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Changes in frailty status in a community-dwelling cohort of older adults: The VERISAÚDE study

Laura Lorenzo-López, Rocío López-López, Ana Maseda, Ana Buján, José L. Rodríguez-Villamil, José C.Millán-Calenti

Universidade da Coruña, Gerontology Research Group, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), SERGAS, 15071 A Coruña, Spain

Abstract

Objectives: Greater understanding of changes in the degree of frailty is important for clarifying the natural history of frailty and may help clinical decision-making regarding preventive interventions. The objectives of this study were to explore natural frailty transition rates at 1-year follow-up and to identify the main determinants of such transitions.

Study design: Prospective longitudinal study covering a representative sample of community-dwelling older adults aged ≥65 years (n = 749) at baseline, and transition information at 1-year follow-up (n = 537).

Mean outcome measures: The assessment of frailty status was based on phenotypic criteria (unintentional weight loss, weakness, exhaustion, slow walking speed, low physical activity). Frailty transitions (progressed, regressed, no change, or death) and associated factors were assessed.

Results: Most participants remained unchanged from their baseline status (57.1% non-frail, 83.4% pre-frail, 66.7% frail). Regarding frailty transitions, 42.9% of non-frail older adults at baseline had progressed to a pre-frail status by the 1-year follow-up, and 7.9% of pre-frail older adults had become frail. Importantly, 33.3% of frail older adults regressed to a pre-frail status and 8.7% of pre-frail adults had regressed to a non-frail status. Non-frail females tended to progress to pre-frailty significantly more than males ($p = 0.006$), and mortality was higher among participants classified as frail at baseline (10.7%). Logistic regression showed that the main determinants of worsening frailty were hearing impairment (OR 3.180; 95% CI 1.078–9.384), congestive heart failure (OR 10.864; 95% CI 1.379–85.614), and polypharmacy (OR 2.572, 95% CI 1.096–6.037).

Conclusion: Our results confirm the dynamic of frailty and the bidirectional nature of frailty transitions, and indicate the need for preventing and treating these conditions in later life in order to minimize the burden of frailty.

Keywords

Frailty transitions; Pre-frailty; Older adults; Mortality; Hearing impairment

1. Introduction

Physical frailty has been described along a continuum of severity (fitness-frailty spectrum) with three stages: non-frailty or robustness, pre-frailty (precursor or latent state) and frailty, and it has been associated with adverse health outcomes such as incident falls and fractures, hospitalization, disability, dependence and premature death [[1], [2], [3]]. Pre-frail state identifies a subset at high risk of progressing to clinically identifiable frail state [2]. Recent literature exploring the natural course of frailty in older adults suggests that it is a gradual dynamic process, characterized by frequent transitions between frailty states in both directions (worsening or improvement) over time [[4], [5], [6], [7], [8], [9], [10]]. It has been shown that transitions are more common between adjacent states (one-step transitions) and from states of lesser frailty to states of greater frailty [6,8,[10], [11], [12]], and they appear to be independent of progression in cognitive status in earliest stages of cognitive impairment [13]. Recent studies have shown that frailty transitions could be modulated by several health and social-related factors [14]. Although these findings suggest that frailty is potentially reversible, pharmacological and nonpharmacological interventions aimed at preventing and reversing the frailty syndrome or its clinical consequences remain elusive [15,16]. In general, it has been suggested that multi-domain (physical and nutritional) interventions may delay or even reverse physical frailty [[17], [18], [19], [20], [21], [22], [23]]. Therefore, the developing and implementation of specific interventions and effective health-care policies aimed at preventing or reducing the level of frailty and postponing its adverse health consequences in old age is one of the most important public health challenges.

An important subset of Galician (Northwest of Spain) community-dwelling older adults has been shown to be pre-frail and at high risk of progressing to frailty [24]. Evidence about the natural history of frailty as a modifiable, bidirectional, and dynamic process is scarce, particularly in the reversion of the frailty status. Further understanding of the processes underlying transitions between frailty states (factors that positively or negatively contribute to changing the frailty state) is important for clarifying the natural history of frailty and may help clinical decision-making related to preventive interventions. The adverse health outcomes related to frailty contribute to an increased demand for medical and social care and are associated with increased economic costs. For these reasons, it is important that clinicians know the frailty process and the main determinants of transitions among its levels, so that effective preventive and rehabilitative actions can be taken as early as possible. Since changes in frailty states are of considerable clinical and public health interest, the aim of the present study was to explore the natural transition rates between states of frailty over a 1-year period and identify the determinants or precipitants of such transitions over time in a community-dwelling cohort of older adults.

2. Methods

2.1. Study population

This study was drawn from a sample population of 537 community-dwelling older people aged 65 and over who participated in the Effectiveness of the Comprehensive Gerontological Assessment and longitudinal follow-up in the healthy aging promotion (VERISAÚDE) project Considering the reference population of 632,381 individuals, which represented the absolute number of older adults aged 65 years or older from Galicia according to the municipal register of the 2011 National Health Survey, a sample of 749 older individuals was defined. To ensure a representative sample, the distribution of the sample by age and sex was similar to that of the entire Galician older population. The level of confidence was 95%, accuracy ±4.0% and estimation of data losses 20.0%. The VERISAÚDE study included a first comprehensive gerontological assessment (CGA) with frailty state classified according to the Fried phenotypic criteria [2], and a second CGA one year later. The study protocol has been approved by the Ethics Committee of the University of A Coruña (CE 09/2013) and was in conformity with the principles embodied in the Declaration of Helsinki. Before the data collection, all participants have been informed about the study and signed the corresponding informed consent form. The inclusion criteria for the participants were as follows: (a) being ≥65 years of age, and (2) willingness to sign the informed consent

form. The exclusion criterion for the sample was inability to perform the CGA. The manuscript was written according to the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement [25].

2.2. Frailty assessment and measurement of frailty transitions

Fried phenotype was used to objectively diagnose frailty [2]. The 5 frailty criteria were: (a) Unintentional weight loss of ≥4.5 kg in previous year, (b) Self-reported exhaustion, identified by two questions (items 7 and 20) from the Center for Epidemiological Studies-Depression (CES-D) scale, (c) Weakness, defined by handgrip strength in the dominant hand measured with a dynamometer in kilograms, adjusted for gender and body mass index, (d) Slow walking speed, assessed by the walking time (in seconds) over a distance of 4.57 m, adjusting for gender and height, and (e) Low physical activity, measured by the weighted score of kilocalories expended per week, calculated on the basis of the Minnesota Leisure Time Activity Questionnaire, based on each participant's report, and adjusting for gender. The cut-points used were those proposed by Fried et al. (2001) [2]. At each assessment, participants were classified as non-frail (robust) if they met none of the criteria, pre-frail if they met 1 or 2 criteria, and frail if they met ≥3 criteria [2]. Frailty transitions (progressed, regressed, no change, or death) and associated factors were assessed.

2.3. Comprehensive gerontological assessment

The CGA included the assessment of sociodemographic characteristics, sensory impairments, toxic habits, self-rated health, polypharmacy, comorbidity, nutritional status, cognitive and affective function, and functional status at baseline and 1-year follow-up.

2.3.1. Socio-demographic characteristics

Information on date of birth, age, sex, and level of education was self-reported. Educational level has been classified into three categories according to years of formal education completed: ≤8 years, 9–17 years, and ≥18 years.

2.3.2. Visual impairment

A Snellen eye chart located at a distance of 2.8 m from participant's eyes was used for screening for visual acuity impairment. Decreased visual acuity was defined as best corrected vision worse than 20/50.

2.3.3. Hearing impairment

To determine hearing loss, the whispered-voice test was used [26]. The participants were considered to have a normal hearing if they repeat back at least 3 out of a possible total of 6 letters/numbers correctly, whispered at a distance of 0.6 m behind the participant's field of vision.

2.3.4. Toxic habits

Tobacco and alcohol consumption was self-reported. The variable smoking status (smoker or non-smoker) was assessed based on the 30 days' prevalence of cigarette smoking [27]. The exact number of Standard Drink Units (SDU) was calculated using the formula: size of drink in milliliters (Vol) x percent by volume of alcohol (%) x density of ethanol at room temperature (0.789 g/ml) / by gram in standard drink (10 g in Spain). We defined "alcohol abuse" with an upper level of daily consumption >30 g of pure alcohol (3 SDU) per day [28].

2.3.5. Self-rated health

Self-rated health was assessed with a single question: In general, would you say your health is excellent, good, fair, or poor [29]?

2.3.6. Medication consumption

Participants were asked to present their medication history (dispensed medications by their general practitioner), and polypharmacy was defined as the concurrent use of five or more different prescribed medications [30].

2.3.7. Comorbidity

Comorbidity was measured using Charlson Comorbidity Index (CCI) [31]. All the 19 medical conditions assessed were assigned a CCI weight (1, 2, 3 or 6) taking into account their number and seriousness, which ranges from 0 to 37 points. For each patient, the CCI-aged adjusted score was computed, defining three comorbidity levels: 0–1 (no comorbidity), 2 (low comorbidity), and ≥3 (high comorbidity).

2.3.8. Nutritional status

The Spanish version (Nestlé Nutrition Institute) of the Mini-Nutritional Assessment-Short Form (MNA-SF) [32] was used for nutritional screening. The sum of the MNA-SF score distinguishes between patients with: 1) normal nutritional status, 12–14 points; 2) at risk of malnutrition, 8–11 points; and 3) malnutrition, 0–7 points.

2.3.9. Cognitive assessment

The global cognitive status was assessed using the Spanish version of the Mini-Mental State Examination (MMSE) [33]. Scores, ranging from 0 to 30, were adjusted for age and level of education, and participants were considered as cognitively impaired if they scored <25.

2.3.10. Affective assessment

Depressive symptoms were assessed using the Spanish-validated version of the short-form of the Geriatric Depression Scale (GDS-SF) [34], which recommends using a cut-off of ≥5 points to consider the existence of probable clinical depression.

2.3.11. Functional status

Functional status was measured using Lawton and Brody Index [35] for the instrumental activities of daily living. The score ranges from 0 (low function, dependence) to 8 (high function, independence). Participants who were unable to perform any one of the activities without the help of another person were considered to be dependent.

2.4. Statistical analysis

The frequencies of natural transitions between the three frailty states (non-frail, pre-frail, frail) and death were calculated for those participants who completed the follow-up or died. Thus, worsening transitions (from non-frail to pre-frail states and from pre-frail to frail states) and improvement transitions (from frail to pre-frail states and from pre-frail to non-frail states) at 1-year follow-up were considered as primary outcomes. Participant characteristics were compared across transitions in frailty status using student *t*-tests for continuous variables, and chi-square tests for categorical variables. For multiresponse variables, column proportions were compared using custom tables (z test). Cohen's *d* and *h* values were reported as indicators of effect size for comparing the mean and proportion values respectively, using the benchmarks for "small" (0.2), "medium" (0.5) and "large" (0.8) in both cases [36].

Frailty transition analyses were performed using a forward stepwise multivariate logistic regression method. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each covariate included in the model. A *p*-value of <0.05 was taken to define statistical significance. The data analyses were performed using the software package IBM SPSS Statistics v.24.0 (IBM Corp, Armonk, NY, USA).

3. Results

Among the 749 older adults evaluated at baseline, 537 (71.7%) were re-evaluated one year later, and 212 (28.3%) were lost to follow-up. Drop-out rates as a function of frailty level are shown in Fig. 1. An independent *t*-test revealed that participants who dropped out (n = 212) were slightly older than those who participated in the follow-up assessment (n = 537) (76.6 ± 7.5 *vs* 75.4 ± 7.0 years respectively; $p = 0.035$). The characteristics of the participants at baseline (n=749) and follow-up (n=537) are shown in Table 1.

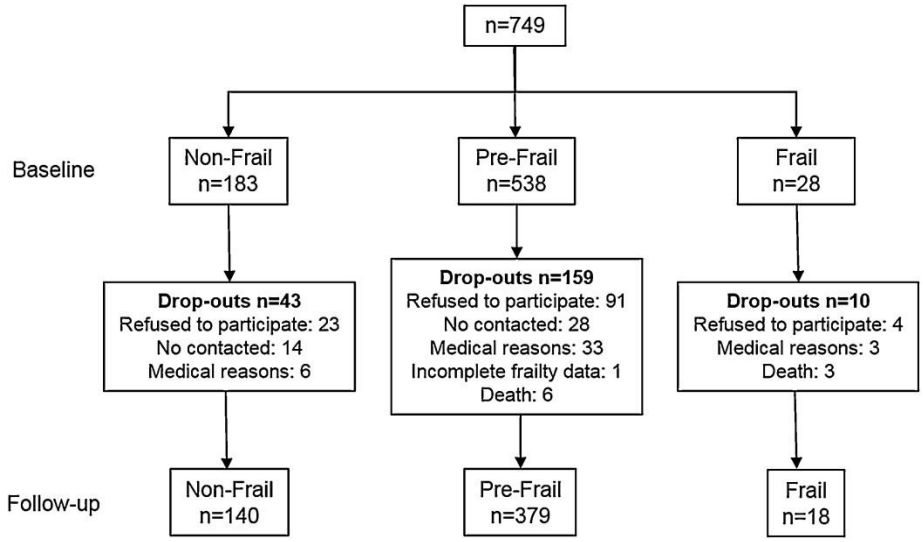

Fig. 1. Drop-out Rates as a Function of Frailty Level.

Table 1. Characteristics of Participants at Baseline and at 1-Year Follow-Up.

	Baseline n = 749	Follow-up n = 537
Age (years)	75.8 ± 7.2	76.3 ± 7.0
Gender		
Females	454 (60.6%)	331 (61.6%)
Males	295 (39.4%)	206 (38.4%)
Education		
≤8 years	451 (60.2%)	323 (60.1%)
9-17 years	179 (23.9%)	126 (23.5%)
≥18 years	119 (15.9%)	88 (16.4%)
Sensory Impairments		
Visual	63 (8.6%)	64 (11.9%)
Hearing	209 (27.9%)	182 (33.9%)
Toxic Habits		
Tobacco consumption	22 (2.9%)	11 (2.1%)
Alcohol abuse	83 (11.1%)	71 (13.2%)
Self-Rated Health,		
Excellent	165 (22.1%)	84 (15.6%)
Good	420 (56.1%)	318 (59.2)
Fair	142 (19.0%)	124 (23.1%)
Poor	21 (2.8%)	11 (2.0%)
Number of Medications	4.8 ± 3.3	4.8 ± 3.2
Polypharmacy, ≥5 Medications per day	360 ± 48.1	260 ± 48.4
Comorbidity		
No comorbidity	580 (77.4%)	416 (77.5%)
Low comorbidity	109 (14.6%)	72 (13.4%)
High comorbidity	60 (8.0%)	49 (9.1%)
Nutritional Status, MNA-SF		
Normal	642 (85.7%)	472 (88.1%)
Malnutrition risk	101 (13.5%)	62 (11.6%)
Malnourished	6 (0.4%)	2 (0.4%)
Cognitive Impairment		
MMSE <25	49 (6.5%)	34 (6.3%)
MMSE score	28.3 ± 0.8	28.4 ± 2.1
Depressive Symptoms		
GDS-SF ≥5	61 (8.1%)	47 (8.8%)
GDS-SF score	1.5 ± 2.1	1.6 ± 2.1
IADL Dependence	93 (12.4%)	48 (8.9%)

Values are presented as means ± standard deviation for continuous variables or as frequencies (percentages) for categorical variables. MNA-SF: Mini-Nutritional Assessment-Short Form (ranges 0–14 points; 12–14 points indicate normal nutritional status, 8–11 points indicate risk of malnutrition, and 0–7 points indicate malnutrition). MMSE: Mini-Mental State Examination (ranges 0–30 points; <25 points indicate cognitive impairment), GDS-SF: Geriatric Depression Scale-Short Form (ranges 0–15 points; ≥5 points indicate probable clinical depression). IADL: Instrumental Activities of Daily Living (the score ranges from 0 (low function, dependence) to 8 (high function, independence)).

3.1. Frailty transitions' rates

At baseline, 183 (24.4%) of the participants were non-frail, 538 (71.8%) were pre-frail, and 28 (3.7%) were frail. At 1-year follow-up, 113 (21.0%) were non-frail, 382 (71.1%) were pre-frail, and 42 (7.8%) were frail.

Fig. 2 shows changes in frailty status from baseline to 1-year follow-up. During the study period, a total of 408 (76.0%) participants retained their baseline frailty state, and 129 (24.0%) made transitions between states of frailty (16.7% progressed, and 7.3% regressed). Most participants, mainly pre-frail subjects, remained unchanged at their baseline state (57.1% non-frail, 83.4% pre-frail, 66.7% frail). Regarding frailty transitions, 42.9% of non-frail older adults at baseline progressed to pre-frailty status, and 7.9% of pre-frail older adults became frail at 1-year follow-up. Importantly, 33.3% of frail older adults regressed to pre-frailty status and 8.7% of pre-frail older adults regressed to non-frailty status. As expected, none frail subject regressed to non-frailty status directly. Frailty transition patterns at 1-year follow-up are shown in Table 2. As expected, only transitions between adjacent states of frailty were observed. As shown in Fig. 2 and Table 2, direct transitions between states of non-frailty and frailty were not observed. Non-frail females tended to progress into pre-frailty more than non-frail males, who remained unchanged more than females ($p = 0.006$, $h = .321$, small effect size).

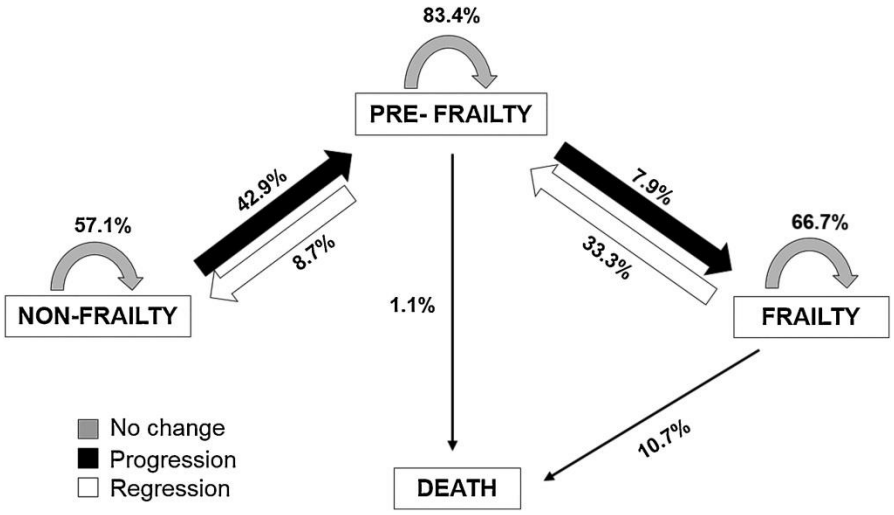

Fig. 2. Percentage of Frailty Transitions in the VERISAÚDE Population from Baseline to 1-Year Follow-Up. Stability in frailty status is represented as grey thick arrows, worsening is shown in black color, regression (improvement) is shown in white, and percentages of deaths are represented as black thin arrows.

Table 2. Frailty Transitions at 1-Year Follow-Up.

Frailty Transitions, n (%)	Baseline to 1-Year Follow-Up		
	Females (n = 331)	Males (n = 206)	Total (n = 537)
Non-Frail to:	n = 63	n = 77	n = 140
Non-Frail	28 (35.0%)	52 (65.0%)	80 (57.1%)
Pre-Frail	35 (58.3%)	25 (41.7%)	60 (42.9%)
Frail	0 (0%)	0 (0%)	0 (0%)
Pre-Frail to:	n = 253	n = 126	n = 379
Non-Frail	21 (63.6%)	12 (36.4%)	33 (8.7%)
Pre-Frail	208 (65.8%)	108 (34.2%)	316 (83.4%)
Frail	24 (80.0%)	6 (20.0%)	30 (7.9%)
Frail to:	n = 15	n = 3	n = 18
Non-Frail	0 (0%)	0 (0%)	0 (0%)
Pre-Frail	4 (66.7%)	2 (33.3%)	6 (33.3%)
Frail	11 (91.7%)	1 (8.3%)	12 (66.7%)

The prevalence of each clinical condition evaluated by the Charlson Comorbidity Index in the worsening and improvement groups was calculated, showing that just the prevalence of congestive heart failure was significantly different between the groups (24.4% in worsening versus 2.6% in improvement groups, $p = 0.003$, $h = .676$, medium effect size).

A forward stepwise multivariate logistic regression analysis was made using frailty transitions as a dichotomy dependent variable (worsening versus improvement). Age, hearing impairment, congestive heart failure, number of medications and polypharmacy were included as independent variables, because of the significant differences between groups shown by the bivariate analysis (see Table 3, all medium effect sizes). Results of the regression model revealed that hearing impairment (OR = 3.180, 95% CI 1.078–9.384, $p = 0.036$), congestive heart failure (OR=10.864, 95% CI 1.379–85.614, $p = 0.024$), and polypharmacy (OR=2.572, 95% CI 1.096–6.037, $p = 0.030$) at baseline represent more chance of experience a transition toward a worse frailty state at 1-year follow-up, with the model accurately predicting 70.5% of the worsening cases.

Table 3. Determinants of Transitions Between Frailty States.

	Frailty Progression (Worsening) n = 90	Frailty Regression (Improvement) n = 39	*p*-value	Effect Size
Age (years), mean (SD)	76.1 (7.1)	73.0 (7.1)	0.025*	0.433[a]
Gender, n (%)			0.874	
Females	59 (65.6)	25 (64.1)		
Males	31 (34.4)	14 (35.9)		
Education, n (%)			0.689	
≤8 years	57 (63.3)	23 (59.0)		
9-17 years	22 (24.5)	9 (23.1)		
≥18 years	11 (12.2)	7 (17.9)		
Sensory Impairments, n (%)				
Visual	11 (12.6)	3 (7.7)	0.414	
Hearing	28 (31.1)	5 (12.8)	0.029*	0.443[b]
Toxic Habits, n (%)				
Tobacco consumption	1 (1.1)	2 (5.1)	0.383	
Alcohol abuse	16 (17.8)	4 (10.3)	0.278	
Self-Rated Health, n (%)			0.103	
Excellent	22 (24.5)	7 (17.9)		
Good	45 (50.0)	28 (71.8)		
Fair	20 (22.2)	4 (10.3)		
Poor	3 (3.3)	0 (0.0)		
Number of Medications, mean (SD)	5.1 (3.3)	3.8 (2.6)	0.039	0.416[a]
Polypharmacy, ≥5 Medications per day, n (%)	47 (52.2)	11 (28.2)	0.012*	0.474[b]
Comorbidity, n (%)			0.217	
No comorbidity	67 (74.4)	34 (87.2)		
Low comorbidity	14 (15.6)	4 (10.3)		
High comorbidity	9 (10.0)	1 (2.5)		
Nutritional Status, MNA-SF, n (%)			0.795	
Normal	74 (82.2)	32 (82.1)		
Malnutrition risk	15 (16.7)	7 (17.9)		
Malnourished	1 (1.1)	0 (0.0)		
Cognitive Impairment				
MMSE <25, n (%)	5 (5.6)	1 (2.6)	0.459	
MMSE score, mean (SD)	28.7 (1.9)	28.8 (1.5)	0.858	
Depressive Symptoms				
GDS-SF ≥5, n (%)	9 (10.0)	2 (5.1)	0.363	
GDS-SF score, mean (SD)	1.6 (2.2)	1.1 (1.5)	0.107	
IADL Dependence, n (%)	13 (14.4)	3 (7.7)	.285	

SD: Standard Deviation.
MNA-SF: Mini-Nutritional Assessment-Short Form (ranges 0–14 points; 12–14 points indicate normal nutritional status, 8–11 points indicate risk of malnutrition, and 0–7 points indicate malnutrition). MMSE: Mini-Mental State Examination (ranges 0–30 points; <25 points indicate cognitive impairment), GDS-SF: Geriatric Depression Scale-Short Form (ranges 0–15 points; ≥5 points indicate probable clinical depression). IADL: Instrumental Activities of Daily Living (the score ranges from 0 (low function, dependence) to 8 (high function, independence)).
* $p < .005$.
[a] Cohen's *d* effect size.
[b] Cohen's *h* effect size.

3.2. Mortality rates

Mortality rate was higher among participants classified as frail at baseline, with no direct transitions from non-frailty to death. Specifically, 1.1% of pre-frail (0.3% females, 2.7% males) and 10.7% of frail (13.0% females, none male) participants at baseline died at 1-year follow-up. Females who were frail at baseline were more likely to die compared to frail males at baseline.

4. Discussion

In the present study, the spontaneous course of frailty was explored in a large community-dwelling cohort of older adults estimating the transition rates among states over a 1-year period, and the main predictors associated with frailty transitions were identified. This is of clinical and public health interest since little is known regarding frailty trajectories within short periods, and the risk factors involved in the transitions.

According to previous studies [8,10], most participants (76.0%) remained unchanged at their baseline state, with pre-frail individuals being more likely to remain stable than non-frail and frail individuals. It is important to note that the prevalence of pre-frailty was considerably high in the studied population [24]. Almost a quarter of the participants made transitions between states of frailty (16.7% progressed, and 7.3% regressed), confirming the dynamic and bidirectional nature of frailty syndrome [8]. As expected, transitions towards a worse frailty state were more likely than transitions towards a better frailty state.

In previous studies, pre-frail individuals were shown to be more likely to regress or improve than frail individuals [6,10]. Importantly, in our study an important proportion of frail individuals (33.3%) regressed to the pre-frailty state, suggesting that even frail state may be an optimal target for intervention. According to these findings, a significant proportion of participants (9–16%) improved in frailty status in previous studies [6,8,37]. Additionally, females were more likely to decline in frailty status than males in the present study. In contrast, a better chance of frailty improvement has been previously reported in females [9].

Risk and protective factors associated with frailty have been widely explored in longitudinal studies [38]. Socioeconomic, functional or psychological determinants of transitions, or individual clinical/medical characteristics associated with progression or regression over time have been also explored in community-dwelling older adults [4,6,7,[9], [10], [11],39]. In a recent innovative study, it has been shown that factors that determine the worsening or improvement of frailty state differ as a function of gender and that more males than females deteriorate into frailty [9]. In contrast to this finding, females were more likely to decline in frailty status than males in the present study.

Our results showed that hearing impairment, congestive heart failure, and polypharmacy were significantly associated with worsening within a relatively short period.

According to these findings, in a recent 4-year follow-up study, it was shown that self-reported hearing impairment was significantly associated with greater risk of becoming frail in pre-frail community-dwelling older adults [40]. Hearing impairment, evaluated by the pure-tone-average of hearing thresholds, has been also associated with the risk of frailty and with greater odds of falling in older adults [41]. Altogether, these results suggest that hearing impairment, a common condition in later life associated with comorbidity, disability and poor quality of life [42,43], may accelerate the progression of frailty.

Polypharmacy has been also recently associated with a higher incidence of frailty [44,45] and greater mortality [10,46] in longitudinal studies. Specifically, the cumulative exposure to sedative and anticholinergic medications was associated with greater risk of transitioning from the robust to the pre-frail state, and each additional medication was associated with greater risk of transitioning from the robust state to death in community-dwelling older men aged 70 and older [44].

Finally, according to our results, the presence of congestive heart failure was associated with lower likelihood of improvement in frailty status [9,37].

The main strengths of this research are the large representative sample of community-dwelling older adults assessed, and the study of frailty transitions occurring within a short time interval. It is important to highlight that only active older participants in senior centers were assessed in the present study, possibly affecting the generalization of the findings.

A limitation of our study is the little information regarding acute events or factors that may have contributed to progression in frailty, such as injury or surgery, acute disease and/or psychological stress. Some losses occurred in the 1-year follow-up period with a 28.3% drop-out rate. It is also unclear how the use of an alternative operationalization of frailty would have influenced the observed transition rates. Finally, it is possible that rates of progression to frailty are related to the presence of specific initial physical criteria (different patterns of frailty), and this point should be further explored, together with frailty transitions at higher time intervals.

To sum up, our results confirm the dynamic and bidirectional nature of frailty and suggest the need of preventing and early treating the hearing impairment and cardiovascular diseases, and tightly monitoring polypharmacy in later life in order to optimize health outcomes and minimize the public health burden of frailty. It is important that clinicians know the natural frailty process and the main determinants of changes in frailty status, in order to take early preventive and rehabilitative actions.

Contributors

Laura Lorenzo-López made substantial contributions to the study's conception and design, actively participated in acquisition of data, analysis, and interpretation of data, and drafted the article.

Rocío López-López actively participated in acquisition of data, analysis, and interpretation of data, and drafted the article.

Ana Maseda made substantial contributions to the study's conception and design, actively participated in acquisition of data, analysis, and interpretation of data, and revised the article critically for important intellectual content.

Ana Buján revised the article critically for important intellectual content.

José L. Rodríguez-Villamil revised the article critically for important intellectual content.

José C. Millán-Calenti made substantial contributions to the study's conception and design, and revised the article critically for important intellectual content.

All authors saw and approved the final version.

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The work was done at the University of A Coruña (Spain), in compliance with institutional guidelines and approved by the Ethics Committee at the University of A Coruña (CE 09/2013) and has conformed to the principles embodied in the Declaration of Helsinki.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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