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PREDICTORS OF FRAILTY IN OLD AGE – RESULTS OF A LONGITUDINAL STUDY

A. HAJEK[1], C. BRETTSCHNEIDER[1], T. POSSELT[2], C. LANGE[2], S. MAMONE[3], B. WIESE[3], S. WEYERER[4], J. WERLE[4], A. FUCHS[5], M. PENTZEK[5], J. STEIN[6], T. LUCK[6], H. BICKEL[7], E. MÖSCH[7], K. HESER[8], F. JESSEN[8,9], W. MAIER[8,10], M. SCHERER[2], S.G. RIEDEL-HELLER[6,11], H.-H. KÖNIG[1,11] FOR THE AGECODE STUDY GROUP

1. Department of Health Economics and Health Services Research, Hamburg Center for Health Economics, University Medical Center Hamburg-Eppendorf, Germany; 2. Department of Primary Medical Care, Center for Psychosocial Medicine, University Medical Center, Hamburg-Eppendorf, Germany; 3. Institute of General Practice, Hannover Medical School, Germany; 4. Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Germany; 5. Institute of General Practice, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany; 6. Institute of Social Medicine, Occupational Health and Public Health, University of Leipzig, Germany; 7. Department of Psychiatry, Technical University of Munich, Germany; 8. Department of Psychiatry, University of Bonn, Germany; 9. Department of Psychiatry and Psychotherapy, University of Cologne, Germany; 10. German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; 11. These authors contributed equally to this work. Corresponding author: Dr. André Hajek, University Medical Center, Hamburg-Eppendorf, Hamburg Center for Health Economics, Department of Health Economics and Health Services Research, Telephone +49 40 7410 52877; Fax +49 40 7410 40261, E-mail: a.hajek@uke.de

Abstract: *Objectives:* To investigate time-dependent predictors of frailty in old age longitudinally. *Design:* Population-based prospective cohort study. *Setting:* Elderly individuals were recruited via GP offices at six study centers in Germany. The course of frailty was observed over 1.5 years (follow up wave 4 and follow up wave 5). *Participants:* 1,602 individuals aged 80 years and older (mean age 85.4 years SD 3.2, with mean CSHA CFS 3.5 SD 1.6) at follow up wave 4. *Measurements:* Frailty was assessed by using the Canadian Study of Health and Aging Clinical Frailty Scale (CSHA CFS), ranging from 1 (very fit) to 7 (severely frail). *Results:* Fixed effects regressions revealed that frailty increased significantly with increasing age (β=.2) as well as the occurrence of depression (β=.5) and dementia (β=.8) in the total sample. Changes in marital status and comorbidity did not affect frailty. While the effects of depression and dementia were significant in women, these effects did not achieve statistical significance in men. *Conclusion:* Our findings highlight the role of aging as well as the occurrence of dementia and depression for frailty. Specifically, in order to delay frailty in old age, developing interventional strategies to prevent depression might be a fruitful approach.

Key words: Frailty, depression, dementia, older people, longitudinal study.

Introduction

Since 1991 the term "frail elderly" has been a Medline Medical Subject Heading and is defined as "older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity". Thus, frailty can be characterized by increased vulnerability to stressors and a lack of physiological reserve (1, 2). Due to demographic ageing, the prevalence of frailty is expected to increase considerably (3). It is well-known that frailty is a major predictor of mortality (4, 5) and institutionalization [6] as well as other adverse health outcomes (5, 7–16), underlining the need for interventional strategies.

Numerous cross-sectional studies have examined factors associated with frailty (17–23). However, these studies fail to identify causal mechanisms. Longitudinal studies are needed in order to get insights into the causality. Yet, only a few studies (24–29) have investigated the predictors of frailty in old age longitudinally. Most of these studies used a static set of baseline characteristics as predictors. Thus, they could not account for changes in these characteristics. So far, only very few longitudinal (30–32) studies have investigated how changes in predictors affect frailty. Yet, in order to identify causal effects it is crucial to examine changes in predictors.

The aim of our study was to identify time-dependent factors affecting frailty in old age. Therefore, we investigated time-dependent variables which may be relevant for frailty, including sociodemographic (26, 33), psychological (25–27, 34) and cognitive factors (26, 35) as well as comorbidity (26) in a longitudinal approach. Knowledge of the factors leading to frailty in a longitudinal setting is important in order to develop strategies for prevention or delay of frailty.

Methods

Sample

Data were used from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe) which is a population based prospective cohort study. At six study centers in Germany (Leipzig, Hamburg, Dusseldorf, Mannheim, Bonn and Munich) individuals were recruited by general practitioners' (GP) offices, beginning in 2003/2004. From this time onwards, trained staff interviewed individuals as well as their proxies every 18 months. Thus, follow-up (FU) wave 5 took place in 2011/2012.

Individuals were only included in the sample, if they met three conditions at baseline (n=3,217): 75 years and older, absence of dementia and at least one contact with the GP during the last 12 months. If they met at least one of the following conditions at baseline, individuals were excluded: insufficient knowledge of the German language, consultations only via

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home visits, residence in a nursing home, severe illness the GP would deem fatal within 3 months, deafness, blindness, lack of ability to provide informed consent and irregular patient of the participating practice. Luck et al. (36) provided more details concerning the sampling frame. The study has been approved by the local ethics boards of all participating centers and written informed consent was obtained from all patients.

Since frailty was assessed from FU wave 4 upwards, we draw on two waves (FU wave 4: n=1,602; FU wave 5: n=1,307). Major reasons for lack of follow-up data were death (n=763) and refused participation (n=828).

Frailty

Frailty was assessed using the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (CFS) (37), ranging from 1 (very fit) to 7 (severely frail). The meaning of each of the seven steps of the rating scale was indicated as follows (37): 1. Very fit - robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age; 2. Well - without active disease, but less fit than people in category 1; 3. Well, with treated comorbid disease - disease symptoms are well controlled compared with those in category 4; 4. Apparently vulnerable - although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms; 5. Mildly frail - with limited dependence on others for instrumental activities of daily living; 6. Moderately frail - help is needed with both instrumental and non-instrumental activities of daily living; 7. Severely frail - completely dependent on others for the activities of daily living, or terminally ill. Thus, the trained staff considers information about mobility, function, cognition and comorbidities to assign the frailty level. It was demonstrated that the CSHA CFS is a valid measure of frailty (37).

Independent variables

As for sociodemographic variables, age, sex, education (CASMIN classification [38] with primary, secondary and tertiary education), family situation (Ref.: married; others (single, widowed, divorced)) and living situation (Ref.: living alone in private household; others (with spouse/partner, with other relatives, nursing home, assisted living, retirement home, other)) were used. Please note that the variables living situation as well as education was solely used for sample descriptions.

To assess depressive symptoms, the 15-item version of the Geriatric Depression Scale (39) was used. The scale was dichotomized (1 (= depression) if Geriatric Depression Scale ≥ 5; 0 (= no depression) otherwise).

The Global Deterioration Scale (40) (1 = no impairment to 7 = severe dementia) was used to quantify dementia. The presence of dementia (= 1) was assumed if Global Deterioration Scale ≥ 4 (0 otherwise).

The presence of 28 chronic conditions was recorded by the GP: Diabetes, hypertension, cardiac arrhythmia, coronary heart disease, myocardial infarction, hyperlipidemia, hypercholesteremia, chronic heart failure, peripheral arterial disease, Parkinson's disease, epilepsy, depression, alcohol abuse, stenosis, transient ischaemic attack, stroke, hyperthyroidism, hypothyroidism, renal insufficiency, chronic liver disease, traumatic brain injury, back pain, arthrosis, obesity, gout, varicose veins, chronic obstructive pulmonary disease, asthma and gastritis. The GP rated the severity (1 = mild to 4 = severe) if a chronic condition was present. We calculated a weighted count comorbidity score by summing the severity ratings for chronic conditions as present.

Additionally, we included dummy-coded variables for region in all regressions (results not shown, but available upon request from the authors). The proportion of missing values was below 5% in all variables.

Independent variables in additional analysis

The severity of dementia symptoms was quantified by the Clinical Dementia Rating (CDR) (41), with scores of 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia) and 3 (severe dementia). We generated a score with CDR < 1 (very mild dementia), CDR = 1 (mild dementia) and CDR ≥ 2 (moderate to severe dementia). Moreover, the MMSE (42) was used to assess cognitive impairment, ranging from 30 (best) to 0 (worst). Presence of dementia was assumed if MMSE ≤ 21.

Statistical Analysis

In our analyses, we used linear fixed effects (FE) regressions to estimate the effects of time-dependent predictors on frailty. This is the preferred strategy as the alternative strategy, the use of random effects (RE) regression, is inconsistent (indicated by Sargan Hansen test) (43). The RE regressions are inconsistent since the assumption of no correlation between unobserved time-constant factors and predictors is violated. In such a case, FE regressions are the method of choice (since FE regressions provide consistent estimations under the assumption of strict exogeneity (43)). It is worth mentioning that FE regressions only use within-variations over time. Thus, the FE estimator is also called 'within-estimator'.

In order to deal with serial correlation and heteroscedasticity, cluster-robust standard errors were estimated (44). The statistical significance was defined as P value of ≤ .05. All statistical analyses were conducted using Stata 13.1 (Stata Corp., College Station, Texas).

In our main model, dementia was quantified by using the Global Deterioration Scale. In order to test whether the effect of dementia on frailty was sensitive to the measure of dementia used, we also used CDR and MMSE as a measure of dementia in additional analyses. Moreover, the robustness of our findings (in terms of significance) was checked by applying a FE poisson model with cluster-robust standard errors.

Results

Sample characteristics

Mean age at FU wave 4 was 85.4 years (±3.2), ranging from 80 to 98 years. The majority of the individuals was female (66.8%), had low education (57.9%), was either single, widowed, or divorced (67.0%) and was living alone in private household (50.3%). The vast majority had no depression (82.2%) and no dementia (90.3%). Moreover, the mean comorbidity score was 4.5 (±3.9) and mean CSHA CFS was 3.5 (±1.6).

18 months later (FU wave 5), the proportion of single, widowed, or divorced individuals increased slightly (72.0%) due to the death of spouses. Other sociodemographic variables remained almost the same. Moreover, the mean comorbidity score decreased to 3.9 (±3.8), whereas mean CSHA CFS increased to 3.8 (±1.6).

Table 1
Descriptive statistics over time (FU Waves 4-5)

	Follow-Up Wave 4 (n=1,602)	Follow-Up Wave 5 (n=1,307)
Age: Mean (SD)	85.4 (3.2)	86.9 (3.1)
Female: N (%)	1070 (66.8)	894 (68.4)
Education: N (%)		
Low Education	928 (57.9)	753 (57.6)
Middle Education	479 (29.9)	390 (29.8)
High Education	195 (12.2)	164 (12.6)
Single, widowed, or divorced individuals: N (%)	1072 (67.0)	940 (72.0)
Living alone in private household: N (%)	805 (50.3)	640 (49.0)
Absence of depression (Geriatric Depression Scale ≥ 5): N (%)	1,264 (82.2)	983 (79.2)
Absence of dementia (Global Deterioration Scale ≥ 4): N (%)	1,446 (90.3)	1,148 (87.8)
Comorbidity (Weighted count score): Mean (SD)	4.5 (3.9)	3.9 (3.8)
Frailty (CSHA CFS): Mean (SD)	3.5 (1.6)	3.8 (1.6)

Regression analysis: Main model and additional analysis

Results of FE regressions are depicted in table 2. Regressions were estimated for the total sample (column 1) and gender specific (columns 2-3). Frailty increased significantly with increasing age (β=.2), depression (β=.5) and dementia (β=.8), whereas changes in marital status, living situation and comorbidity score did not affect frailty in the total sample.

While the effects of depression (β=.5) and dementia (β=.7) were significant in women, these predictors (depression: β=.3; dementia: β=1.0) did not achieve statistical significance in men. However, the interaction terms were not significant (depression x sex, p=.26, dementia x sex, p = .83).

Moreover, analyses were repeated with CDR or MMSE instead of Global Deterioration Scale. The effect of dementia on the risk of frailty was insensitive to the measure of dementia (CDR, MMSE) used. Additionally, we redid everything with FE poisson models, leading to the same results in terms of significance (results of alternate models are not shown, but are available upon request from the authors).

Discussion

Main findings

FE regressions revealed that frailty increased significantly with increasing age (β=.2) as well as the occurrence of depression (β=.5) and dementia (β=.8) in the total sample. Changes in marital status and comorbidity score did not affect frailty. While the effects of depression and dementia were significant in women, these effects did not achieve statistical significance in men.

Previous research

Our findings based on time-dependent variables (solely within-variations over time were used) extend previous studies that used a static set of baseline characteristics as predictors for frailty in subsequent waves. These differences in statistical models can explain differences in results. For instance, a previous study (26) found that the baseline number of self-reported comorbid conditions (diagnosis of heart attack, stroke, arthritis, cancer, hip fracture, or diabetes) was a predictor of follow-up frailty. Yet, in our study an increase in comorbidity did not affect frailty.

In sum, our findings clearly corroborate the hypothesis that dementia and depression are causal factors for frailty and consequently extend previous knowledge (depression: (27, 28); dementia: (45, 46)) about an association of these factors. As for depression, the aforementioned studies found that depression at baseline predicted subsequent frailty. The depression-effect may be mainly explained by decreased social ties and less physical activities (34, 47) which can lead to frailty. The non-significant effect in men might be partially explained by a lack of statistical power. As for cognitive impairment, our findings support a previous study using time-dependent variables (35) and extend previous knowledge about an association between baseline characteristics and future frailty (27) and about an association between baseline characteristics and changes in frailty status (35). This relation might be explained by the association between Alzheimer's disease and decreasing physical activity as well as weight loss (48, 49) which could eventually lead to frailty. The non-significant effect in men might be mainly explained by the low statistical power.

As for sociodemographic variables, our findings based on changes in independent variables correspond to previous studies using a static set of baseline characteristics as

Table 2
Longitudinal predictors of frailty (CSHA CFS): Results of fixed effects regressions (FU Waves 4-5)

	(1)	(2)	(3)
Independent variables	**Frailty - All**	**Frailty - Women**	**Frailty - Men**
Loss of spouse	0.0117	-0.149	0.145
	(0.196)	(0.262)	(0.285)
Age	0.215***	0.248***	0.145***
	(0.0206)	(0.0255)	(0.0342)
Occurrence of depression	0.468***	0.515***	0.275
	(0.0991)	(0.107)	(0.233)
Changes in comorbidity (Weighted count score)	0.0133	0.0172	0.00603
	(0.00969)	(0.0128)	(0.0147)
Occurrence of dementia	0.794***	0.700**	1.044+
	(0.223)	(0.227)	(0.600)
Constant	-16.10***	-18.87***	-9.327**
	(1.802)	(2.239)	(2.949)
R^2	0.143	0.179	0.078
Observations	2,777	1,864	913
Number of Individuals	1,569	1,048	521

Comments: Beta-Coefficients were reported; Cluster-robust standard errors in parentheses; Regressions are also controlled for region; *** p<0.001, ** p<0.01, * p<0.05, + p<0.10; Observations with missing values were dropped (listwise deletion).

predictors (26, 33). The age-effect found in our study is worth highlighting since we controlled for sociodemographic factors, depression, dementia as well as comorbidity in regression analysis.

Strength and Limitations

This is one of few longitudinal studies aimed at determining factors affecting frailty in individuals aged 80 years and older. Unlike other studies, our study examined the effect of time-dependent predictors. Thus, the FE model provides insights into the causality, albeit with some limitations since we did not have a controlled stimulus (as opposed to a randomized controlled trial where treatment is randomly assigned).

Even though there is some non-response bias in the AgeCoDe sample (36), we should highlight that our study population was a nearly representative sample of elderly individuals in Germany (36). This can be explained by the fact that the individuals were recruited via GP offices and over 90% of individuals in old age have regular GP visits in Germany (50). However, our estimates might be biased downwards for reasons of panel attrition. Therefore, we examined whether differences at baseline between individuals with complete follow-up data and individuals who dropped out after baseline exist. At baseline, the latter group was older, more depressed, more cognitively impaired (Global Deterioration Scale, MMSE, CDR) and had a higher comorbidity score (results are not shown, but are available upon request from the authors).

Moreover, we cannot rule out the possibility that a simultaneity bias (43) between depression and frailty exists (51). Longitudinal evidence suggests that depression is a predictor of frailty (25, 26, 34). However, there is also evidence that frailty is a predictor of future depression (52, 53). Thus, the causal effects might be bidirectional and should be further investigated in future studies.

Conclusion

Our findings highlight the meaning of increasing age as well as the occurrence of dementia and depression for frailty. Specifically, in order to delay frailty in old age, developing interventional strategies to prevent depression (54) might be a fruitful approach.

It is most likely that the number of frail individuals in old age will increase in the next decades since the number of elderly individuals with dementia (55) and depression (56) is expected to increase due to demographic changes. The expected rise in frail individuals will most probably increase the need for care in upcoming decades which should be taken into account by policy makers.

Ethics statement: The ethics committees of the participating centers approved the study (reference numbers: 050/02 (University of Bonn), 2079 (Faculty of Medicine, University of Düsseldorf), 2817/2007 (Hamburg Medical Association), 309/2007 (Faculty of Medicine, University of Leipzig), 2007-253E-MA (Medical Ethics Commission II, University of Heidelberg at the University Medical Center of Mannheim), 713/02 (Faculty of Medicine, Technical University of Munich)). The study was conducted according to the

principles expressed in the Declaration of Helsinki. All participants gave written informed consent prior to study entry.

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