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Complete List of Authors:	Jepsen, Randi; Nykøbing F Sygehus Jacobsen, Katja Lembeck, Maurice; Nykobing F Sygehus, Medical Department Nilssen, Charlotte; University of Copenhagen Holm, Ellen; Nykøbing F Sygehus, Internal medicine; University of Copenhagen, Institute of clinical medicine
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Validation of a frailty phenotype, a registry based study

Katja K. Jacobsen, Ph.D. Department of Technology, Faculty of Health and Technology, University College Copenhagen, and Lolland-Falster Health Study, Center for Epidemiological Research, Nykøbing Falster Hospital.

Randi Jepsen, Ph.D., MSc, RN, Project manager, Lolland-Falster Health Study, Center for Epidemiological Research, Nykøbing Falster Hospital.

Maurice Lembeck, MD, Consultant at the Medical Department, Nykøbing Falster Hospital

Charlotte J. Nilsson, MD, Ph.d., Associate professor at Section of Social Medicine, Department of Public Health, University of Copenhagen

Ellen A. Holm, MD, Consultant at the Medical Department, Nykøbing Falster Hospital, Associated clinical professor at the University of Copenhagen.

Responsible for correspondence: Ellen Holm, Medical Department, Nykøbing Falster Hospital, Fjordvej 15, 4800 Nykøbing Falster. E-mail: ellh@regionsjaelland.dk

Abstract

Objectives: Frailty is a major clinical geriatric syndrome associated with serious adverse events including functional disability, falls, hospitalization, increased morbidity, and mortality. The aim of this study was to validate the frailty measure used in the Danish population study Lolland-Falster Health Study (LOFUS).

Design: registry based cross sectional study

Setting: The target population consists of inhabitants above the age of 50 living in the Danish municipalities of Lolland and Guldborgsund. Excluded are incapacitated people, inhabitants unable to understand Danish or English and inhabitants without a permanent residence.

Participants: 7,327 individuals aged 50+ years were included.

Outcome measures: The frailty measurement was validated by examining associations with factors known to be associated with frailty: sex, age, income insufficiency, education, comorbidity, self-assessed health, morbidity, and mortality.

Results: 7,327 individuals aged 50+ years were included. Of these, 6.5% had ≥3 frailty components (frail), 46.7% had 1-2 components (prefrail) and 46.9% had none (non-frail). Those who were frail were older and more likely female than those who were non-frail or prefrail. There was a step-wise decrease in educational level, and in self-assessed health with increasing frailty status, and a stepwise increase in difficulty in making ends meet, number of hospital contacts, and mortality with increasing frailty status, $p<0.0001$ for each comparison. Compared to individuals who were non-frail, mortality was higher among those who were prefrail (HR: 2.90; 95% CI: 1.30-6.43) or frail (HR: 8.21; 95% CI: 3.37-20.0).

Conclusions: Based on these findings we consider the LOFUS frailty assessment a valid instrument demonstrating the same characteristics as other validated frailty measures concerning associations with sex, age, income insufficiency, education, comorbidity, self-assessed health, morbidity, and mortality.

Keywords: frailty, physical functional performance, healthy ageing

Strengths and limitations of this study

- The frailty measurement studied is close to a widely recognized instrument used in the Senior Health and Retirement study in Europe (SHARE)
- The frailty measurement was studied in a large representative population
- The LOFUS study is cross sectional but by coupling with national registries, we were able to follow the participants over time.
- Due to lack of follow up data concerning morbidity, we assessed associations between morbidity and frailty by using data on morbidity during a period of 6 months before the frailty measurement

Background

Frailty is a major clinical geriatric syndrome associated with serious adverse outcomes including functional disability, falls, hospitalization, increased morbidity, and mortality. The pathophysiology of frailty includes age-related decline in the function of multiple organ systems leading to insufficient homeostatic mechanisms and thereby increased vulnerability to minor stressor events.[1] Two principally different approaches are used in order to operationalize the measurement of frailty. Linda Fried et al. described a physical frailty phenotype based on five criteria including exhaustion (fatigue), weight loss (unintentional), weakness, slowness, and low activity. Individuals fulfilling three or more of the five criteria are defined as frail and individuals fulfilling 1-2 as prefrail.[2] If an individual is frail according to the physical frailty phenotype, it is not necessarily obvious without measurement of the five included criteria. In contrast, Mitnitski et al. described frailty as an accumulation of health deficits occurring with aging and operationalized this approach in the frailty index.[3] A frailty index consists of a predefined list of deficits. The proportion of deficits present in a specific person defines the frailty index. If for instant the chosen list of deficits consists of 50 items, of which the individual has 10, the frailty index of this individual is 10/50=0.2. The frailty index includes traditional health items like medical diagnoses but also other factors describing

cognitive function, social circumstances, and functional loss. Although there is thus no universally accepted operational definition of frailty, the Fried frailty phenotype is widely used and validated in several studies.[4-7]

The Senior Health in Aging and Retirement study in Europe (SHARE) is a population study including questions, which have been used to develop a Share-Frailty Instrument (SHARE-FI).[8,9]Validation studies have demonstrated that SHARE-FI is associated with mortality[9] and with loss of functional capacity.[10]

The SHARE study included in its first wave 1699 Danish citizens above the age of 50. These participants were drawn by the Danish National Institute of Statistics in order to reflect the Danish population. The SHARE questionnaires were translated into Danish following recommendations from the SHARE organization.[11] The questions used in the SHARE-FI were chosen retrospectively based on their similarity to the items in the frailty phenotype originally developed by Fried et al.[8]

The Danish population study, the Lolland-Falster Health Study (LOFUS)[12] includes items very similar to the items used in the SHARE-FI, but with small variations.

Epidemiology, morbidity, and mortality associated with frailty

A systematic review found the prevalence of frailty among individuals aged 65+ varying between 4 and 59.1% with an overall weighted prevalence of 10.7%. Prevalence increased with age and was higher in women.[13] The prevalence of frailty in Europe among 7,510 participants aged 65+ enrolled in SHARE 2004 varied between 8.6% (Sweden) and 27.3% (Spain). The prevalence among 877 Danish participants aged 50-64 years was 3.0% and among 635 participants aged 65+ 12.4%.[8]

Two metaanalyses including studies using the Fried phenotype found significant higher hospitalization risk in frail compared to non-frail elderly individuals (OR 1.49, CI 1.26 -1.76),[14] and significant increased mortality (HR 1.874, CI 1.635-2.150).[15]

Objectives

The aim of this study is to validate the frailty measurement used in LOFUS. We will do this by examining to what degree the frailty measurement is associated with factors known to be associated with frailty: age, sex, multi morbidity, level of education, income insufficiency, self-assessed health, morbidity, and mortality.[2,16]

Design and participants

LOFUS has been described in detail elsewhere.[12] In summary, it is a household-based cross-sectional study including people of all ages. Lolland-Falster consists of two islands in the southern part of Denmark. It is a rural area where income is lower and life expectancy shorter than in the general Danish population. The target population for the present sub-study consists of inhabitants above the age of 50 living in the Danish municipalities of Lolland and Guldborgsund. Excluded are incapacitated people, inhabitants unable to understand Danish or English and inhabitants without a permanent residence.

The data collection started in February 2016 and is still ongoing; with currently 7,992 individuals aged 50+ years recruited.

Methods

Frailty

LOFUS includes the following variables used to assess frailty:

1) Exhaustion/Fatigue: the criterion was fulfilled by answering yes in response to the question “In the last month or so, have you had too little energy to do things you wanted to do?” (Yes/No)
2) Shrinking: the criterion was fulfilled by answering yes in response to the question “What has your appetite been like? Do you feel a diminution in desire for food?” (Yes/No)

3) Weakness was derived from the highest of three consecutive dynamometer measurements of handgrip strength in the dominant hand applying gender and body mass index cutoffs set by Fried et al.[2]
4) Slowness: A positive answer to either of the following two items " Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 meters" or "climbing one flight of stairs without resting"
5) Low activity was fulfilled in participants responding one to three times a month, hardly ever, or never to the question "How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?"

Individuals fulfilling 1-2 of the above mentioned criteria were characterized as prefrail while those fulfilling 3-5 criteria were characterized as frail. If none of the criteria were fulfilled individuals were characterized as non-frail.

Factors assessed for association with frailty, data from LOFUS

The following factors were extracted from the LOFUS questionnaires: Age, sex, self-assessed health, educational background, financial difficulties, comorbidity, and mortality. Educational level was categorized according to highest obtained education into four categories: "Primary school", "Short education", "Medium higher education", and "Long higher education".

Comorbidity was assessed by asking participants if they suffered from angina, migraine or headache, arthritis, cancer, diabetes, hypertension, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, depression, anxiety, kidney disease, asthma, dementia, or Parkinson's disease. Socioeconomic status was assessed by the question "During the last twelve months, how often did you find difficulty in making ends meet?"

Data from national health registers

Every person residing in Denmark is uniquely registered in the Danish Civil Registration System (CRS).[17] The LOFUS database receives daily updates from CRS on all inhabitants of Lolland-Falster regarding births, deaths, immigration, and moving of residents. Individuals were followed up in CRS until date of death or February 2019. Additionally, we assessed data on hospitalization by merging the LOFUS database with the Danish National Patient Register.[18]

Number of hospital contacts was defined as hospital contacts within 2 years prior to the date of participation in LOFUS. Hospital contacts were categorized as no admission days registered in the National Patient Register (ambulant contacts) or admission days registered (hospital admission).

Statistical Analysis

For associations of frailty with other factors, the p-trend value based on Cochran-Mantel-Haenszel test was used. Cox proportional hazard regression model using length of follow-up as the time metric estimated hazard ratios (HRs) and 95% confidence intervals (95% CI) for the association between frailty phenotype and mortality. The model was adjusted for age group and sex.

Patient and public involvement

Patients and public were not involved in the development of this study.

Ethics

LOFUS (SJ-421) as well as the present sub-study on frailty (SJ-486) was approved by Region Zealand's Ethical Committee on Health Research. The Danish Protection Agency approved the LOFUS study (REG-24-2015). LOFUS is registered in Clinical Trials (NCT02482896).

Results

Of a total of 7,992 individuals 50+ years old, 656 (12.2%) were excluded as they did not answer the questions on frailty. Nine individuals were considered not available for frailty measurement as they had three or more missing frailty components, leaving 7,327 individuals for analysis. Of these, 6.5% had ≥3 frailty components, 46.7% had 1-2 components and 46.8% had none. The most frequent frailty component was exhaustion (41.5%), followed by slowness (12.8%), and low activity (12.2%) (Table 1). Overall, 55.8 % reported "good" self-assessed health and 93.6% never had difficulty in making ends meet (Table 2). Those who were frail were older and more likely female than those who were non-frail or prefrail. There was a step-wise decrease in education level and self-assessed health and a stepwise increase in difficulty in making ends meet and number of hospital contacts and hospital admissions with increasing frailty status, $p<0.0001$ for each comparison. Notably, 14.7% of those who were frail had no hospital contacts (table 3). Frail persons had significantly higher prevalence of myocardial infarction, angina, migraine or headache, cancer, diabetes, hypertension, respiratory disease, depression, anxiety, kidney disease, asthma, and dementia. Notably, 7.8% of those who were frail had none of these chronic diseases and 20.0% had just one which were: 43.2% arthritis, 21.1% hypertension, 8.4% migraine or headache, 7.4% cancer, 6.3% respiratory disease, and 5.3% depression. The remaining chronic diseases were each represented by less than 2.5%. Figure 1 shows the overlap between frailty and comorbidity.

Mean follow-up time was 1.13 years for all-cause mortality, giving a total of 8,314,568 person-years and 49 deaths (0.7%). Compared to individuals who were non-frail, mortality was higher among those who were prefrail (HR: 2.90; 95% CI: 1.30-6.43) or frail (HR: 8.21; 95% CI: 3.37-20.0) (Table 4).

Discussion

In this study we aimed at validating a frailty measurement based on the criteria characterizing the frailty phenotype described by Fried et al.[2] Our frailty measurement builds on the work by Santo-Eggimann et al.,

which showed that a subset of questions in the Senior Health and Aging Study in Europe could be operationalized as a frailty measurement.[8] Romero-Ortuno et al. further developed this approach into the SHARE-FI and validated this instrument in several studies.[9,19-21] Our study was part of a Danish population study (LOFUS). The questionnaires used in LOFUS included questions similar to those included in SHARE-FI but with small discrepancies. We therefore found it necessary to validate our frailty measurement.

We validated our frailty measurement by examining to what degree it was associated with factors known to be associated with frailty: age, sex, multi morbidity, level of education, income insufficiency, self-assessed health, and mortality.[2,16] In all these factors, we found significant gradients over the frailty groups. Due to present lack of follow up data, we could not test the predictive value concerning morbidity. We therefore decided to examine the association between frailty and number of hospitalizations in a 2 year period previously to the frailty measurement and found a significant trend with an increasing number of hospital contacts with increasing frailty. We only had a short follow up period to examine mortality (1.13 years) but in spite of this, there was a significant increasing mortality rate with increasing frailty.

Overall we found the prevalence of frailty to be 6.5%. In the age group 50-64 it was 4.7% and in the 65+ it was 8.4%. This is an overall lower prevalence and a different pattern than what was seen in the group of Danish SHARE participants, in which the overall prevalence was 8.8%, in the 50-64 years 3%, and in the 65+ years old 12.4%. The explanation might be that our study is taking place in a rural area with a relatively high proportion of socioeconomically deprived individuals in the younger age groups, while the Danish participants in SHARE were drawn randomly in order to select a representative sample of Danes from the whole country in these age groups. The population covered by LOFUS compared to the general Danish population has lower income, less education, higher burden of disease, higher prevalence of unhealthy lifestyle factors, and an average life expectancy approximately two years lower than mean average life expectancy in Denmark (80.8 years).[12]This could result in higher prevalence of frailty in the youngest age groups due to high burden of risk factors, and a lower prevalence in the older age groups due to selection leading to a healthy survivor effect.[22]

The overall lower prevalence compared to SHARE might also be explained by characteristics of non-respondents in LOFUS. Halfway through the LOFUS data collection subjects with lower socio-economic status and age above 80 were found to have lower participation rates compared to more well off and younger age groups (article in press). This implicates that our study may underestimate the prevalence of frailty.

The prevalence of 0, 1, 2, 3, 4, or 5 frailty criteria was very similar to the findings by Fried et al.[2] The distribution of prevalence of the single frailty criteria has been differing in several studies. In our study, we found a very high prevalence of exhaustion 41,5% versus 17% in the study by Fried et al.[2] and 27% in the cross European study by Santos-Eggimann et al.[8] The way we measured exhaustion was exactly the same way as Santos-Eggiman by asking: "In the last month or so, have you had too little energy to do things you wanted to do?" and in case of a "Yes" this criteria was considered fulfilled. Fried et al. used a more detailed report from the participants based on answers from 2 items from the modified 10-item Centre for Epidemiology Studies Depression Scale[23] and this may explain some of the rather large difference in prevalence of the exhaustion criteria. We found a distribution of prevalence for the criteria slowness, weakness, and physical activity similar to the findings by Eggimann et al. but again somewhat different from the findings by Fried et al. This may be due to the fact that Fried et al. defined the cut-off values for these frailty criteria according to the population assessed by defining the criteria fulfilled if the values were included in the lowest quintile of the study sample distribution. Bouzòn et al. recently showed that the standardization to the population assessed makes a difference for the predictive ability of the frailty diagnosis.[24]

Strengths and limitations

Our study is a large population study with a representative sample for the geographical area covered by LOFUS. At the present LOFUS is a cross-sectional study, however due to the national health registries we

were able to follow the participants over a time period. The Danish registries are of high quality and the unique personal identification numbers of all Danish inhabitants made it possible to include valid data concerning morbidity (hospital contacts) and mortality.[25] Due to the present lack of follow up data concerning morbidity we had to assess hospital contacts in a period before the frailty measurement instead of assessing the predictive ability concerning hospital contacts. However, frailty is considered a syndrome developing over time and not evolving as an acute event. We therefore consider the findings of association with previous hospital contacts equally valuable compared to an association with future hospital contacts.

Conclusion

We have described a frailty instrument close to but not exactly the same as the frailty instrument developed in a large European population study, SHARE (SHARE-FI). Our frailty instrument shows the same characteristics as the SHARE-FI and other validated frailty measures concerning associations with sex, age, income insufficiency, education, comorbidity, self-assessed health, multimorbidity, and mortality. Based on these findings we consider our frailty measure a valid instrument.

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Table 1: Prevalence of phenotype frailty components

		Total (n=7,327)	Men (n=3,498)	Women (n=3,829)
Frequency of frailty components	Exhaustion	41.5	38.8	43.9
	Shrinking	6.3	5.0	7.5
	Weakness	8.2	8.1	8.2
	Slowness	12.8	11.8	13.8
	Low activity	12.2	11.1	13.1
Number of frailty components	0	46.8	49.7	44.2
	1	33.8	32.9	34.6
	2	12.9	11.8	13.9
	3	4.7	4.4	4.9
	4	1.7	1.1	2.1
	5	0.1	0.1	0.2

Table 2: Association of demographic and health characteristics with frailty phenotype.

Factors		Total 7,327 (%)	Non-frail 3,432 (%)	Prefrail 3,419 (%)	Frail 476 (%)	Trend, *p* value	Age adjusted trend, *p* value
Age	50-65	3,749 (51.2)	1,673 (48.8)	1,900 (55.6)	176 (37.0)	<0.0001	
	65-74	2,578 (35.2)	1,399 (40.8)	1,017 (29.7)	162 (34.0)		
	75-84	892 (12.2)	342 (10.0)	441 (12.9)	109 (22.9)		
	85+	108 (1.5)	18 (0.5)	61 (1.8)	29 (6.1)		
Sex	Female	3,829 (52.3)	1,693 (49.3)	1,859 (54.4)	277 (58.2)	<0.0001	<0.0001
	Male	3,498 (47.7)	1,739 (50.7)	1,560 (45.6)	199 (41.8)		
Education	Primary school	816 (11.1)	295 (8.6)	429 (12.6)	92 (19.3)	<0.0001	<0.0001
	Short (1-3 years)	4,197 (57.3)	1,987 (57.9)	1,959 (57.3)	251 (52.7)		
	Medium (3-4 years)	1,465 (20.0)	737 (21.5)	659 (19.3)	69 (14.5)		
	Long (>4 years)	301 (4.1)	162 (4.7)	127 (3.7)	12 (2.5)		
Self-assessed health	Very good	838 (11.5)	626 (18.3)	203 (6.0)	9 (1.9)	<0.0001	<0.0001
	Good	4,077 (55.8)	2,337 (68.2)	1,661 (48.7)	79 (16.7)		
	Fair	2,048 (28.0)	450 (13.1)	1,326 (38.9)	272 (57.6)		
	Bad	310 (4.2)	13 (0.4)	198 (5.8)	99 (21.0)		
	Very bad	32 (0.4)	0 (0.0)	19 (0.6)	13 (2.8)		
Difficulty in making ends meet	Never	6,813 (93.6)	3,290 (96.4)	3,122 (92.1)	401 (84.4)	<0.0001	<0.0001
	A few months	353 (4.9)	101 (3.0)	200 (5.9)	52 (11.0)		
	Approximately half of a year's months	54 (0.7)	9 (0.3)	31 (0.9)	14 (3.0)		
	Every month	58 (0.8)	13 (0.4)	37 (1.1)	8 (1.7)		
Chronic diseases	Myocardial infarction	296 (4.0)	96 (2.8)	161 (4.7)	39 (8.2)	<0.0001	<0.0001
	Angina	241 (3.3)	56 (1.6)	132 (3.9)	53 (11.1)	<0.0001	<0.0001
	Migraine or headache	842 (11.5)	234 (6.8)	516 (15.1)	92 (19.3)	<0.0001	<0.0001
	Arthritis	2,849 (38.9)	1,025 (29.9)	1,538 (45.0)	286 (60.1)	<0.0001	<0.0001
	Cancer	379 (5.2)	137 (4.0)	193 (5.6)	49 (10.3)	<0.0001	<0.0001
	Diabetes	525 (7.2)	154 (4.5)	285 (8.3)	86 (18.1)	<0.0001	<0.0001
	Hypertension	2,425 (33.1)	969 (28.2)	1,227 (35.9)	229 (48.1)	<0.0001	<0.0001

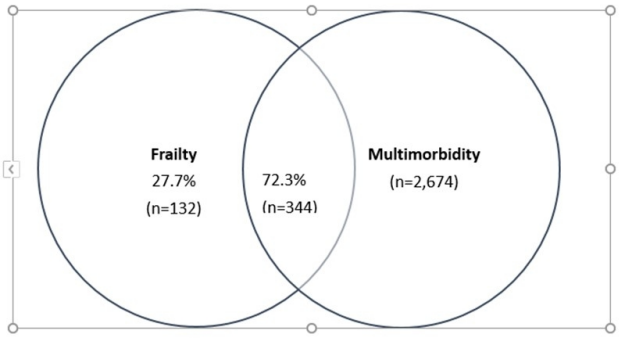
	Respiratory disease*	429 (5.9)	100 (2.9)	234 (6.8)	95 (20.0)	<0.0001	<0.0001
	Depression	548 (7.5)	104 (3.1)	331 (9.7)	113 (23.7)	<0.0001	<0.0001
	Anxiety	426 (5.8)	92 (2.7)	256 (7.5)	78 (16.4)	<0.0001	<0.0001
	Kidney disease	122 (1.7)	31 (0.9)	66 (1.9)	25 (5.3)	<0.0001	<0.0001
	Asthma	425 (5.8)	135 (3.9)	225 (6.6)	65 (13.7)	<0.0001	<0.0001
	Dementia	21 (0.3)	4 (0.12)	13 (0.4)	4 (0.8)	0.01	0.03
	Parkinson's disease	45 (0.6)	18 (0.5)	23 (0.7)	4 (0.8)	0.59	0.72
Chronic diseases	0	2,238 (30.5)	1,408 (41.0)	793 (23.2)	37 (7.8)	<0.0001	<0.0001
	1	2,415 (33.0)	1,214 (35.4)	1,106 (32.4)	95 (20.0)		
	2	1,537 (21.0)	569 (16.6)	845 (24.7)	123 (25.8)		
	3-4	971 (13.3)	224 (6.5)	585 (17.1)	162 (34.0)		
	≥5	166 (2.3)	17 (0.5)	90 (2.6)	59 (12.4)		

Table 3: Association between number of hospital contacts and frailty status

Category		Total 7,327 (%)	Non-frail 3,432 (%)	Pre-frail 3,419 (%)	Frail 476 (%)	Trend, *p* value	Age adjusted trend, *p* value
Ambulatory contacts							
	0	3,088 (42.2)	1,628 (47.4)	1,312 (38.4)	148 (31.1)	<0.0001	<0.0001
	<5	3,893 (53.1	1,696 (49.4)	1,908 (55.8)	289 (60.7)		
	5-10	335 (4.6)	105 (3.1)	193 (5.6)	37 (7.8)		
	>10	11 (0.2)	<5	6 (0.2)	<5		
Hospital admissions							
	0	3,471 (47.4)	1,865 (53.3)	1,470 (43.0)	136 (28.6)	<0.0001	<0.0001
	<5	2,987 (40.8)	1,299 (37.9)	1,464 (42.8)	224 (47.1)		
	5-10	727 (9.9)	235 (6.9)	402 (11.8)	90 (18.9)		
	>10	142 (1.9)	33 (1.0)	83 (2.4)	26 (5.5)		
Hospital stay, number of days							
	0	3,471 (47.4)	1,865 (54.3)	1,470 (43.0	136 (28.6)	<0.0001	<0.0001
	<5	2,329 (31.8)	1,062 (30.9)	1,121 (32.8)	146 (30.7)		
	5-10	889 (12.1)	324 (9.4)	473 (13.8)	92 (19.3)		
	>10	638 (8.7)	181 (5.3)	355 (10.4)	102 (21.4)		

Table 4: Frailty status and mortality

	Number of deaths	Mortality HR 95%CI*
Non-Frail (reference group)	8	1.00
Pre-frail	26	2.90 (1.30-6.43)
Frail	15	8.21 (3.37-20.0)



This Venn diagram shows the overlap between co-morbidity and frailty

338x190mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(e) Describe any sensitivity analyses

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Associations between the SHARE frailty phenotype and common frailty characteristics: evidence from a large Danish population study

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Associations between the SHARE frailty phenotype and common frailty characteristics: evidence from a large Danish population study

Katja K. Jacobsen, Ph.D. Department of Technology, Faculty of Health and Technology, University College Copenhagen, and Lolland-Falster Health Study, Center for Epidemiological Research, Nykøbing Falster Hospital.

Randi Jepsen, Ph.D., MSc, RN, Project manager, Lolland-Falster Health Study, Center for Epidemiological Research, Nykøbing Falster Hospital.

Maurice Lembeck, MD, Consultant at the Medical Department, Nykøbing Falster Hospital

Charlotte J. Nilsson, MD, Ph.d., Associate professor at Section of Social Medicine, Department of Public Health, University of Copenhagen

Ellen A. Holm, MD, Consultant at the Medical Department, Nykøbing Falster Hospital, Associated clinical professor at the University of Copenhagen.

Responsible for correspondence: Ellen Holm, Medical Department, Nykøbing Falster Hospital, Fjordvej 15, 4800 Nykøbing Falster. E-mail: ellh@regionsjaelland.dk

Abstract

Objectives: Frailty is a major clinical geriatric syndrome associated with serious adverse events including functional disability, falls, hospitalization, increased morbidity, and mortality. The aim of this study was to study associations between a frailty phenotype and frailty characteristics well known from the literature.

Design: Registry based cross sectional study

Setting: The target population consists of inhabitants above the age of 50 living in the Danish municipalities of Lolland and Guldborgsund. Excluded are incapacitated people, inhabitants unable to understand Danish or English and inhabitants without a permanent residence.

Participants: 7,327 individuals aged 50+ years were included.

Outcome measures: We examined associations between the frailty measurement and factors known to be associated with frailty: sex, age, income insufficiency, education, comorbidity, self-assessed health, morbidity, and mortality.

Results: 7,327 individuals aged 50+ years were included. Of these, 6.5% had ≥3 frailty components (frail), 46.7% had 1-2 components (prefrail) and 46.9% had none (non-frail). Those who were frail were older and more likely female than those who were non-frail or prefrail. There was a step-wise decrease in educational level, and in self-assessed health with increasing frailty status, and a stepwise increase in difficulty in making ends meet, number of hospital contacts, and mortality with increasing frailty status, $p<0.0001$ for each comparison. Compared to individuals who were non-frail, mortality was higher among those who were prefrail (HR: 2.90; 95% CI: 1.30-6.43) or frail (HR: 8.21; 95% CI: 3.37-20.0).

Conclusions: Based on these findings we consider the LOFUS frailty assessment a valid instrument demonstrating the same characteristics as other validated frailty measures concerning associations with sex, age, income insufficiency, education, comorbidity, self-assessed health, morbidity, and mortality.

Keywords: frailty, physical functional performance, healthy ageing

Strengths and limitations of this study

- The frailty measurement studied has only minor deviations from a widely recognized instrument used in the Senior Health and Retirement study in Europe (SHARE)
- The frailty measurement was studied in a large representative population
- The LOFUS study is cross sectional but by coupling with national registries, we were able to follow the participants over time.
- Due to lack of follow up data concerning morbidity, we assessed associations between morbidity and frailty by using data on morbidity during a period of 6 months before the frailty measurement

Background

Frailty is a major clinical geriatric syndrome associated with serious adverse outcomes including functional disability, falls, hospitalization, increased morbidity, and mortality. The pathophysiology of frailty includes age-related decline in the function of multiple organ systems leading to insufficient homeostatic mechanisms and thereby increased vulnerability to minor stressor events.[1] Two principally different approaches are used in order to operationalize the measurement of frailty. Linda Fried et al. described a physical frailty phenotype based on five criteria including exhaustion (fatigue), weight loss (unintentional), weakness, slowness, and low activity. Individuals fulfilling three or more of the five criteria are defined as frail and individuals fulfilling 1-2 as prefrail.[2] If an individual is frail according to the physical frailty phenotype, it is not necessarily obvious without measurement of the five included criteria. In contrast, Mitnitski et al. described frailty as an accumulation of health deficits occurring with aging and operationalized this approach in the frailty index.[3] A frailty index consists of a predefined list of deficits. The proportion of deficits present in a specific person defines the frailty index. If for instant the chosen list of deficits consists of 50 items, of which the individual has 10, the frailty index of this individual is 10/50=0.2. The frailty index includes traditional health items like medical diagnoses but also other factors describing

cognitive function, social circumstances, and functional loss. Although there is thus no universally accepted operational definition of frailty, the Fried frailty phenotype is widely used and validated in several studies.[4-7]

The Senior Health in Aging and Retirement study in Europe (SHARE) is a population study including questions, which have been used to develop a Share-Frailty Instrument (SHARE-FI).[8,9]Validation studies have demonstrated that SHARE-FI is associated with mortality[9] and with loss of functional capacity.[10]

The SHARE study included in its first wave 1699 Danish citizens above the age of 50. These participants were drawn by the Danish National Institute of Statistics in order to reflect the Danish population. The SHARE questionnaires were translated into Danish following recommendations from the SHARE organization.[11] The questions used in the SHARE-FI were chosen retrospectively based on their similarity to the items in the frailty phenotype originally developed by Fried et al.[8]

The Danish population study, the Lolland-Falster Health Study (LOFUS)[12] includes frailty items almost the same as those used in the SHARE-FI.

Epidemiology, morbidity, and mortality associated with frailty

A systematic review found the prevalence of frailty among individuals aged 65+ varying between 4 and 59.1% with an overall weighted prevalence of 10.7%. Prevalence increased with age and was higher in women.[13] The prevalence of frailty in Europe among 7,510 participants aged 65+ enrolled in SHARE 2004 varied between 8.6% (Sweden) and 27.3% (Spain). The prevalence among 877 Danish participants aged 50-64 years was 3.0% and among 635 participants aged 65+ 12.4%.[8]

Two metaanalyses including studies using the Fried phenotype found significant higher hospitalization risk in frail compared to non-frail elderly individuals (OR 1.49, CI 1.26 -1.76),[14] and significant increased mortality (HR 1.874, CI 1.635-2.150).[15]

Objectives

The aim of this study was to examine whether the frailty measurement used in LOFUS was able to identify frail individuals. We did this by examining to what degree the frailty measurement is associated with factors known to be associated with frailty: age, sex, multi morbidity, level of education, income insufficiency, self-assessed health, morbidity, and mortality.[2,16]

Design and participants

LOFUS has been described in detail elsewhere.[12] In summary, it is a household-based cross-sectional study including people of all ages. Lolland-Falster consists of two islands in the southern part of Denmark. It is a rural area where income is lower and life expectancy shorter than in the general Danish population. The target population for the present sub-study consists of inhabitants above the age of 50 living in the Danish municipalities of Lolland and Guldborgsund. Excluded are incapacitated people, inhabitants unable to understand Danish or English and inhabitants without a permanent residence.

The data collection started in February 2016 and is still ongoing; with currently 7,992 individuals aged 50+ years recruited.

Methods

Frailty

LOFUS includes the following variables used to assess frailty:

1) Exhaustion/Fatigue: the criterion was fulfilled by answering yes in response to the question “In the last month or so, have you had too little energy to do things you wanted to do?” (Yes/No)
2) Shrinking: the criterion was fulfilled by answering yes in response to the question “What has your appetite been like? Do you feel a diminution in desire for food?” (Yes/No)

3) Weakness was derived from the highest of three consecutive dynamometer measurements of handgrip strength in the dominant hand applying gender and body mass index cutoffs set by Fried et al.[2]
4) Slowness: A positive answer to either of the following two items " Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 meters" or "climbing one flight of stairs without resting"
5) Low activity was fulfilled in participants responding one to three times a month, hardly ever, or never to the question "How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?"

Individuals fulfilling 1-2 of the above mentioned criteria were characterized as prefrail while those fulfilling 3-5 criteria were characterized as frail. If none of the criteria were fulfilled individuals were characterized as non-frail.

Factors assessed for association with frailty, data from LOFUS

The following factors were extracted from the LOFUS questionnaires: Age, sex, self-assessed health, educational background, financial difficulties, comorbidity, and mortality. Educational level was categorized according to highest obtained education into four categories: "Primary school", "Short education", "Medium higher education", and "Long higher education".

Comorbidity was assessed by asking participants if they suffered from angina, migraine or headache, arthritis, cancer, diabetes, hypertension, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, depression, anxiety, kidney disease, asthma, dementia, or Parkinson's disease. Socioeconomic status was assessed by the question "During the last twelve months, how often did you find difficulty in making ends meet?"

Data from national health registers

Every person residing in Denmark is uniquely registered in the Danish Civil Registration System (CRS).[17] The LOFUS database receives daily updates from CRS on all inhabitants of Lolland-Falster regarding births, deaths, immigration, and moving of residents. Individuals were followed up in CRS until date of death or February 2019. Additionally, we assessed data on hospitalization by merging the LOFUS database with the Danish National Patient Register.[18]

Number of hospital contacts was defined as hospital contacts within 2 years prior to the date of participation in LOFUS. Hospital contacts were categorized as no admission days registered in the National Patient Register (ambulant contacts) or admission days registered (hospital admission).

Sample size

For the sub-study on aging-related outcomes in LOFUS, that is among the 50+ year-olds, the original idea was to study the association between social factors (socioeconomic position and social relations respectively) and physical function and frailty. Initially we performed power calculations for all social variables in relation to detection of their impact on physical function as well as frailty. The prevalence estimates used in these power calculations were calculated from previous Danish population surveys applying similar measures, and previous literature. Based on these calculations we requested inclusion of 5800 individuals aged 50+, in order to detect an association between *each* of the social variables and physical function *or* frailty at a significance level of 0.05 and with 80% power. However, based on the power calculations performed for frailty as dependent variable, we only needed 1600 individuals aged 50+ in order to detect an association between socio-economic position and frailty at a significance level of 0.05 and with 80% power. Therefore we found it feasible to perform this study when more than 7000 individuals aged 50+ were included, even though the LOFUS study is still recruiting.

Statistical Analysis

For associations of frailty phenotype with demographic and health characteristics, and hospital contacts, the p-trend values based on the Cochran-Mantel-Haenszel test was used, using the cmh function in STATA/SE 15.1. For associations between frailty phenotype and mortality, the Cox proportional hazard regression model, using length of follow-up as the time metric, estimated hazard ratios (HRs) and 95% confidence intervals (95% CI). The Cox model was adjusted for age group and sex.

Patient and public involvement

Patients and public were not involved in the development of this study.

Ethics

LOFUS (SJ-421) as well as the present sub-study on frailty (SJ-486) was approved by Region Zealand's Ethical Committee on Health Research. The Danish Protection Agency approved the LOFUS study (REG-24-2015). LOFUS is registered in Clinical Trials (NCT02482896).

Results

Of a total of 7,992 individuals 50+ years old, 656 (12.2%) were excluded as they did not answer the questions on frailty. Nine individuals were considered not available for frailty measurement as they had three or more missing frailty components, leaving 7,327 individuals for analysis. Of these, 6.5% had ≥3 frailty components, 46.7% had 1-2 components and 46.8% had none. The most frequent frailty component was exhaustion (41.5%), followed by slowness (12.8%), and low activity (12.2%) (Table 1). Overall, 55.8 % reported "good" self-assessed health and 93.6% never had difficulty in making ends meet (Table 2).

Table 1: Prevalence of phenotype frailty components

		Total (n=7,327)	Men (n=3,498)	Women (n=3,829)
Frequency of frailty components	Exhaustion	41.5	38.8	43.9
	Shrinking	6.3	5.0	7.5
	Weakness	8.2	8.1	8.2
	Slowness	12.8	11.8	13.8
	Low activity	12.2	11.1	13.1
Number of frailty components	0	46.8	49.7	44.2
	1	33.8	32.9	34.6
	2	12.9	11.8	13.9
	3	4.7	4.4	4.9
	4	1.7	1.1	2.1
	5	0.1	0.1	0.2

Table 2: Association of demographic and health characteristics with frailty phenotype.

Factors		Total 7,327 (%)	Non-frail 3,432 (%)	Prefrail 3,419 (%)	Frail 476 (%)	Trend, *p* value	Age adjusted trend, *p* value
Age	50-65	3,749 (51.2)	1,673 (48.8)	1,900 (55.6)	176 (37.0)	<0.0001	
	65-74	2,578 (35.2)	1,399 (40.8)	1,017 (29.7)	162 (34.0)		
	75-84	892 (12.2)	342 (10.0)	441 (12.9)	109 (22.9)		
	85+	108 (1.5)	18 (0.5)	61 (1.8)	29 (6.1)		
Sex	Female	3,829 (52.3)	1,693 (49.3)	1,859 (54.4)	277 (58.2)	<0.0001	<0.0001
	Male	3,498 (47.7)	1,739 (50.7)	1,560 (45.6)	199 (41.8)		
Education	Primary school	816 (11.1)	295 (8.6)	429 (12.6)	92 (19.3)	<0.0001	<0.0001
	Short (1-3 years)	4,197 (57.3)	1,987 (57.9)	1,959 (57.3)	251 (52.7)		
	Medium (3-4 years)	1,465 (20.0)	737 (21.5)	659 (19.3)	69 (14.5)		
	Long (>4 years)	301 (4.1)	162 (4.7)	127 (3.7)	12 (2.5)		
Self-assessed health	Very good	838 (11.5)	626 (18.3)	203 (6.0)	9 (1.9)	<0.0001	<0.0001
	Good	4,077 (55.8)	2,337 (68.2)	1,661 (48.7)	79 (16.7)		
	Fair	2,048 (28.0)	450 (13.1)	1,326 (38.9)	272 (57.6)		
	Bad	310 (4.2)	13 (0.4)	198 (5.8)	99 (21.0)		
	Very bad	32 (0.4)	0 (0.0)	19 (0.6)	13 (2.8)		
Difficulty in making ends meet	Never	6,813 (93.6)	3,290 (96.4)	3,122 (92.1)	401 (84.4)	<0.0001	<0.0001
	A few months	353 (4.9)	101 (3.0)	200 (5.9)	52 (11.0)		
	Approximately half of a year's months	54 (0.7)	9 (0.3)	31 (0.9)	14 (3.0)		
	Every month	58 (0.8)	13 (0.4)	37 (1.1)	8 (1.7)		
Chronic diseases	Myocardial infarction	296 (4.0)	96 (2.8)	161 (4.7)	39 (8.2)	<0.0001	<0.0001
	Angina	241 (3.3)	56 (1.6)	132 (3.9)	53 (11.1)	<0.0001	<0.0001
	Migraine or headache	842 (11.5)	234 (6.8)	516 (15.1)	92 (19.3)	<0.0001	<0.0001
	Arthritis	2,849 (38.9)	1,025 (29.9)	1,538 (45.0)	286 (60.1)	<0.0001	<0.0001
	Cancer	379 (5.2)	137 (4.0)	193 (5.6)	49 (10.3)	<0.0001	<0.0001
	Diabetes	525 (7.2)	154 (4.5)	285 (8.3)	86 (18.1)	<0.0001	<0.0001

	Hypertension	2,425 (33.1)	969 (28.2)	1,227 (35.9)	229 (38.1)	<0.0001	<0.0001
	Respiratory disease*	429 (5.9)	100 (2.9)	234 (6.8)	95 (20.0)	<0.0001	<0.0001
	Depression	548 (7.5)	104 (3.1)	331 (9.7)	113 (23.7)	<0.0001	<0.0001
	Anxiety	426 (5.8)	92 (2.7)	256 (7.5)	78 (16.4)	<0.0001	<0.0001
	Kidney disease	122 (1.7)	31 (0.9)	66 (1.9)	25 (5.3)	<0.0001	<0.0001
	Asthma	425 (5.8)	135 (3.9)	225 (6.6)	65 (13.7)	<0.0001	<0.0001
	Dementia	21 (0.3)	4 (0.12)	13 (0.4)	4 (0.8)	0.01	0.03
	Parkinson's disease	45 (0.6)	18 (0.5)	23 (0.7)	4 (0.8)	0.59	0.72
Chronic diseases	0	2,238 (30.5)	1,408 (41.0)	793 (23.2)	37 (7.8)	<0.0001	<0.0001
	1	2,415 (33.0)	1,214 (35.4)	1,106 (32.4)	95 (20.0)		
	2	1,537 (21.0)	569 (16.6)	845 (24.7)	123 (25.8)		
	3-4	971 (13.3)	224 (6.5)	585 (17.1)	162 (34.0)		
	≥5	166 (2.3)	17 (0.5)	90 (2.6)	59 (12.4)		

Those who were frail were older and more likely female than those who were non-frail or prefrail. There was a step-wise decrease in education level and self-assessed health and a stepwise increase in difficulty in making ends meet and number of hospital contacts and hospital admissions with increasing frailty status, p<0.0001 for each comparison. Notably, 14.7% of those who were frail had no hospital contacts (table 3).

Table 3: Association between number of hospital contacts and frailty status

Category		Total 7,327 (%)	Non-frail 3,432 (%)	Pre-frail 3,419 (%)	Frail 476 (%)	Trend, *p* value	Age adjusted trend, *p* value
Ambulatory contacts							
	0	3,088 (42.2)	1,628 (47.4)	1,312 (38.4)	148 (31.1)	<0.0001	<0.0001
	<5	3,893 (53.1	1,696 (49.4)	1,908 (55.8)	289 (60.7)		
	5-10	335 (4.6)	105 (3.1)	193 (5.6)	37 (7.8)		
	>10	11 (0.2)	<5	6 (0.2)	<5		
Hospital admissions							
	0	3,471 (47.4)	1,865 (53.3)	1,470 (43.0)	136 (28.6)	<0.0001	<0.0001
	<5	2,987 (40.8)	1,299 (37.9)	1,464 (42.8)	224 (47.1)		
	5-10	727 (9.9)	235 (6.9)	402 (11.8)	90 (18.9)		
	>10	142 (1.9)	33 (1.0)	83 (2.4)	26 (5.5)		
Hospital stay, number of days							
	0	3,471 (47.4)	1,865 (54.3)	1,470 (43.0	136 (28.6)	<0.0001	<0.0001
	<5	2,329 (31.8)	1,062 (30.9)	1,121 (32.8)	146 (30.7)		
	5-10	889 (12.1)	324 (9.4)	473 (13.8)	92 (19.3)		
	>10	638 (8.7)	181 (5.3)	355 (10.4)	102 (21.4)		

Frail persons had significantly higher prevalence of myocardial infarction, angina, migraine or headache, cancer, diabetes, hypertension, respiratory disease, depression, anxiety, kidney disease, asthma, and dementia. Notably, 7.8% of those who were frail had none of these chronic diseases and 20.0% had just

one which were: 43.2% arthritis, 21.1% hypertension, 8.4% migraine or headache, 7.4% cancer, 6.3% respiratory disease, and 5.3% depression. The remaining chronic diseases were each represented by less than 2.5%. Figure 1 shows the overlap between frailty and comorbidity.

Mean follow-up time was 1.13 years for all-cause mortality, giving a total of 8,314,568 person-years and 49 deaths (0.7%). Compared to individuals who were non-frail, mortality was higher among those who were prefrail (HR: 2.90; 95% CI: 1.30-6.43) or frail (HR: 8.21; 95% CI: 3.37-20.0) (Table 4).

Table 4: Frailty status and mortality

	Number of deaths	Mortality HR 95%CI*
Non-Frail (reference group)	8	1.00
Pre-frail	26	2.90 (1.30-6.43)
Frail	15	8.21 (3.37-20.0)

Discussion

In this study we aimed at examining whether the frailty measurement used in a Danish population study was able to identify frail individuals. The frailty instrument used is based on the criteria characterizing the frailty phenotype described by Fried et al.[2] Our frailty measurement builds on the work by Santo-Eggimann et al., which showed that a subset of questions in the Senior Health and Aging Study in Europe could be operationalized as a frailty measurement.[8] Romero-Ortuno et al. further developed this approach into the SHARE-FI and validated this instrument in several studies.[9,19-21] . The frailty items used in LOFUS were almost identical to those included in SHARE-FI..

We have examined to what degree our frailty meaurement was associated with factors already known to be associated with frailty: age, sex, multi morbidity, level of education, income insufficiency, self-assessed health, and mortality.

Higher levels of education and income sufficiency were protective factors. Being female, of higher age, and having more comorbidity were associated with increasing frailty. These findings are in agreement with a

large number of other frailty studies.[2,16]. Due to present lack of follow up data, we could not test the predictive value concerning morbidity. We therefore decided to examine the association between frailty and number of hospitalizations in a 2 year period previously to the frailty measurement and found a significant trend with an increasing number of hospital contacts with increasing frailty. We only had a short follow up period to examine mortality (1.13 years) but in spite of this, there was a significant increasing mortality rate with increasing frailty.

Overall we found the prevalence of frailty to be 6.5%. In the age group 50-64 it was 4.7% and in the 65+ it was 8.4%. This is an overall lower prevalence and a different pattern than what was seen in the group of Danish SHARE participants, in which the overall prevalence was 8.8%, in the 50-64 years 3%, and in the 65+ years old 12.4%. The explanation might be that our study is taking place in a rural area with a relatively high proportion of socioeconomically deprived individuals in the younger age groups, while the Danish participants in SHARE were drawn randomly in order to select a representative sample of Danes from the whole country in these age groups. The population covered by LOFUS compared to the general Danish population has lower income, less education, higher burden of disease, higher prevalence of unhealthy lifestyle factors, and an average life expectancy approximately two years lower than mean average life expectancy in Denmark (80.8 years).[12]This could result in higher prevalence of frailty in the youngest age groups due to high burden of risk factors, and a lower prevalence in the older age groups due to selection leading to a healthy survivor effect.[22]

The overall lower prevalence compared to SHARE might also be explained by characteristics of non-respondents in LOFUS. Halfway through the LOFUS data collection subjects with lower socio-economic status and age above 80 were found to have lower participation rates compared to more well off and younger age groups (article in press). This implicates that our study may underestimate the prevalence of frailty.

The prevalence of 0, 1, 2, 3, 4, or 5 frailty criteria was very similar to the findings by Fried et al.[2] The distribution of prevalence of the single frailty criteria has been differing in several studies. In our study, we

found a very high prevalence of exhaustion 41,5% versus 17% in the study by Fried et al.[2] and 27% in the cross European study by Santos-Eggimann et al.[8] The way we measured exhaustion was exactly the same way as Santos-Eggiman by asking: “In the last month or so, have you had too little energy to do things you wanted to do?” and in case of a “Yes” this criteria was considered fulfilled. Fried et al. used a more detailed report from the participants based on answers from 2 items from the modified 10-item Centre for Epidemiology Studies Depression Scale[23] and this may explain some of the rather large difference in prevalence of the exhaustion criteria. We found a distribution of prevalence for the criteria slowness, weakness, and physical activity similar to the findings by Eggimann et al. but again somewhat different from the findings by Fried et al. This may be due to the fact that Fried et al. defined the cut-off values for these frailty criteria according to the population assessed by defining the criteria fulfilled if the values were included in the lowest quintile of the study sample distribution. Bouzòn et al. recently showed that the standardization to the population assessed makes a difference for the predictive ability of the frailty diagnosis.[24]

Strengths and limitations

Our study is a large population study with a representative sample for the geographical area covered by LOFUS. At the present LOFUS is a cross-sectional study, however due to the national health registries we were able to follow the participants over a time period. The Danish registries are of high quality and the unique personal identification numbers of all Danish inhabitants made it possible to include valid data concerning morbidity (hospital contacts) and mortality.[25] Due to the present lack of follow up data concerning morbidity we had to assess hospital contacts in a period before the frailty measurement instead of assessing the predictive ability concerning hospital contacts. However, frailty is considered a syndrome developing over time and not evolving as an acute event. We therefore consider the findings of association with previous hospital contacts equally valuable compared to an association with future hospital contacts.

Conclusion

We have described a frailty instrument that has only minor deviations from the frailty instrument developed in a large European population study, SHARE (SHARE-FI). Our frailty instrument shows the same characteristics as the SHARE-FI and other validated frailty measures concerning associations with sex, age, income insufficiency, education, comorbidity, self-assessed health, multimorbidity, and mortality. Based on these findings we consider our frailty measure a valid instrument.

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Author contribution:

Jacobsen KK made substantial contributions in designing and performing the statistical analysis. Jepsen R and Lembeck M contributed in interpretation of data analysis. Nielsson CJ contributed to the design of the study and interpretation of data, and Holm EA contributed to design of the study and interpretation of data analysis and made the first draft of the article. All authors performed critical revision of the article draft and all authors approved the final version. All authors agree to be accountable for all aspects of the work.

Competing interest

Non of the authors have reported competing interests.

Data sharing statement

The authors are not in a position to share the data, since we have used registry data from a population study and from national registries. We do not own the data used.

Figure legend

Figure 1. Venn diagram displaying extent of overlap of frailty with multi morbidity (≥2 chronic diseases) in the Lolland Falster Health Study. Total represented by 2,674 individuals with frailty and/or multi morbidity.

Percentages are percentages of individuals with frailty (n=476). Frailty is based on the criteria characterizing the frailty phenotype described by Fried et al. (2).

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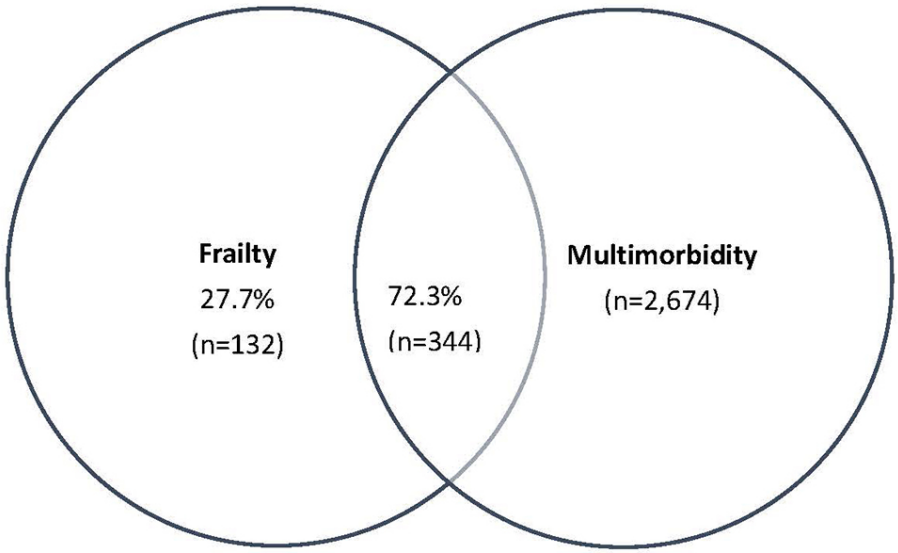

Figure 1. Venn diagram displaying extent of overlap of frailty with multi morbidity (≥2 chronic diseases) in the Lolland Falster Health Study. Total represented by 2,674 individuals with frailty and/or multi morbidity. Percentages are percentages of individuals with frailty (n=476). Frailty is based on the criteria characterizing the frailty phenotype described by Fried et al. (2).

90x90mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(e) Describe any sensitivity analyses

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Associations between the SHARE frailty phenotype and common frailty characteristics: evidence from a large Danish population study

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Associations between the SHARE frailty phenotype and common frailty characteristics: evidence from a large Danish population study

Katja K. Jacobsen, Ph.D. Department of Technology, Faculty of Health and Technology, University College Copenhagen, and Lolland-Falster Health Study, Center for Epidemiological Research, Nykøbing Falster Hospital.

Randi Jepsen, Ph.D., MSc, RN, Project manager, Lolland-Falster Health Study, Center for Epidemiological Research, Nykøbing Falster Hospital.

Maurice Lembeck, MD, Consultant at the Medical Department, Nykøbing Falster Hospital

Charlotte J. Nilsson, MD, Ph.d., Associate professor at Section of Social Medicine, Department of Public Health, University of Copenhagen

Ellen A. Holm, MD, Consultant at the Medical Department, Nykøbing Falster Hospital, Associated clinical professor at the University of Copenhagen.

Responsible for correspondence: Ellen Holm, Medical Department, Nykøbing Falster Hospital, Fjordvej 15, 4800 Nykøbing Falster. E-mail: ellh@regionsjaelland.dk

Abstract

Objectives: Frailty is a major clinical geriatric syndrome associated with serious adverse events including functional disability, falls, hospitalization, increased morbidity, and mortality. The aim of this study was to study associations between a frailty phenotype and frailty characteristics well known from the literature.

Design: Registry based cross sectional study

Setting: The target population consists of inhabitants above the age of 50 living in the Danish municipalities of Lolland and Guldborgsund. Excluded are incapacitated people, inhabitants unable to understand Danish or English and inhabitants without a permanent residence.

Participants: 7,327 individuals aged 50+ years were included.

Outcome measures: We examined associations between the frailty measurement and factors known to be associated with frailty: sex, age, income insufficiency, education, comorbidity, self-assessed health, morbidity, and mortality.

Results: 7,327 individuals aged 50+ years were included. Of these, 6.5% had ≥3 frailty components (frail), 46.7% had 1-2 components (prefrail) and 46.9% had none (non-frail). Those who were frail were older and more likely female than those who were non-frail or prefrail. There was a step-wise decrease in educational level, and in self-assessed health with increasing frailty status, and a stepwise increase in difficulty in making ends meet, number of hospital contacts, and mortality with increasing frailty status, $p<0.0001$ for each comparison. Compared to individuals who were non-frail, mortality was higher among those who were prefrail (HR: 2.90; 95% CI: 1.30-6.43) or frail (HR: 8.21; 95% CI: 3.37-20.0).

Conclusions: Based on these findings we consider the LOFUS frailty assessment a valid instrument demonstrating the same characteristics as other validated frailty measures concerning associations with sex, age, income insufficiency, education, comorbidity, self-assessed health, morbidity, and mortality.

Keywords: frailty, physical functional performance, healthy ageing

Strengths and limitations of this study

- The frailty measurement studied has only minor deviations from a widely recognized instrument used in the Senior Health and Retirement study in Europe (SHARE)
- The frailty measurement was studied in a large representative population
- The LOFUS study is cross sectional but by coupling with national registries, we were able to follow the participants over time.
- Due to lack of follow up data concerning morbidity, we assessed associations between morbidity and frailty by using data on morbidity during a period of 6 months before the frailty measurement

Background

Frailty is a major clinical geriatric syndrome associated with serious adverse outcomes including functional disability, falls, hospitalization, increased morbidity, and mortality. The pathophysiology of frailty includes age-related decline in the function of multiple organ systems leading to insufficient homeostatic mechanisms and thereby increased vulnerability to minor stressor events.[1] Two principally different approaches are used in order to operationalize the measurement of frailty. Linda Fried et al. described a physical frailty phenotype based on five criteria including exhaustion (fatigue), weight loss (unintentional), weakness, slowness, and low activity. Individuals fulfilling three or more of the five criteria are defined as frail and individuals fulfilling 1-2 as prefrail.[2] If an individual is frail according to the physical frailty phenotype, it is not necessarily obvious without measurement of the five included criteria. In contrast, Mitnitski et al. described frailty as an accumulation of health deficits occurring with aging and operationalized this approach in the frailty index.[3] A frailty index consists of a predefined list of deficits. The proportion of deficits present in a specific person defines the frailty index. If for instant the chosen list of deficits consists of 50 items, of which the individual has 10, the frailty index of this individual is 10/50=0.2. The frailty index includes traditional health items like medical diagnoses but also other factors describing

cognitive function, social circumstances, and functional loss. Although there is thus no universally accepted operational definition of frailty, the Fried frailty phenotype is widely used and validated in several studies.[4-7]

The Senior Health in Aging and Retirement study in Europe (SHARE) is a population study including questions, which have been used to develop a Share-Frailty Instrument (SHARE-FI).[8,9]Validation studies have demonstrated that SHARE-FI is associated with mortality[9] and with loss of functional capacity.[10]

The SHARE study included in its first wave 1699 Danish citizens above the age of 50. These participants were drawn by the Danish National Institute of Statistics in order to reflect the Danish population. The SHARE questionnaires were translated into Danish following recommendations from the SHARE organization.[11] The questions used in the SHARE-FI were chosen retrospectively based on their similarity to the items in the frailty phenotype originally developed by Fried et al.[8]

The Danish population study, the Lolland-Falster Health Study (LOFUS)[12] includes frailty items almost the same as those used in the SHARE-FI.

Epidemiology, morbidity, and mortality associated with frailty

A systematic review found the prevalence of frailty among individuals aged 65+ varying between 4 and 59.1% with an overall weighted prevalence of 10.7%. Prevalence increased with age and was higher in women.[13] The prevalence of frailty in Europe among 7,510 participants aged 65+ enrolled in SHARE 2004 varied between 8.6% (Sweden) and 27.3% (Spain). The prevalence among 877 Danish participants aged 50-64 years was 3.0% and among 635 participants aged 65+ 12.4%.[8]

Two metaanalyses including studies using the Fried phenotype found significant higher hospitalization risk in frail compared to non-frail elderly individuals (OR 1.49, CI 1.26 -1.76),[14] and significant increased mortality (HR 1.874, CI 1.635-2.150).[15]

Objectives

The aim of this study was to examine whether the frailty measurement used in LOFUS was able to identify frail individuals. We did this by examining to what degree the frailty measurement is associated with factors known to be associated with frailty: age, sex, multi morbidity, level of education, income insufficiency, self-assessed health, morbidity, and mortality.[2,16]

Design and participants

LOFUS has been described in detail elsewhere.[12] In summary, it is a household-based cross-sectional study including people of all ages. Lolland-Falster consists of two islands in the southern part of Denmark. It is a rural area where income is lower and life expectancy shorter than in the general Danish population. The target population for the present sub-study consists of inhabitants above the age of 50 living in the Danish municipalities of Lolland and Guldborgsund. Excluded are incapacitated people, inhabitants unable to understand Danish or English and inhabitants without a permanent residence.

The data collection started in February 2016 and is still ongoing; with currently 7,992 individuals aged 50+ years recruited.

Methods

Frailty

LOFUS includes the following variables used to assess frailty:

1) Exhaustion/Fatigue: the criterion was fulfilled by answering yes in response to the question “In the last month or so, have you had too little energy to do things you wanted to do?” (Yes/No)
2) Shrinking: the criterion was fulfilled by answering yes in response to the question “What has your appetite been like? Do you feel a diminution in desire for food?” (Yes/No)

3) Weakness was derived from the highest of three consecutive dynamometer measurements of handgrip strength in the dominant hand applying gender and body mass index cutoffs set by Fried et al.[2]
4) Slowness: A positive answer to either of the following two items " Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 meters" or "climbing one flight of stairs without resting"
5) Low activity was fulfilled in participants responding one to three times a month, hardly ever, or never to the question "How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?"

Individuals fulfilling 1-2 of the above mentioned criteria were characterized as prefrail while those fulfilling 3-5 criteria were characterized as frail. If none of the criteria were fulfilled individuals were characterized as non-frail.

Factors assessed for association with frailty, data from LOFUS

The following factors were extracted from the LOFUS questionnaires: Age, sex, self-assessed health, educational background, financial difficulties, comorbidity, and mortality. Educational level was categorized according to highest obtained education into four categories: "Primary school", "Short education", "Medium higher education", and "Long higher education".

Comorbidity was assessed by asking participants if they suffered from angina, migraine or headache, arthritis, cancer, diabetes, hypertension, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, depression, anxiety, kidney disease, asthma, dementia, or Parkinson's disease. Socioeconomic status was assessed by the question "During the last twelve months, how often did you find difficulty in making ends meet?"

Data from national health registers

Every person residing in Denmark is uniquely registered in the Danish Civil Registration System (CRS).[17] The LOFUS database receives daily updates from CRS on all inhabitants of Lolland-Falster regarding births, deaths, immigration, and moving of residents. Individuals were followed up in CRS until date of death or February 2019. Additionally, we assessed data on hospitalization by merging the LOFUS database with the Danish National Patient Register.[18]

Number of hospital contacts was defined as hospital contacts within 2 years prior to the date of participation in LOFUS. Hospital contacts were categorized as no admission days registered in the National Patient Register (ambulant contacts) or admission days registered (hospital admission).

Sample size

For the sub-study on aging-related outcomes in LOFUS, that is among the 50+ year-olds, the original idea was to study the association between social factors (socioeconomic position and social relations respectively) and physical function and frailty. Initially we performed power calculations for all social variables in relation to detection of their impact on physical function as well as frailty. The prevalence estimates used in these power calculations were calculated from previous Danish population surveys applying similar measures, and previous literature[16,19,20]. Based on these calculations we requested inclusion of 5800 individuals aged 50+, in order to detect an association between *each* of the social variables and physical function *or* frailty at a significance level of 0.05 and with 80% power. However, based on the power calculations performed for frailty as dependent variable, we only needed 1600 individuals aged 50+ in order to detect an association between socio-economic position and frailty at a significance level of 0.05 and with 80% power. Therefore we found it feasible to perform this study when more than 7000 individuals aged 50+ were included, even though the LOFUS study is still recruiting.

Statistical Analysis

For associations of frailty phenotype with demographic and health characteristics, and hospital contacts, the p-trend values based on the Cochran-Mantel-Haenszel test was used, using the cmh function in STATA/SE 15.1. For associations between frailty phenotype and mortality, the Cox proportional hazard regression model, using length of follow-up as the time metric, estimated hazard ratios (HRs) and 95% confidence intervals (95% CI). The Cox model was adjusted for age group and sex.

Patient and public involvement

Patients and public were not involved in the development of this study.

Ethics

LOFUS (SJ-421) as well as the present sub-study on frailty (SJ-486) was approved by Region Zealand's Ethical Committee on Health Research. The Danish Protection Agency approved the LOFUS study (REG-24-2015). LOFUS is registered in Clinical Trials (NCT02482896).

Results

Of a total of 7,992 individuals 50+ years old, 656 (12.2%) were excluded as they did not answer the questions on frailty. Nine individuals were considered not available for frailty measurement as they had three or more missing frailty components, leaving 7,327 individuals for analysis. Of these, 6.5% had ≥3 frailty components, 46.7% had 1-2 components and 46.8% had none. The most frequent frailty component was exhaustion (41.5%), followed by slowness (12.8%), and low activity (12.2%) (Table 1). Overall, 55.8 % reported "good" self-assessed health and 93.6% never had difficulty in making ends meet (Table 2).

Table 1: Prevalence of phenotype frailty components

		Total (n=7,327)	Men (n=3,498)	Women (n=3,829)
Frequency of frailty components	Exhaustion	41.5	38.8	43.9
	Shrinking	6.3	5.0	7.5
	Weakness	8.2	8.1	8.2
	Slowness	12.8	11.8	13.8
	Low activity	12.2	11.1	13.1
Number of frailty components	0	46.8	49.7	44.2
	1	33.8	32.9	34.6
	2	12.9	11.8	13.9
	3	4.7	4.4	4.9
	4	1.7	1.1	2.1
	5	0.1	0.1	0.2

Table 2: Association of demographic and health characteristics with frailty phenotype.

Factors		Total 7,327 (%)	Non-frail 3,432 (%)	Prefrail 3,419 (%)	Frail 476 (%)	Trend, *p* value	Age adjusted trend, *p* value
Age	50-65	3,749 (51.2)	1,673 (48.8)	1,900 (55.6)	176 (37.0)	<0.0001	
	65-74	2,578 (35.2)	1,399 (40.8)	1,017 (29.7)	162 (34.0)		
	75-84	892 (12.2)	342 (10.0)	441 (12.9)	109 (22.9)		
	85+	108 (1.5)	18 (0.5)	61 (1.8)	29 (6.1)		
Sex	Female	3,829 (52.3)	1,693 (49.3)	1,859 (54.4)	277 (58.2)	<0.0001	<0.0001
	Male	3,498 (47.7)	1,739 (50.7)	1,560 (45.6)	199 (41.8)		
Education	Primary school	816 (11.1)	295 (8.6)	429 (12.6)	92 (19.3)	<0.0001	<0.0001
	Short (1-3 years)	4,197 (57.3)	1,987 (57.9)	1,959 (57.3)	251 (52.7)		
	Medium (3-4 years)	1,465 (20.0)	737 (21.5)	659 (19.3)	69 (14.5)		
	Long (>4 years)	301 (4.1)	162 (4.7)	127 (3.7)	12 (2.5)		
Self-assessed health	Very good	838 (11.5)	626 (18.3)	203 (6.0)	9 (1.9)	<0.0001	<0.0001
	Good	4,077 (55.8)	2,337 (68.2)	1,661 (48.7)	79 (16.7)		
	Fair	2,048 (28.0)	450 (13.1)	1,326 (38.9)	272 (57.6)		
	Bad	310 (4.2)	13 (0.4)	198 (5.8)	99 (21.0)		
	Very bad	32 (0.4)	0 (0.0)	19 (0.6)	13 (2.8)		
Difficulty in making ends meet	Never	6,813 (93.6)	3,290 (96.4)	3,122 (92.1)	401 (84.4)	<0.0001	<0.0001
	A few months	353 (4.9)	101 (3.0)	200 (5.9)	52 (11.0)		
	Approximately half of a year's months	54 (0.7)	9 (0.3)	31 (0.9)	14 (3.0)		
	Every month	58 (0.8)	13 (0.4)	37 (1.1)	8 (1.7)		
Chronic diseases	Myocardial infarction	296 (4.0)	96 (2.8)	161 (4.7)	39 (8.2)	<0.0001	<0.0001
	Angina	241 (3.3)	56 (1.6)	132 (3.9)	53 (11.1)	<0.0001	<0.0001
	Migraine or headache	842 (11.5)	234 (6.8)	516 (15.1)	92 (19.3)	<0.0001	<0.0001
	Arthritis	2,849 (38.9)	1,025 (29.9)	1,538 (45.0)	286 (60.1)	<0.0001	<0.0001
	Cancer	379 (5.2)	137 (4.0)	193 (5.6)	49 (10.3)	<0.0001	<0.0001
	Diabetes	525 (7.2)	154 (4.5)	285 (8.3)	86 (18.1)	<0.0001	<0.0001

	Hypertension	2,425 (33.1)	969 (28.2)	1,227 (35.9)	229 (48.1)	<0.0001	<0.0001
	Respiratory disease*	429 (5.9)	100 (2.9)	234 (6.8)	95 (20.0)	<0.0001	<0.0001
	Depression	548 (7.5)	104 (3.1)	331 (9.7)	113 (23.7)	<0.0001	<0.0001
	Anxiety	426 (5.8)	92 (2.7)	256 (7.5)	78 (16.4)	<0.0001	<0.0001
	Kidney disease	122 (1.7)	31 (0.9)	66 (1.9)	25 (5.3)	<0.0001	<0.0001
	Asthma	425 (5.8)	135 (3.9)	225 (6.6)	65 (13.7)	<0.0001	<0.0001
	Dementia	21 (0.3)	4 (0.12)	13 (0.4)	4 (0.8)	0.01	0.03
	Parkinson's disease	45 (0.6)	18 (0.5)	23 (0.7)	4 (0.8)	0.59	0.72
Chronic diseases	0	2,238 (30.5)	1,408 (41.0)	793 (23.2)	37 (7.8)	<0.0001	<0.0001
	1	2,415 (33.0)	1,214 (35.4)	1,106 (32.4)	95 (20.0)		
	2	1,537 (21.0)	569 (16.6)	845 (24.7)	123 (25.8)		
	3-4	971 (13.3)	224 (6.5)	585 (17.1)	162 (34.0)		
	≥5	166 (2.3)	17 (0.5)	90 (2.6)	59 (12.4)		

Those who were frail were older and more likely female than those who were non-frail or prefrail. There was a step-wise decrease in education level and self-assessed health and a stepwise increase in difficulty in making ends meet and number of hospital contacts and hospital admissions with increasing frailty status, p<0.0001 for each comparison. Notably, 14.7% of those who were frail had no hospital contacts (table 3).

Table 3: Association between number of hospital contacts and frailty status

Category		Total 7,327 (%)	Non-frail 3,432 (%)	Pre-frail 3,419 (%)	Frail 476 (%)	Trend, *p* value	Age adjusted trend, *p* value
Ambulatory contacts							
	0	3,088 (42.2)	1,628 (47.4)	1,312 (38.4)	148 (31.1)	<0.0001	<0.0001
	<5	3,893 (53.1	1,696 (49.4)	1,908 (55.8)	289 (60.7)		
	5-10	335 (4.6)	105 (3.1)	193 (5.6)	37 (7.8)		
	>10	11 (0.2)	<5	6 (0.2)	<5		
Hospital admissions							
	0	3,471 (47.4)	1,865 (53.3)	1,470 (43.0)	136 (28.6)	<0.0001	<0.0001
	<5	2,987 (40.8)	1,299 (37.9)	1,464 (42.8)	224 (47.1)		
	5-10	727 (9.9)	235 (6.9)	402 (11.8)	90 (18.9)		
	>10	142 (1.9)	33 (1.0)	83 (2.4)	26 (5.5)		
Hospital stay, number of days							
	0	3,471 (47.4)	1,865 (54.3)	1,470 (43.0	136 (28.6)	<0.0001	<0.0001
	<5	2,329 (31.8)	1,062 (30.9)	1,121 (32.8)	146 (30.7)		
	5-10	889 (12.1)	324 (9.4)	473 (13.8)	92 (19.3)		
	>10	638 (8.7)	181 (5.3)	355 (10.4)	102 (21.4)		

Frail persons had significantly higher prevalence of myocardial infarction, angina, migraine or headache, cancer, diabetes, hypertension, respiratory disease, depression, anxiety, kidney disease, asthma, and dementia. Notably, 7.8% of those who were frail had none of these chronic diseases and 20.0% had just

one which were: 43.2% arthritis, 21.1% hypertension, 8.4% migraine or headache, 7.4% cancer, 6.3% respiratory disease, and 5.3% depression. The remaining chronic diseases were each represented by less than 2.5%. Figure 1 shows the overlap between frailty and comorbidity.

Mean follow-up time was 1.13 years for all-cause mortality, giving a total of 8,314,568 person-years and 49 deaths (0.7%). Compared to individuals who were non-frail, mortality was higher among those who were prefrail (HR: 2.90; 95% CI: 1.30-6.43) or frail (HR: 8.21; 95% CI: 3.37-20.0) (Table 4).

Table 4: Frailty status and mortality

	Number of deaths	Mortality HR 95%CI*
Non-Frail (reference group)	8	1.00
Pre-frail	26	2.90 (1.30-6.43)
Frail	15	8.21 (3.37-20.0)

Discussion

In this study we aimed at examining whether the frailty measurement used in a Danish population study was able to identify frail individuals. The frailty instrument used is based on the criteria characterizing the frailty phenotype described by Fried et al.[2] Our frailty measurement builds on the work by Santo-Eggimann et al., which showed that a subset of questions in the Senior Health and Aging Study in Europe could be operationalized as a frailty measurement.[8] Romero-Ortuno et al. further developed this approach into the SHARE-FI and validated this instrument in several studies.[9,21-23] . The frailty items used in LOFUS were almost identical to those included in SHARE-FI..

We have examined to what degree our frailty meaurement was associated with factors already known to be associated with frailty: age, sex, multi morbidity, level of education, income insufficiency, self-assessed health, and mortality.

Higher levels of education and income sufficiency were protective factors. Being female, of higher age, and having more comorbidity were associated with increasing frailty. These findings are in agreement with a

large number of other frailty studies.[2,16]. Due to present lack of follow up data, we could not test the predictive value concerning morbidity. We therefore decided to examine the association between frailty and number of hospitalizations in a 2 year period previously to the frailty measurement and found a significant trend with an increasing number of hospital contacts with increasing frailty. We only had a short follow up period to examine mortality (1.13 years) but in spite of this, there was a significant increasing mortality rate with increasing frailty.

Overall we found the prevalence of frailty to be 6.5%. In the age group 50-64 it was 4.7% and in the 65+ it was 8.4%. This is an overall lower prevalence and a different pattern than what was seen in the group of Danish SHARE participants, in which the overall prevalence was 8.8%, in the 50-64 years 3%, and in the 65+ years old 12.4%. The explanation might be that our study is taking place in a rural area with a relatively high proportion of socioeconomically deprived individuals in the younger age groups, while the Danish participants in SHARE were drawn randomly in order to select a representative sample of Danes from the whole country in these age groups. The population covered by LOFUS compared to the general Danish population has lower income, less education, higher burden of disease, higher prevalence of unhealthy lifestyle factors, and an average life expectancy approximately two years lower than mean average life expectancy in Denmark (80.8 years).[12]This could result in higher prevalence of frailty in the youngest age groups due to high burden of risk factors, and a lower prevalence in the older age groups due to selection leading to a healthy survivor effect.[24]

The overall lower prevalence compared to SHARE might also be explained by characteristics of non-respondents in LOFUS. Halfway through the LOFUS data collection subjects with lower socio-economic status and age above 80 were found to have lower participation rates compared to more well off and younger age groups (article in press). This implicates that our study may underestimate the prevalence of frailty.

The prevalence of 0, 1, 2, 3, 4, or 5 frailty criteria was very similar to the findings by Fried et al.[2] The distribution of prevalence of the single frailty criteria has been differing in several studies. In our study, we

found a very high prevalence of exhaustion 41,5% versus 17% in the study by Fried et al.[2] and 27% in the cross European study by Santos-Eggimann et al.[8] The way we measured exhaustion was exactly the same way as Santos-Eggiman by asking: “In the last month or so, have you had too little energy to do things you wanted to do?” and in case of a “Yes” this criteria was considered fulfilled. Fried et al. used a more detailed report from the participants based on answers from 2 items from the modified 10-item Centre for Epidemiology Studies Depression Scale[25] and this may explain some of the rather large difference in prevalence of the exhaustion criteria. We found a distribution of prevalence for the criteria slowness, weakness, and physical activity similar to the findings by Eggimann et al. but again somewhat different from the findings by Fried et al. This may be due to the fact that Fried et al. defined the cut-off values for these frailty criteria according to the population assessed by defining the criteria fulfilled if the values were included in the lowest quintile of the study sample distribution. Bouzòn et al. recently showed that the standardization to the population assessed makes a difference for the predictive ability of the frailty diagnosis.[26]

Strengths and limitations

Our study is a large population study with a representative sample for the geographical area covered by LOFUS. At the present LOFUS is a cross-sectional study, however due to the national health registries we were able to follow the participants over a time period. The Danish registries are of high quality and the unique personal identification numbers of all Danish inhabitants made it possible to include valid data concerning morbidity (hospital contacts) and mortality.[27] Due to the present lack of follow up data concerning morbidity we had to assess hospital contacts in a period before the frailty measurement instead of assessing the predictive ability concerning hospital contacts. However, frailty is considered a syndrome developing over time and not evolving as an acute event. We therefore consider the findings of association with previous hospital contacts equally valuable compared to an association with future hospital contacts.

Conclusion

We have described a frailty instrument that has only minor deviations from the frailty instrument developed in a large European population study, SHARE (SHARE-FI). Our frailty instrument shows the same characteristics as the SHARE-FI and other validated frailty measures concerning associations with sex, age, income insufficiency, education, comorbidity, self-assessed health, multimorbidity, and mortality. Based on these findings we consider our frailty measure a valid instrument.

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Author contribution:

Jacobsen KK made substantial contributions in designing and performing the statistical analysis. Jepsen R and Lembeck M contributed in interpretation of data analysis. Nilsson CJ contributed to the design of the study and interpretation of data, and Holm EA contributed to design of the study and interpretation of data analysis and made the first draft of the article. All authors performed critical revision of the article draft and all authors approved the final version. All authors agree to be accountable for all aspects of the work.

Competing interest

Non of the authors have reported competing interests.

Data sharing statement

The authors are not in a position to share the data, since we have used registry data from a population study and from national registries. We do not own the data used.

Figure legend

Figure 1. Venn diagram displaying extent of overlap of frailty with multi morbidity (≥2 chronic diseases) in the Lolland Falster Health Study. Total represented by 2,674 individuals with frailty and/or multi morbidity.

Percentages are percentages of individuals with frailty (n=476). Frailty is based on the criteria characterizing the frailty phenotype described by Fried et al. (2).

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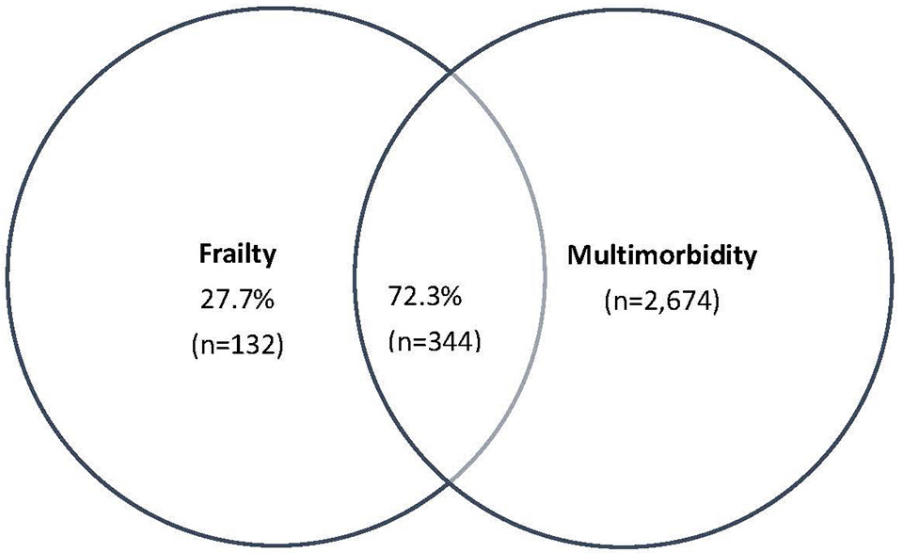

Figure 1. Venn diagram displaying extent of overlap of frailty with multi morbidity (≥2 chronic diseases) in the Lolland Falster Health Study. Total represented by 2,674 individuals with frailty and/or multi morbidity. Percentages are percentages of individuals with frailty (n=476). Frailty is based on the criteria characterizing the frailty phenotype described by Fried et al. (2).

90x90mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Not relevant
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	

(e) Describe any sensitivity analyses

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.