited to participate in our longitudinal studies. The response rate was 77% (n=2,420). Of these 2,420 persons, outcome data was missing at the 2-year follow-up as follows: n=537 for (I)ADL disability/dependency and n=617 for hospitalization. Missing values can be partially explained by persons who were admitted to a nursing home (i.e. no longer community-dwelling, n=53) or died (n=182) during the study period. Every consecutive questionnaire during the 2-year study period was only sent to persons who had not been admitted to a nursing home, were still alive, and had not explicitly stated that they no longer wanted to participate in our

study. Of those who received a consecutive questionnaire, at every time point the response rate was about 90%; this rate can be considered high, because response rates in studies involving older people generally vary between 60% and 90%.[11] Compared with valid cases, people with missing values were older, more often frail, less educated and more often living alone, and had a lower sense of mastery, fewer self-management abilities, and more (I)ADL disability at the start of the study. It is possible that these people were severely frail and therefore easier to classify as such by the four frailty instruments. If so, our study underestimated the performance of the frailty instruments. However, this cannot be stated with certainty.[12]

Follow-up

Measurements in our longitudinal study were conducted every six months for a total period of two years. An older person's health can change significantly in this timeframe. Previous studies among frail older people have demonstrated that adverse outcomes relating to frailty can occur within a follow-up period of one year.[7,13] In our sample of pre-frail and frail persons, the 2-year follow-up period should therefore be long enough for adverse outcomes to manifest. However, the six-monthly measurements might not be frequent enough to capture the outcome of hospitalization. Participants were asked whether they had been admitted to a hospital in the past six months. Although hospital admission can be a major event, this is not always the case; where people have to stay one night in a hospital for a minor medical problem, they may have trouble recalling when this occurred or even forget that it took place. However, in such a large cohort study more frequent measurements were not feasible.

For the moderating effects of resources studied in Chapter 3, and other potential resources, it is not known what an optimal follow-up period would be. The presence of the resources was determined at baseline and the adverse outcomes at the 2-year time-point. It is not known whether all the resources remained unchanged during the whole two years.

Lessons learned

The studies conducted resulted in a number of lessons learned. Three topics will be discussed in this section: the frailty concept, future frailty measures, and reasons for (not) screening.

Frailty concept

When screening for frailty, most researchers and healthcare professionals agree that the aim is to identify people at risk for adverse outcomes, such as mortality, hospitalization, and (I)ADL disability.[14] However, there is still no consensus on the conceptualization and definition of frailty.[15] As mentioned before, there are several views on whether to include one (physical) or multiple (e.g. social or psychological) domains. This uncertainty makes it very hard to determine which questions older people should be asked during screening. In Chapter 2 we divided people into three groups (non-frail, pre-frail, frail) based on their FP physical frailty measurement. Then, we compared the scores of these groups on functioning in the social, psychological, and physical domains. Physically frail persons had consistently worse scores in all domains compared with non-frail and pre-frail persons, non-frail persons had the best scores, and the scores of the pre-frail group were intermediate. Because this was a cross-sectional study, causal relations between domains could not be determined. However, there appeared to be an accumulation of problems across all domains. To date, there are broadly two approaches to frailty that are frequently used: a solely physical approach, and a multidimensional approach. The results of Chapter 2 can therefore be interpreted in two ways: 1) It might be sufficient to ask questions in the physical domain to determine who is frail—although problems in other domains may co-exist, just identifying physical frailty is less burdensome for both the older person and healthcare professional; 2) Because frailty can be present in multiple domains, more domains than solely the physical one (e.g. social and/or psychological domains) should be covered by the frailty instrument.

It is not known which approach and associated frailty instrument is best at identifying people at risk. Therefore, we tested this in Chapter 5. The results demonstrated that the predictive ability of the four different frailty instruments reflecting different underlying concepts and domains of frailty, was poor. Other studies have reported slightly better performance.[6,16] For example, Theou and colleagues found AUCs between 0.70 and 0.77 for 2-year mortality for eight different frailty instruments (including the FP, GFI, TFI, and FI), although several instruments were not administered as originally intended by their developers and were therefore created from one available dataset.[6] Another example is the study by Gobbens and colleagues, in which the TFI showed an AUC of 0.80-0.83 for predicting 1- and 2-year disability.[16] However, longitudinal studies comparing multiple instruments are scarce.

On the basis of our results, we cannot recommend one instrument or underlying concept over another for use in research or daily practice. Given the facts that many

frailty instruments have been developed in recent decades[17] and that hardly any of them show good predictive ability,[18,19] it is questionable whether screening for frailty with the instruments currently available is useful for identifying people at greater risk for adverse outcomes. An alternative approach might be to take a different look at frailty and consider it as "a balance," as described previously by, for example, Rockwood and colleagues in 1994.[20] They proposed a dynamic model of frailty in which both deficits (illness, disability, dependence on others, burden on caregiver) and assets (health, attitudes toward health and health practices, social, spiritual, financial, and environmental resources, and having a caregiver) determine whether a person can maintain independence in the community. They argued that if considerably more assets than deficits are present, a person may be doing well; whereas, if the deficits outweigh the assets, a person may be frail and institutionalized. If, however, the assets and deficits are in balance, a person could be frail but still be living in the community, although a small change could tip the balance to the negative side. This latter group is the one that healthcare professionals are interested in when they screen for frailty. Nevertheless, up until now this balance model has not been transformed into an instrument including both deficits and assets. The Detection, Support and Care for frail older people: Prevention and Empowerment (D-SCOPE) consortium has recently adopted the idea of including balancing factors in a frailty instrument. Researchers from this consortium are developing a new frailty balance instrument,[21] and the results of their studies could contribute to a better understanding and measurement of frailty.

Future frailty instruments

Choice of outcomes

As discussed above, the frailty instruments examined in this dissertation had poor predictive ability. The outcomes of interest were mortality, hospitalization, and (I)ADL dependency. We chose these outcomes because they are often investigated by researchers.[14,22] Nevertheless, they are all more or less related to physical functioning and signify a rather negative approach. Older people themselves prefer a more positive, strengths-based, approach.[23] Therefore, another option could be to look at more 'perceived' or 'qualitative' outcomes, such as quality of life, wellbeing, or the ability to achieve certain personal goals. Consequently, screening instruments and intervention programs might therefore be adjusted in order to fit in with this different approach.

Resources

The goal when screening for frailty in older people is to initiate an intervention for those who are frail aimed at preventing the occurrence of adverse outcomes. In order to determine what components the intervention should comprise in addition to 'treatment' for frailty, it is important to know what resources can influence the pathway from frailty to adverse outcomes. In their disablement process, Verbrugge and Jette in 1994 had already postulated a pathway linking pathology through impairments and functional limitations to disability.[24] They argued that this pathway could be moderated by intra- and extra-individual factors that could be thought of as resources. The association between frailty and adverse outcomes might similarly be moderated by resources. However, very little is known about this as yet. In Chapter 3 we investigated six resources and their potentially moderating effect on the occurrence of three adverse outcomes.[25] We found no clear moderating effect, which is in line with other studies investigating potentially moderating factors.[26-28]

Several intervention programs for frail older people have been developed and studied in past years. A recent literature review by Van der Elst and colleagues concluded that the effects of such programs are unclear and inconsistent.[29] The results of a meta-analysis failed to provide sufficient scientific evidence that interventions can be protective against adverse outcomes. In addition, Smit and colleagues found nine proactive primary care programs in the Netherlands to demonstrate no clinically relevant effects on daily functioning.[30] This could be explained, at least partially, by the fact that the components of the intervention programs had no a moderating effect on frailty. Nevertheless, many potentially moderating resources have not yet been investigated in relation to different outcomes. Furthermore, combinations of resources should also be investigated, as they may potentially lead to more effective intervention programs.

One size fits all?

One feature that almost all frailty instruments have in common is that they are designed to divide people up into categories: frail or non-frail (and sometimes pre-frail).[1,4,31] Since frailty is such a complex concept, this classification may be too simplistic. Thus, a more refined classification should be considered. Investigating subtypes or profiles of frailty could be a first step towards more tailored care. The principle of forming subtypes has been of increasing interest to researchers in the past decade. People with the same disease, such as rheumatoid arthritis or pre-diabetes, are divided into several clusters in which all members have comparable characteristics.[32,33] These so-called subtypes might also be found in older people who are (pre-) frail. Liu and colleagues proposed three distinct subtypes of physical frailty besides non-frail

people.[34] They used the criteria from the physical FP to distinguish between non-mobility-type frailty (including people with mainly weight loss and exhaustion), mobility-type frailty (including people with mainly slowness and weakness) and a type with low physical activity. These subtypes presumably have different underlying mechanisms and the pathways to adverse outcomes may vary. Extending the idea of physical frailty subtypes, Looman and colleagues used a multidimensional approach and included self-reported health, social functioning, cognitive functioning, morbidity status, mental health, and functional limitations in their analysis.[35] They distinguished six profiles of frailty: 'relatively healthy', 'mild physically frail', 'psychologically frail', 'severe physically frail', 'medically frail', and 'multi-frail'. People with the first profile had limited problems across all domains. The next three profiles comprised people with problems in either the physical or psychological domain. The last two profiles comprised people with problems in the physical, psychological and social domain, with cognitive problems additionally in the multi-frail profile. Further investigation of these subtypes could lead to more personalized care being applied and a possible decreased occurrence of adverse outcomes.

Community approach

Nowadays, screening older people for frailty is mostly carried out by healthcare professionals such as general practitioners (GP) or practice nurses. GPs can, for example, screen everyone in their clinic who reaches a certain age (e.g. 75 years) or ask people to fill out a questionnaire when they visit for a consultation. However, not all older people visit their GP regularly and some may not comply with a request to fill in a frailty questionnaire. This makes frailty screening in daily practice difficult.

Using the help of the community could be a solution. For example, a mailman or -woman walking the same route every day might get to know the (older) people and their routines in their area. Similarly, a cashier at a local grocery store might see older people buying groceries on the same days or times of day. Both might watch and talk to older people and notice whether the latter are showing signs of frailty; or, they might notice deviations in older people's routines that could be an indication of frailty. This principle has already been applied in some countries to identify lonely people. For instance, in the city of Rotterdam in the Netherlands the mailmen and -women, amongst others, participate in a project called "report isolation."[36] Under this project, they are able to report worrisome situations on a website, in response to which a (healthcare) professional can take action where needed. Other similar examples include the use of mailmen and -women in the UK and Belgium,[37,38] who visit lonely people and ask questions in order to assess their needs. Again, the results are sent to a healthcare professional who can take action if needed.

The same community strategy could be used to assess frailty in older people. However, while this may appear a promising route, it would be sensible to investigate it further first because mailmen/-women and cashiers are not trained healthcare professionals and it may be difficult for them to spot the 'red flags' that signal frailty. Furthermore, ethical issues could be at stake here and should therefore be examined too. Additionally, as with initiatives tackling loneliness, there should be consequences when a person at risk is identified; without subsequent interventions being available, such an approach would be of limited use.

Is screening useful?

Many frailty instruments were developed in practice and appear to have no strong theoretical foundation. Such developments were not thoroughly thought through, or at least were not reported as such, with regard to the selection of items or the suitability of frailty for screening. As far back as 1968, Wilson and Jungner published a report commissioned by the World Health Organization in which 10 screening criteria were established to guide the selection of diseases suitable for screening.[39] The value of these criteria remains undisputed to this day.[40] Although some might argue that they were developed for screening for diseases, most could also be applied to the screening for frailty. However, when we do so, several problems emerge. One of the criteria is that "*The natural history of the condition, including development from latent to declared disease, should be adequately understood."* It is unclear what exactly frailty is and how it develops over time. And as mentioned before, there is no consensus on its conceptualization and definition. Another criterion is that "*There should be a suitable test or examination."* Because of its many definitions, many different instruments for measuring frailty are available.[17] It is not known which instrument is the best and in general their psychometric properties are either not known or not very good.[41,42] A third criterion is that "*There should be an accepted treatment for patients with recognized disease."* As described before, a large number of intervention programs have been tested on (frail) older people, with most showing no clear beneficial effects.

Given the aforementioned points, it is highly debatable whether we should continue to screen for frailty in the way we do now or even whether we should screen for frailty at all. Clearly, decades of research on frailty have not yet provided researchers and healthcare professionals with a clear understanding of the concept of frailty or adequate tools to identify people at risk. Therefore, we should probably not proceed in the way we have been to date. When healthcare professionals want to gain insight into a person's frailty level, sum scores and cut-off points should not be used. Instead, it may be that the available frailty instruments could be used at item level in order to better understand areas of concern for a specific person.

Implications

This section summarizes the implications of the findings of this dissertation for future research, practice, and education.

Implications for research

Researchers in the field of frailty should be aware that:

- there appears to be a relationship between functioning in the social, psychological, and physical domains;
- the six resources investigated here were unable to moderate the pathway from frailty to adverse outcomes;
- despite their different underlying concepts of frailty, the predictive ability of the frequently used instruments Frailty Phenotype, Groningen Frailty Indicator, Tilburg Frailty Indicator, and Frailty Index is comparably poor;
- combining a highly specific with a highly sensitive frailty instrument does not increase predictive ability;
- it is important to use a frailty instrument exactly as recommended by its developers.

For researchers in the field of frailty it is recommended that they:

- look at new approaches and investigate the possibility of frailty as a balance between deficits and resources, because this might provide a better starting point for identifying people at risk for adverse outcomes;
- investigate the use and value of more positive outcome measures;
- explore other (combinations of) resources that might moderate the pathway from frailty to adverse outcomes;
- study different subtypes of frailty rather than using a 'one size fits all' concept;
- investigate a community approach as a potentially better method of identifying people at risk.

Implications for practice

For healthcare professionals working with frail older people, it is recommended that they:

- be aware that the predictive ability of frailty instruments is limited and that misclassification frequently occurs. They should therefore be cautious when using any of the frailty instruments investigated here for screening purposes;
- acknowledge that frailty is a complex concept that we might never fully understand;
- be aware that on the whole, intervention programs for frail older people have yet to show any clear beneficial effects;
- consider using the available frailty instruments at item level in order to identify areas of concern, rather than using sum scores and cut-off values.

Implications for education

For developers of educational programs for (future) healthcare professionals it is recommended that they:

- provide students with information displaying the complexity of frailty and its measures;
- make students aware that the predictive ability of frailty instruments is limited and that misclassifications occur frequently;
- make sure that students look critically at available frailty instruments and the way they should be applied;
- inform students about the lack of clear evidence for the effectiveness of intervention programs for frail older people.

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Summary

SUMMARY

Chapter 1 provided an introduction to the aging society and the complex concept of frailty. People worldwide are living longer and the pace of population aging is increasing. This is leading in turn to increasing numbers of frail older people. Although the term 'frailty' is frequently used, there is no consensus yet on its nature and concept. Although researchers and healthcare professionals use different approaches and associated instruments, numerous studies confirm that frail older people are at greater risk for adverse outcomes, such as mortality, hospitalization and (worsening) disability. Therefore, it is important to focus on the correct identification of frail older people. Treatment and support should be targeted at those in need of care. If people are incorrectly identified as frail, the effect of treatment is likely to be minimal and healthcare costs will rise unnecessarily. More importantly, those in need of treatment will not always be referred to the appropriate care. Therefore, in this dissertation we aimed: (1) to expand our knowledge about profiles of older persons with different levels of frailty in terms of functioning in multiple health domains; (2) to examine which resources influence the pathway from frailty to several adverse outcomes; and (3) to increase our knowledge of the psychometric properties of frequently used frailty instruments. This chapter ends with a description of the inclusion of participants in the studies in this dissertation, and a dissertation outline.

Researchers most often use Fried and colleagues' description of the frailty phenotype (FP). The authors describe five physical criteria to identify frail older people. Other researchers prefer a combination of measurements across the social, psychological and/or physical domains. The first aim of this dissertation was addressed in **Chapter 2**. Levels of social, psychological, and physical functioning were measured in accordance with the frailty stages of the FP using a large cohort of Dutch community-dwelling older people. Cross-sectional data from 8,684 community-dwelling older people (65+) in the Netherlands was used. Based on Fried's five frailty criteria (weight loss, exhaustion, low physical activity, slowness, weakness), participants were divided into three stages: non-frail (score 0), pre-frail (score 1-2) and frail (score 3-5). These stages related to scores on the social (social network type, informal care use, loneliness), psychological (psychological distress, mastery, self-management), and physical (chronic diseases, GARS IADL-disability, OECD disability) domains. Most participants were non-frail (63.2%), 28.1% were pre-frail and 8.7% frail. Frail people tended to be older, were more likely to be female, were more often unmarried or living alone, and had a lower level of education compared with their pre-frail and non-frail counterparts. When scores for the social, psychological, and physical domains were compared, the best scores

(i.e. indicating higher functioning) were apparent for the non-frail group, while the least favorable scores (i.e. indicating lower functioning) were found for the frail group. People in the pre-frail group had intermediate scores. For example, the scores for use of informal care were as follows: non-frail 3.9%, pre-frail 23.8%, frail 60.6%; and mean scores for GARS IADL-disability were: non-frail 9.2, pre-frail 13.0, frail 19.7. This suggests that the Fried frailty criteria could be an efficient way for healthcare professionals to identify frail older people, and indicate possible problems in other domains.

Higher levels of frailty result in higher risks for adverse frailty outcomes such as hospitalization and mortality. There are, however, indications that more factors than frailty alone play a role in the development of these outcomes. The presence of resources, e.g. sufficient income and good self-management abilities, could slow down the pathway from level of frailty to adverse outcomes (e.g. mortality). Therefore, to address the second aim of the dissertation, we examined in **Chapter 3** whether six resources (i.e. educational level, income, availability of informal care, living situation, sense of mastery, and self-management abilities) were able to moderate the impact of level of frailty on the adverse outcomes of mortality, hospitalization, and the development of disability over a two-year period. Longitudinal data from a sample of 2,420 community-dwelling pre-frail and frail older people was collected. Analyses revealed that frail older participants did indeed show a higher risk for mortality, hospitalization, and disability compared with their pre-frail counterparts. To study the moderating effects of the selected resources, their interaction effects with levels of frailty on outcomes were studied. In total, 18 potentially moderating effects were investigated (six resources x three outcomes). Only for the outcome disability were two statistically significant moderating effects present (income and living situation); however, these effects were in the opposite direction to what we expected. Overall, the resources examined here showed hardly any moderating effects. More research, in which other resources or outcome measures are considered, is needed to increase our understanding of the role of moderating factors.

The third aim, regarding the psychometric properties of frequently used frailty instruments, was addressed in **Chapters 4, 5,** and **6**. The five criteria of Fried's frailty phenotype are the ones most often used by researchers to identify frail older people. However, the FP includes two performance-based tests that are often not feasible to use in large-scale research or daily practice. **Chapter 4** describes what self-report questions should be used as a substitute for Fried's performance-based tests of handgrip strength and walk time. A cross-sectional study of 135 community-dwelling

non-frail, pre-frail, and frail older people was conducted. Participants completed the original instrument (including the performance-based tests) as well as 10 questions about handgrip strength and 11 questions on walk time. Regression analyses revealed four questions for walk time (e.g. “Do you walk more slowly than you'd like?”) and two for handgrip strength (e.g. “Do you feel like you have less hand strength than other people your age?”) as most optimal for substitution. These two sets of questions might be used in settings where the performance-based tests of walk time and handgrip strength are unfeasible, such as in daily practice or large-scale research.

Chapter 5 assessed the predictive ability of four frequently used frailty instruments, related to different approaches to frailty: the physical Frailty Phenotype (FP), the multidimensional Groningen Frailty Indicator (GFI) and Tilburg Frailty Indicator (TFI) with fixed domains and questions, and the multidimensional Frailty Index (FI) with no pre-defined domains and questions. The predictive ability of these instruments has been investigated before, however not prospectively, and using the same large sample with the same multiple outcomes in the same timeframe. This prospective cohort study with two-year follow-up included 2,420 community-dwelling older people who were pre-frail and frail (according to the FP). Mortality, hospitalization, and increasing dependency in (instrumental) activities of daily living ((I)ADL) were used as outcome measures. Calculations of the area under the receiver operating characteristic curves (AUCs) showed that the predictive ability of all four frailty instruments was poor for mortality (AUCs 0.62-0.65), hospitalization (AUCs 0.59-0.63), and (I)ADL dependency (AUCs 0.60-0.64). Differences between the instruments were found for levels of sensitivity which were higher for the GFI and TFI, and levels of specificity which were higher for the FP and FI.

It has been suggested that combining two frailty instruments might increase their predictive ability. In the previous chapter, differences in levels of sensitivity and specificity between the investigated frailty instruments were reported. **Chapter 6** therefore explored sequential and parallel combinations of the sensitive (GFI, TFI) with the specific (FP, FI) instruments. Again, data from the prospective cohort study of 2,420 older people was used, while mortality, hospitalization, and (I)ADL dependency were the outcome measures. Sequential use increased the levels of specificity, as expected, but the positive predictive value barely increased. Likewise, parallel use increased the levels of sensitivity, but the negative predictive value barely increased. These results indicate that combining frailty instruments, either sequentially or in parallel, may not be a solution for achieving better predictive ability. As this is one of the first studies to

investigate the combined use of frailty instruments, further exploration of other combinations of instruments on other study populations is advised.

Chapter 7 began by describing the main findings for each of the three aims of this dissertation. This was followed by methodological considerations: the correct use of frailty instruments, selection of the study population, response rate and missing values, and follow-up. Then, lessons learned concerning the frailty concept were discussed, as were the choice of outcomes and resources, the use of a one-size-fits-all approach, a community approach, and the usefulness of screening. Frailty is a complex concept and the four instruments investigated reflecting different approaches to frailty, were all poorly able to predict adverse outcomes. Continuing to screen for frailty in the way we do now does not appear very useful. Other perspectives should be considered, such as approaching frailty as a balance that also includes assets rather than only deficits. In this more strengths-based approach, the use of more 'perceived' outcomes (e.g. quality of life, wellbeing) might also be considered. Additionally, a more refined classification, using subtypes or profiles of frailty, could lead to a better identification of people at risk for adverse outcomes. At the end of this chapter, implications for research, practice and education were given.

Samenvatting

SAMENVATTING

Hoofdstuk 1 geeft een introductie met betrekking tot de ouder wordende bevolking en het complexe begrip kwetsbaarheid. Wereldwijd worden mensen steeds ouder en het aandeel ouderen binnen de bevolking neemt toe. Dit leidt ook tot een toename van het aantal ouderen dat kwetsbaar is. Ondanks dat de term kwetsbaarheid, in het Engels 'frailty' genoemd, vaak gebruikt wordt, is er nog geen consensus over wat dit precies inhoudt. Onderzoekers en zorgprofessionals gebruiken diverse benaderingen met diverse, bijbehorende meetinstrumenten. Desondanks is men het er wel over eens dat kwetsbaarheid leidt tot negatieve gezondheidsuitkomsten. Onderzoek laat zien dat kwetsbare ouderen een verhoogd risico hebben op bijvoorbeeld overlijden, opname in een ziekenhuis en beperkingen in het uitvoeren van dagelijkse activiteiten (ADL). Om dit te voorkomen en mensen te ondersteunen of een behandeling aan te bieden, is het van belang dat we ouderen die kwetsbaar zijn goed kunnen identificeren. Op die manier worden mensen niet onterecht als kwetsbaar aangemerkt. Als namelijk de verkeerde groep mensen behandeld wordt zal het effect van een eventuele behandeling minimaal zijn en zullen de zorgkosten onnodig stijgen. Daarentegen zullen kwetsbare mensen die de zorg wel nodig hebben, deze wellicht niet ontvangen wanneer ze verkeerd gediagnostiseerd worden.
De doelen van dit proefschrift zijn: (1) het verkrijgen van meer inzicht in de functionele profielen die behoren bij verschillende stadia van kwetsbaarheid; (2) het onderzoeken welke beschermende factoren het pad van kwetsbaarheid naar (verdere) negatieve gezondheidsuitkomsten kunnen beïnvloeden; en (3) het vergroten van de kennis van psychometrische eigenschappen van veelgebruikte vragenlijsten die kwetsbaarheid meten. Dit hoofdstuk eindigt met een beschrijving van de inclusie van de deelnemers aan de verschillende studies en de structuur van dit proefschrift.

Door onderzoekers wordt het meest gebruik gemaakt van Fried's 'frailty phenotype' (FP) om zicht te krijgen op de mate van kwetsbaarheid. Fried en collega's onderscheiden hierbij vijf fysieke criteria om kwetsbaarheid bij ouderen vast te stellen. Andere onderzoekers geven de voorkeur aan een combinatie van vragen over het sociale, psychologische en/of fysieke domein. Het eerste doel van dit proefschrift wordt behandeld in **Hoofdstuk 2**. De mate van sociaal, psychologisch en fysiek functioneren wordt beschreven per stadium van kwetsbaarheid. In deze studie werd gebruik gemaakt van één meetmoment (cross-sectioneel) bij 8.684 thuiswonende Nederlandse ouderen (65+). Op basis van de vijf criteria van Fried (gewichtsverlies, uitputting, verminderde fysieke activiteit, verminderde loopsnelheid en verminderde handknijpkracht) werden de deelnemers ingedeeld in drie stadia:

niet kwetsbaar (score 0), een voorstadium van kwetsbaarheid (score 1-2) en kwetsbaar (score 3-5). Deze stadia werden gerelateerd aan scores in het sociale (sociaal netwerk type, gebruik van mantelzorg, eenzaamheid), psychologische (psychisch onwelbevinden, regie over eigen leven, zelfmanagementvaardigheden) en fysieke (chronische ziekten, beperkingen in het uitvoeren van instrumentele ADL activiteiten (IADL)) domein. Het bleek dat de meeste deelnemers niet kwetsbaar waren (63,2%), 28,1% bevond zich in een voorstadium en 8,7% was kwetsbaar. Kwetsbare personen waren ouder, vaker vrouw, vaker ongetrouwd of alleenwonend en lager opgeleid vergeleken met ouderen in een voorstadium of niet kwetsbare ouderen. Wanneer de scores in het sociale, psychologische en fysieke domein werden vergeleken, waren de beste scores aanwezig in de niet kwetsbare groep, de slechtste scores in de kwetsbare groep en de mensen in een voorstadium van kwetsbaarheid hadden tussenliggende scores. Bijvoorbeeld, voor het gebruik van mantelzorg waren de scores: niet kwetsbaar 3,9%, voorstadium 23,8%, kwetsbaar 60,6%, en scores voor het gemiddelde aantal beperkingen in IADL: niet kwetsbaar 9,2, voorstadium 13,0, kwetsbaar 19,7, waarbij een hogere score duidt op meer beperkingen. Dit wijst erop dat de criteria van Fried zorgprofessionals kunnen helpen om kwetsbare ouderen op een efficiënte manier in te delen en herkennen, en het geeft een indicatie van problemen in andere domeinen.

Een hogere mate van kwetsbaarheid leidt tot meer risico op negatieve gezondheidsuitkomsten gerelateerd aan deze kwetsbaarheid, zoals ziekenhuisopname en overlijden. Er zijn echter aanwijzingen dat meer factoren dan alleen kwetsbaarheid een rol kunnen spelen in het ontstaan van deze uitkomsten. De aanwezigheid van beschermende factoren, zoals bijvoorbeeld voldoende inkomen en goede zelfmanagementvaardigheden, zou het pad van kwetsbaarheid naar negatieve gezondheidsuitkomsten in positieve zin kunnen beïnvloeden. Om het tweede doel van dit proefschrift te behandelen, is in **Hoofdstuk 3** onderzocht of zes factoren (opleidingsniveau, inkomen, beschikbaarheid van mantelzorg, woonsituatie, regie over eigen leven en zelfmanagementvaardigheden) in staat waren om de impact van de mate van kwetsbaarheid op het ontstaan van drie negatieve gezondheidsuitkomsten (overlijden, ziekenhuisopname, ontwikkelen van beperkingen in (I)ADL) te beïnvloeden. Gedurende twee jaar is data van 2.420 thuiswonende kwetsbare ouderen en ouderen in een voorstadium verzameld. Analyses lieten zien dat kwetsbare ouderen inderdaad meer risico lopen op de negatieve gezondheidsuitkomsten dan ouderen in een voorstadium van kwetsbaarheid. Om de beschermende werking van de zes onderzochte factoren te bepalen, werden de interactie-effecten van deze factoren met de mate van kwetsbaarheid op het ontstaan van de drie negatieve gezondheidsuitkomsten onderzocht. In totaal werden derhalve 18 combinaties

onderzocht (zes factoren x drie uitkomsten). Alleen voor beperkingen in (I)ADL werden twee effecten gevonden (inkomen en woonsituatie). De richting van deze effecten was tegengesteld aan de verwachtingen van de onderzoekers. In het algemeen kan gesteld worden dat de onderzochte factoren geen beschermend effect hadden. Meer onderzoek is nodig, waarbij ook andere factoren of andere uitkomstmaten moeten worden betrokken.

Het derde doel van dit proefschrift, het vergroten van de kennis van psychometrische eigenschappen van veelgebruikte kwetsbaarheidsinstrumenten, wordt besproken in **Hoofdstuk 4, 5** en **6**. De vijf criteria van Fried worden het vaakst gebruikt door onderzoekers om kwetsbare ouderen te identificeren. Deze bevatten echter twee fysieke testen die vaak onpraktisch zijn, met name in grootschalig onderzoek. **Hoofdstuk 4** beschrijft welke zelfrapportage vragen gebruikt kunnen worden ter vervanging van Fried's fysieke testen van handknijpkracht en loopsnelheid. Er werd een cross-sectionele studie uitgevoerd onder 135 thuiswonende ouderen met verschillende mate van kwetsbaarheid (niet kwetsbaar, voorstadium en kwetsbaar). Deelnemers voltooiden de originele Fried criteria (inclusief de fysieke testen) evenals 10 vragen over handknijpkracht en 11 vragen over loopsnelheid. Na het uitvoeren van analyses bleken een set van vier vragen voor loopsnelheid (bijv. Loopt u langzamer dan u eigenlijk zou willen kunnen lopen?) en twee vragen voor handknijpkracht (bijv. Heeft u het gevoel dat u minder kracht in uw handen heeft dan leeftijdsgenoten?) het meest optimaal als vervanging van de fysieke testen. Deze twee sets vragen kunnen gebruikt worden in situaties waar het uitvoeren van de fysieke testen niet haalbaar is, zoals in grootschalig onderzoek.

In **Hoofdstuk 5** wordt het voorspellend vermogen beoordeeld van vier veelgebruikte meetinstrumenten die gerelateerd zijn aan verschillende benaderingen van kwetsbaarheid. Het fysieke Frailty Phenotype (FP), de multidimensionale Groningen Frailty Indicator (GFI) en Tilburg Frailty Indicator (TFI) (beide met vastgestelde domeinen en vragen), en de multidimensionale Frailty Index (FI) (zonder vooraf vastgestelde domeinen en vragen), werden bestudeerd. Het voorspellend vermogen van deze instrumenten is eerder onderzocht, echter niet allemaal tegelijk, in één grote steekproef, prospectief en met meerdere uitkomstmaten. In deze prospectieve cohortstudie met een follow-up periode van twee jaar werden 2.420 thuiswonende kwetsbare ouderen en ouderen in een voorstadium van kwetsbaarheid (volgens het FP) geïncludeerd. Overlijden, ziekenhuisopname en een toename van afhankelijkheid in (I)ADL werden gebruikt als uitkomstmaten. Berekeningen lieten zien dat het voorspellend vermogen slecht is voor zowel overlijden als ziekenhuisopname en

afhankelijkheid in (I)ADL. Er werden wel verschillen gevonden in de sensitiviteit, welke hoger was voor de GFI en TFI, en de specificiteit, welke hoger was voor het FP en de FI.

In wetenschappelijke literatuur is gesuggereerd dat het gecombineerd gebruik van twee kwetsbaarheidsinstrumenten het voorspellend vermogen kan verbeteren. In het vorige hoofdstuk zijn verschillen gevonden in de hoogte van de sensitiviteit en specificiteit van de onderzochte instrumenten. **Hoofdstuk 6** verkent combinaties van sensitieve (GFI, TFI) en specifieke (FP, FI) instrumenten. Zowel opeenvolgende als gelijktijdige afname van de instrumenten werden onderzocht. Hierbij werd wederom gebruik gemaakt van de data van het prospectieve cohort van 2.420 ouderen. Overlijden, ziekenhuisopname en een toename van afhankelijkheid in (I)ADL zijn gebruikt als uitkomstmaten. Opeenvolgend gebruik zorgde, zoals verwacht, voor een toename van de specificiteit, echter de positief voorspellende waarde nam nauwelijks toe. Gelijktijdig gebruik zorgde voor een toename van de sensitiviteit, echter de negatief voorspellende waarde nam nauwelijks toe. Deze resultaten wijzen erop dat het gecombineerd gebruik van kwetsbaarheidsinstrumenten, zowel opeenvolgend als gelijktijdig, waarschijnlijk geen oplossing biedt om het voorspellend vermogen te vergroten. Aangezien dit een van de eerste studies is die het gecombineerd gebruik van kwetsbaarheidsinstrumenten heeft onderzocht, wordt geadviseerd om deze en andere combinaties van instrumenten in andere onderzoekspopulaties verder te exploreren.

Hoofdstuk 7 begint met een beschrijving van de belangrijkste conclusies met betrekking tot de drie doelen van dit proefschrift. Daarna volgen enkele methodologische overwegingen: correct gebruik van kwetsbaarheidsinstrumenten, selectie van de studiepopulatie, respons en missende waardes, en follow-up. Daarna worden enkele bespiegelingen gepresenteerd met betrekking tot het concept kwetsbaarheid, de keuze van de uitkomstmaten, beschermende factoren, het gebruik van een 'one-size-fits-all' benadering, een community-benadering, en het nut van screening. Kwetsbaarheid is een complex concept en de vier onderzochte instrumenten, gerelateerd aan verschillende benaderingen van kwetsbaarheid, zijn allen slecht in staat om negatieve gezondheidsuitkomsten te voorspellen. Doorgaan met (grootschalig) screenen op kwetsbaarheid zoals nu vaak gebeurt, lijkt niet erg zinvol. Andere perspectieven zouden overwogen moeten worden, zoals bijvoorbeeld door kwetsbaarheid te beschouwen als een situatie waarbij niet alleen wordt gekeken naar de beperkingen maar tegelijkertijd ook naar de hulpbronnen van een persoon. Kwetsbaarheid is dan te beschouwen als een situatie van disbalans waarbij de hulpbronnen ontoereikend zijn om de beperkingen te compenseren. Binnen deze zogenaamde 'strengths-based' benadering kunnen ook meer 'subjectieve'

uitkomstmaten worden overwogen, zoals kwaliteit van leven en welbevinden. Aanvullend zou een meer verfijnde indeling kunnen leiden tot een betere classificatie van personen die een verhoogd risico hebben op het ontstaan van negatieve gezondheidsuitkomsten. Dit zou bijvoorbeeld gedaan kunnen worden door mensen met bepaalde, overeenkomstige kenmerken te clusteren in subgroepen. Aan het eind van dit laatste hoofdstuk worden de implicaties van de resultaten van dit proefschrift samengevat voor onderzoek, de praktijk en het onderwijs.

S

Valorization

VALORIZATION

This dissertation describes studies that aimed: (1) to expand our knowledge about profiles of older persons with different levels of frailty in terms of functioning in multiple health domains; (2) to examine which resources influence the pathway from frailty to several adverse outcomes; and (3) to increase our knowledge of the psychometric properties of frequently used frailty instruments. This valorization chapter reflects on the relevance and innovativeness of the findings described in this dissertation. It also discusses the value of the findings for different stakeholders. Furthermore, activities for implementation and further dissemination are presented.

Relevance and innovativeness of the findings

The worldwide ageing of the population leads to increasing numbers of frail older people. The past decades frailty has therefore been of increasing interest to researchers and policy makers. Despite all their attention, a clear conceptualization and definition of frailty is lacking. Also measurements of frailty are not uniform. So far, we are not able to adequately identify frail older people. Nevertheless, researchers keep exploring different conceptualizations and measures, aiming at a better identification of frail people, i.e. those at risk for adverse outcomes. Most studies in this field have been conducted to evaluate one or two frailty instruments and often just one outcome measure was used. Also, sample sizes as well as follow-up periods were often limited. The strength of this dissertation is that a large cohort of older people was included, with a follow-up period of two years, simultaneously testing four frailty instruments with different underlying conceptualizations, and the inclusion of three important outcome measures. Using such a large dataset is fairly rare and the results from this dissertation can therefore be considered highly valuable for researchers, healthcare professionals, policy makers, older people, and in health education. The results demonstrate that even with well-known instruments we are hardly able to identify the people at risk for adverse outcomes. Often people are incorrectly classified as frail. The application of such measures may lead to unnecessary treatment for older people who are actually just fine. This is not only an unnecessary burden for older persons themselves but also puts a burden on the healthcare system. Moreover, those who are actually in need of help often do not receive it.

In general, despite decades of research, we should accept that frailty is very complex and we are still unable to define and measure it adequately. Some alternative methods and approaches are suggested in the discussion of this thesis to try to correctly identify

frail older people, such as using a more refined classification instead of a one-size-fits-all approach or a community approach. These options should be explored. However, until one of the alternative methods demonstrates significantly better results than we have found so far, we should not continue with frailty screening as we are doing to date. This will have consequences for various stakeholders which will be discussed below.

Relevance for different stakeholders

There are several stakeholders for whom the results of this dissertation are relevant.

Researchers

Results of the conducted studies in this dissertation demonstrate that the predictive ability of the four investigated frailty instruments is poor. Combining instruments does not lead to a better predictive ability. Also, six investigated resources were unable to moderate the pathway from frailty to adverse outcomes. In general, the results were in line with previous studies. The way researchers handle frailty seems to be insufficient for an accurate identification of people at risk for adverse outcomes. Small changes in conceptualizations or measurement instruments will probably not significantly increase the correct classification of frail people. The focus of research should therefore shift to new, scarcely examined approaches as suggested in the discussion section of this dissertation.

Healthcare professionals

Based on the results of the conducted studies, healthcare professionals should be aware that the predictive ability of the four investigated frailty instruments is limited. Relying solely on a frailty questionnaire to decide if an older person needs help, seems therefore rather unwise. Additionally, other studies showed that intervention programs have not demonstrated convincing positive effects so far. Healthcare professionals are therefore advised to critically consider the value and thus the use of frailty instruments for screening purposes.

Policy makers

The increasing number of older people, and more specific frail older people, put a burden on the healthcare system. Since the classification of the truly frail people is

poor, care is often giving to the wrong people. This leads to an unnecessary increase in healthcare costs. Additionally, the Dutch government supports research on older people including frail ones. For example, the Dutch Ministry of Health, Welfare and Sport initiated the National Care for the Elderly Program between 2008 and 2016. Over 200 projects aiming at improving care for older people, mainly with complex health problems, were funded. The total investment was 89,000,000 euro. Some of those projects aimed at finding better screening methods, assessments and treatments for frail older people. The positive results from those studies were quite limited. In light of those results, the results from this dissertation and from many other studies on frailty (screening), policy makers should seriously consider if they want to further invest in frailty research, frailty screening, or treatment in daily practice, in the way they have been doing so far. An option could be to fund research projects that focus on approaches that are rather distinct from the ones that are used to date.

Lecturers and students in healthcare education

Frailty is a very complex concept. Lecturers in healthcare education should provide students with information displaying this complexity. Awareness should be created among students about the limited predictive ability of frailty instruments. Simply filling out a questionnaire does not automatically lead to providing good care for a patient. Moreover, based on outcomes from other studies, students should be made aware of the fact that evidence for the effectiveness of intervention programs is lacking. Since new instruments are becoming available frequently, students should also be taught that they must always be searching for the best available measurement instrument; especially concerning frailty but also in general. Additionally, they need to learn that it is important to apply an instrument as precisely as possible since deviations might lead to different results.

(Frail) older people

Older (frail) people themselves do not seem to benefit from frailty screening, considering the high rates of misclassification. Nevertheless, most older people do want to know if they are at risk for adverse outcomes, and if so they want help from healthcare professionals. They are also willing to participate in research aimed at improving the identification of frail older people, which has been shown by the high response rates (90%) in this dissertation's studies. We should value their contributions and keep involving older people in our search to a better understanding of frailty and its related measures.

Activities for implementation and further dissemination

All articles included in this dissertation have been published in peer-reviewed international journals. The results have also been presented and discussed at national and international scientific and other conferences (see list of publications) and have thus been made available to researchers and healthcare professionals. Additionally, results from some of the published studies are integrated in a textbook for students (in higher professional education). For the future it is important that the results and recommendations of this dissertation are brought to the attention of other researchers, healthcare professionals and policy makers. Guidelines for healthcare professionals and educational programs should be adjusted in light of our findings. By means of national and international publications and presentations we will aim to further increase awareness among stakeholders about the limitations of (large-scale) frailty screening.

Dankwoord

DANKWOORD

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About the author

ABOUT THE AUTHOR

Linda Op het Veld was born on 16 March 1985 in Heythuysen, the Netherlands. In 2003 she completed secondary school at St. Ursula in Horn. She studied Healthcare Biometrics at Zuyd University of Applied Sciences and graduated as Bachelor of Medical Technology in 2007. Alongside writing her bachelor thesis she started working at CIRO, a center specialized in treating people with chronic lung diseases, heart failure or sleep-related respiratory distress. There, she was involved in setting up the department of biometrics. Alongside her work in practice, she studied Physical Activity and Health, specialization Biology of Human Performance and Health at Maastricht University. She graduated in 2010 as a Master of Science with a thesis about a prospective study of quadriceps muscle weakness in Dutch COPD patients.

In December 2011 she started her PhD project that resulted in this dissertation. This was a collaborative project of the Research Centre for Autonomy and Participation of Persons with a Chronic Illness and the Research Centre of Community Care (Zuyd University), the Department of Family Medicine and the Department of Health Services Research (Maastricht University) and the Community Health Services in Limburg. In 2014, after the birth of her first child, she stopped working at CIRO and focused on her research.

Currently, her work involves a combination of research and lecturing in different educational programs at Zuyd University of Applied Sciences, mostly for the Research Centre for Autonomy and Participation for Persons with a Chronic Illness, and Health Technology | Healthcare Biometrics. She focuses on helping students from several schools in conducting their research.

Linda lives in Heerlen, the Netherlands, together with her boyfriend Roy and their children Eva and Daan.

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List of publications

LIST OF PUBLICATIONS AND PRESENTATIONS

International peer-reviewed publications

- **Op het Veld LPM**, van Rossum E, Kempen GIJM, Beurskens AJHM, Hajema K, de Vet HCW. Can the combined use of two screening instruments improve the predictive power of dependency in (instrumental) activities of daily living ((I)ADL), mortality and hospitalization in old age*? Journal of Frailty and Aging. 2019 Jun 12. http://dx.doi.org/10.14283/jfa.2019.17*
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- **Op het Veld LPM**. De kwaliteit van vier veelgebruikte meetinstrumenten om kwetsbare ouderen te identificeren. Geriatriedagen 2019; 2019 Feb 7; 's-Hertogenbosch.
- **Op het Veld LPM**. Opsporen van kwetsbare ouderen. GGD, Vakgroep Onderzoek Publieke Gezondheid, Themadag Kwetsbare ouderen; 2017 Dec 14; Utrecht.
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