Associations between frailty trajectories and frailty status and adverse outcomes in community-dwelling older adults

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Abstract

Background   The association between frailty and adverse outcomes has been clearly defined. Frailty is associated with age, but different frailty evolution patterns might determine the incidence of adverse outcomes at older ages. So far, few observational studies have examined how distinct frailty trajectories could be associated with differences in the risk of adverse events and assessing whether frailty trajectories could define risk of death, hospitalization, worsening, and incident disability better than one-off assessment. Our hypothesis is that prospective increases in frailty levels are associated with higher risk of adverse events compared with subjects that prospectively decreased frailty levels.

Methods   Participants' data were taken from the Toledo Study of Healthy Ageing. Frailty was evaluated using the Frailty Trait Scale 5 (FTS5), being 0 the lower (*the most robust*) and 50 the highest (*the frailest*) score. FTS5 scores at baseline and follow-up (median 5.04 years) were used to construct frailty trajectories according to group-based trajectory modelling (GBTM). Multivariate Cox proportional hazard and logistic regression models were used to explore associations between frailty status and trajectory membership and the adverse outcomes. Deaths were ascertained through the Spanish National Death Index. Disability was evaluated through the Katz Index. Hospitalization was defined as first admission to Toledo Hospital.

Results   Nine hundred and seventy-five older adults (mean age 73.14 ± 4.69; 43.38% men) were included. GBTM identified five FTS5 trajectories: *worsening from non-frailty* (WNF), *improving to non-frailty* (INF), *developing frailty* (DF), *remaining frail* (RF), and *increasing frailty* (IF). Subjects belonging to trajectories of increasing frailty scores or showing consistently higher frailty levels presented with an increased risk of mortality {DF [hazard ratio (HR), 95% confidence interval (CI)] = 2.01 [1.21–3.32]; RF = 1.92 [1.18–3.12]; IF = 2.67 [1.48–4.81]}, incident [DF (HR, 95% CI) = 2.06 (1.11–3.82); RF = 2.29 (1.30–4.03); IF = 3.55 (1.37–9.24)], and worsening disability [DF (HR, 95% CI) = 2.11 (1.19–3.76); RF = 2.14 (1.26–3.64); IF = 2.21 (1.06–4.62)], compared with subjects prospectively showing decreases in frailty levels or maintaining low FTS5 scores. A secondary result was a significant dose–response relationship between baseline FTS5 score and adverse events.

Conclusions   Belonging to trajectories of prospectively increasing/consistently high frailty scores over time are associated with an increased risk of adverse outcomes compared with maintaining low or reducing frailty scores. Our results support the dynamic nature of frailty and the potential benefit of interventions aimed at reducing its levels on relevant and burdensome adverse outcomes.

Keywords   Frailty; Mortality; Disability; Older adults; Trajectory modelling

Background

Frailty is defined as an age-associated, biological syndrome characterized by decreased physiological reserves, which puts an individual at risk when facing minor stressors. Because of its powerful association with adverse events (i.e. disability, mortality, and hospitalization)[1] and its high prevalence in older adults,[2] frailty has been placed in the geriatric medicine spotlight.[1]

Frailty is dynamic in nature and potentially reversible.[3,4] However, to date, only a limited number of observational studies have examined how changes in frailty status (i.e. trajectories of frailty) can predict usual adverse events. The categorical structure of the classical tools for assessing the frailty status[5] may partially account for the short number of studies assessing such relationship. In fact, most of the previous researches have not considered frailty as a continuum[4,6] or are limited by their analytical approach, ignoring the variability or reversibility in frailty score trajectories.[7,8] Nevertheless, our group has recently developed the so-named Frailty Trait Scale 5 (FTS5),[8] a Short Form of the 12 items one[7] that allows the continuous evaluation of frailty levels, potentially overcoming several of previous frailty assessment pitfalls. This instrument refines risk profiling of the individual and outperforms the predictive ability of adverse events (i.e. mortality, hospitalization, and disability)[8] even better than classical frailty tools, as the two most commonly used tools,[9] the Frailty Phenotype[5] and Frailty Index.[10]

The aim of this study is to explore the existence of different frailty trajectories and to investigate their associations with adverse outcomes (disability, hospitalization, and mortality) in a representative sample of older adults. Our hypothesis is that prospective decreasing frailty levels along ageing are associated with a lower risk of adverse events, compared with developing or maintaining higher frailty levels. A secondary objective is to compare cross-sectionally and longitudinally assessed frailty levels in terms of predictive ability.

Methods

This is a prospective analysis of the Toledo Study of Healthy Ageing (TSHA), a population-based longitudinal study whose main aim is to explore the prevalence, determinants, and impact of frailty in a Spanish cohort of older adults (>65 years).[11]

In the present analysis, we included subjects with frailty and covariates data at TSHA Waves 1 (2006–2009) and 2 (2011–2013) and outcomes data at Wave 3 (2015–2017) or time-censoring, depending on the outcome of interest. Wave 2 occurred 5.04 (range 2.32–6.84) median years after the first wave. Wave 3 visit was performed 2.99 (range 2–5.4) median years after the Wave 2.

TSHA protocol was approved by the Clinical Research Ethics Committee of Toledo Hospital Complex, which was conformed according to the ethical standards defined in the 1964 Declaration of Helsinki. As detailed elsewhere previously,[11] participants signed an informed consent form prior to inclusion.

Frailty Trait Scale 5

Frailty was assessed through the FTS5[8] that evaluates five core aspects of frailty:

- Physical activity was determined using the Physical Activity Scale for the Elderly scale.
- Gait speed was defined using the 3 m walking test at their usual pace, according to the standard protocol. The best time of two performances was chosen. At least, 1 min of resting was given between attempts.
- Hand grip strength was measured using JAMAR Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). The best peak strength of three performances was selected and gathered using international standard procedures. Between performances, at least 1 min of resting was permitted.
- Body mass index was measured according to the standard procedure (weight/height^2).
- Progressive Romberg test was established according to the standing balance feet together, semi-tandem, and tandem position.

Each domain score ranges between 0 and 10, being 0 the best score and 10 the worst. FTS5 items are summed up to obtain a final score between 0 and 50, being 0 the lowest and 50 the highest frailty score. FTS5 scoring process is displayed in Supporting Information, *Appendix S1*.

Adverse outcomes

Mortality

Vital status and death dates were ascertained through the Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare). Participants were followed-up to March 2019 or death. Median follow-up for mortality was 6.76 (range 0.26–7.50) years.

Hospitalization

Hospitalization was defined as the first admission according to the records of the Toledo Hospital Complex. Participants' hospitalizations were followed-up to December 2016 with a median follow-up of 4.18 (range 0.02–5.25) years.

Incident or worsening disability

Basic activities of daily living were evaluated by the Katz Index.[12] Transitions of a score of 6 to 5 or less in the Katz Index at follow-up were considered as incident disability. Worsening disability was defined as a loss of 1 point or more during the same time-period. Median follow-up for incident and worsening disability was 2.99 (range 2–5.4) years.

Covariates

Covariates were selected according to previous research and biological plausibility for confounding effects. Age, gender, and educational level (no school, primary school incomplete, and primary school complete or superior) were registered during visits. Comorbidities were measured using the Charlson Index score.[13] The number of prescription and non-prescription drugs within the Anatomical Therapeutic Chemical Classification System taken by the participant was calculated. Polypharmacy was defined as the use of five or more drugs per day. Cognitive status was evaluated using the Mini-Mental State Examination.[14] Covariates data were assessed at Wave 2 visit.

Trajectory modelling

We used GBTM to identify distinct patterns of evolution in frailty levels according to the baseline FTS5 score and changes in the FTS5 score between Waves 1 and 2 visits. This mixture analysis uses semi-parametric empirical models and tries to identify relatively homogeneous clusters of participants following similar longitudinal patterns of evolution and estimate their shape and direction parameters within a continuous distribution. GBTM assumes that the sample is composed of distinct subpopulations that are not identifiable based on measured characteristics *ex ante*.[15,16]

We compared models defining two with 10 trajectory groups to find the optimal number of trajectories, based on values from the Bayesian Information Criterion (BIC). BIC is an index used in Bayesian statistics to choose between different models. Two times the change in the BIC between models greater than 10 was used as indicative of better fit in order to compare more complex—with a greater number of trajectories—or more parsimonious—with a lower number of trajectories—models.[17] Every subject was assigned to a trajectory depending on their FTS5 score and changes in FTS5 score. The reliability of the final model classification was evaluated using mean posterior probability of membership, which represents their probability of belonging to the group they was assigned to by previous grouping based on their individual features. Trajectories mean posterior probability of membership indicates its internal consistency. A higher value indicates a better classification quality.[15] At last, we checked the number of subjects within each trajectory to confirm adequate sample size for analysing the ensuing risk of adverse outcomes.

Statistical analysis

Descriptive statistics were shown as mean (standard deviation) and frequency (%) for continuous and categorical variables, respectively. Descriptive features of subjects in the different frailty trajectories were compared through the analysis of variance test for continuous variables and χ^2 tests for categorical variables.

Cox proportional hazard regression models were used to explore associations between frailty trajectories and time-censored adverse outcomes (mortality and hospitalization), and logistic regressions were used for incident and worsening disability.

We further explored associations between final FTS5 scores in Wave 2 and adverse events. We studied adverse events risks according to the FTS5 score as the change of one point (continuous) and categorized into five categories: ≤10, 11–15, 16–20, 21–25, and >25.

We used the following set of models: Model 1 was the raw model. Model 2 was adjusted by age and gender. In Model 3, we added the MMSE. In Model 4, we added the Charlson Index, polypharmacy, and Katz Index. Finally, we estimated Model 5 including the educational level.

All analyses were performed using the Statistical Package R Version 3.6.1 for Windows (Vienna, Austria). Statistical significance was set at P value < 0.05.

Results

Participant baseline characteristics are shown in *Table 1*, and 975 subjects (mean age 73.14 ± 4.69; 43.38% men) were included.

Frailty Trait Scale 5 trajectories and adverse outcomes

The GBTM yielded a five-frailty trajectory model as the best fit to the data: *worsening from non-frailty* (WNF) (226, 23.17%), *improving to non-frailty* (INF) (353, 36.20%), *developing frailty* (DF) (127, 13.03%), *remaining frail* (203, 20.82%), and *increasing frailty* (IF) (66, 6.76%) (*Figure 1*). Mean posterior probabilities of membership, an index of quality classification, ranged from 0.74 (±0.14) to 0.77 (±0.18) indicating a moderate fit for this model.

In the fully adjusted models, when comparing with *WNF*, subjects pertaining to trajectories showing both an increase and maintenance in frailty scores showed an increased risk for developing adverse outcomes compared with those

Table 1 Demographic characteristics of the sample according to the FTS5 trajectory

Variable	All	WFN	INF	DF	RF	IF	*P* value
N (%)	975	226 (23.17)	353 (36.20)	127 (13.03)	203 (20.82)	66 (6.76)	
Age, mean (SD)	73.14 (4.69)	71.20 (3.52)	72.48 (4.50)	73.72 (4.75)	75.12 (4.92)	76.05 (4.64)	<**0.001**
Gender, men (%)	423 (43.38)	139 (61.50)	169 (47.88)	55 (43.31)	50 (24.63)	10 (15.15)	<**0.001**
FTS5 basal, mean (SD)	18.08 (6.79)	9.44 (2.48)	19.01 (4.34)	16.02 (2.06)	24.67 (4.23)	26.39 (5.12)	<**0.001**
Change in FTS5 per year, mean (SD)	−0.01 (1.56)	0.80 (1.34)	−1.23 (0.81)	1.61 (1.80)	−0.25 (0.82)	1.37 (0.86)	<**0.001**
Dependent according Katz Index score ≤ 5, *n* (%)	124 (12.72)	11 (4.87)	38 (10.76)	12 (9.45)	41 (20.20)	22 (33.33)	<**0.001**
MMSE, mean (SD)	24.44 (4.39)	26.02 (3.34)	24.68 (4.40)	24.51 (3.81)	22.85 (4.72)	22.22 (5.27)	<**0.001**
Charlson Index, mean (SD)	0.94 (1.43)	0.78 (1.28)	0.83 (1.37)	1.27 (1.60)	1.00 (1.45)	1.29 (1.64)	**0.003**
Educational level							
No school, *n* (%)	647 (66.70)	113 (50.22)	251 (71.71)	91 (71.65)	139 (68.81)	53 (80.30)	<**0.001**
Primary school incomplete, *n* (%)	162 (16.70)	54 (24.00)	36 (10.29)	24 (18.90)	37 (18.32)	11 (16.67)	<**0.001**
Primary school complete or superior, *n* (%)	161 (16.60)	58 (25.78)	63 (18.00)	12 (9.45)	26 (12.87)	2 (3.03)	<**0.001**
Number of drugs per day, mean (SD)	4.06 (2.72)	3.40 (2.59)	3.46 (2.55)	4.72 (2.61)	4.84 (2.62)	5.88 (2.97)	<**0.001**
Polypharmacy, *n* (%)	391 (40.10)	78 (34.51)	104 (29.46)	61 (48.03)	104 (51.23)	44 (66.67)	<**0.001**
Death, *n* (%)	211 (21.64)	31 (13.72)	61 (17.28)	38 (29.92)	56 (27.59)	25 (37.88)	<**0.001**
Hospitalization, *n* (%)	393 (40.31)	83 (36.73)	124 (35.13)	48 (37.80)	100 (49.26)	38 (57.58)	**0.007**
Incident disability, *n* (%)	183 (29.66)	31 (18.90)	64 (26.23)	25 (33.33)	50 (44.64)	13 (59.09)	<**0.001**
Worsening disability, *n* (%)	204 (26.56)	31 (16.76)	69 (23.71)	29 (29.90)	56 (37.33)	19 (42.22)	<**0.001**

DF, developing frailty; FTS5: Frailty Trait Scale 5; IF, increasing frailty; INF, improving to non-frailty; MMSE, Mini-Mental State Examination; RF, remaining frail; WNF, worsening from non-frailty.
In bold: $P < 0.05$. Mean (SD): continuous variables. *N*, %: categorical variable.

showing a decreasing evolution, except for hospitalization. In this latter outcome, only those maintaining or increasing their frailty score, but not those who developed it during the time of the trajectory, *DF*, showed an increased risk (*Table 2*). By opposite, improving the frailty score according to FTS5—*INF*—was associated with a low risk for developing
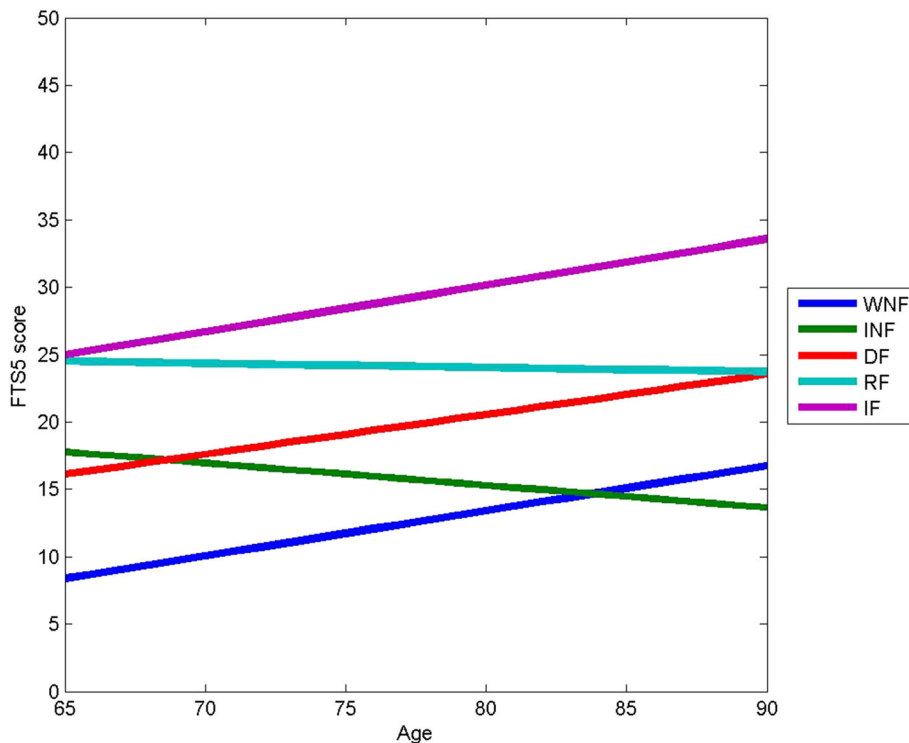
Figure 1 Trajectories according Waves 1 and 2 FTS5 score and changes in FTS5 score. DF, developing frailty; FTS5, Frailty Trait Scale 5; IF, increasing frailty; INF, improving to non-frailty; RF, remaining frail; WNF, worsening from non-frailty.

Table 2 Multivariate regression models showing the association between FTS5 trajectories on different adverse events

Reference (WFN)	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI) 1.00	P value —	HR (95% CI) 1.00	P value —	HR (95% CI) 1.00	P value —	HR (95% CI) 1.00	P value —	HR (95% CI) 1.00	P value —
Death										
INF	1.28 (0.83, 1.97)	0.267	1.13 (0.73, 1.75)	0.587	1.12 (0.72, 1.74)	0.606	1.08 (0.69, 1.68)	0.735	1.11 (0.71, 1.73)	0.654
DF	2.42 (1.51, 3.90)	**<0.001**	2.04 (1.24, 3.33)	**0.005**	2.01 (1.23, 3.29)	**0.006**	1.94 (1.18, 3.19)	**0.009**	2.01 (1.21, 3.32)	**0.007**
RF	2.25 (1.45, 3.49)	**<0.001**	1.99 (1.24, 3.20)	**0.004**	1.95 (1.21, 3.14)	**0.006**	1.88 (1.16, 3.05)	**0.010**	1.92 (1.18, 3.12)	**0.008**
IF	3.18 (1.88, 5.38)	**<0.001**	2.86 (1.62, 5.04)	**<0.001**	2.76 (1.55, 4.89)	**<0.001**	2.55 (1.42, 4.58)	**0.002**	2.67 (1.48, 4.81)	**0.001**
Hospitalization										
INF	0.94 (0.73, 1.22)	0.663	0.95 (0.73, 1.23)	0.680	0.94 (0.72, 1.22)	0.657	0.95 (0.73, 1.24)	0.720	0.94 (0.72, 1.22)	0.637
DF	1.12 (0.81, 1.56)	0.496	1.11 (0.79, 1.55)	0.553	1.10 (0.79, 1.54)	0.576	1.06 (0.75, 1.49)	0.743	1.04 (0.74, 1.47)	0.801
RF	1.57 (1.20, 2.06)	**<0.001**	1.65 (1.23, 2.22)	**<0.001**	1.63 (1.21, 2.19)	**0.001**	1.61 (1.19, 2.16)	**0.002**	1.58 (1.17, 2.14)	**0.003**
IF	1.92 (1.35, 2.75)	**<0.001**	2.03 (1.38, 2.98)	**<0.001**	1.98 (1.34, 2.92)	**<0.001**	1.92 (1.29, 2.85)	**0.001**	1.89 (1.27, 2.82)	**0.002**
Worsening disability										
INF	1.60 (1.03, 2.50)	**0.038**	1.41 (0.90, 2.22)	0.138	1.40 (0.89, 2.20)	0.149	1.38 (0.87, 2.18)	0.173	1.53 (0.96, 2.45)	0.075
DF	2.42 (1.41, 4.15)	**0.001**	1.94 (1.11, 3.39)	**0.020**	1.93 (1.10, 3.37)	**0.021**	1.87 (1.06, 3.29)	**0.030**	2.11 (1.19, 3.76)	**0.011**
RF	3.06 (1.90, 4.94)	**<0.001**	2.27 (1.35, 3.80)	**0.002**	2.18 (1.30, 3.67)	**0.003**	2.01 (1.18, 3.40)	**0.010**	2.14 (1.26, 3.64)	**0.005**
IF	3.81 (1.97, 7.40)	**<0.001**	2.75 (1.36, 5.54)	**0.005**	2.60 (1.28, 5.27)	**0.008**	1.96 (0.95, 4.06)	0.070	2.21 (1.06, 4.62)	**0.035**
Incident disability										
INF	1.58 (1.00, 2.50)	0.050	1.43 (0.90, 2.28)	0.130	1.41 (0.88, 2.24)	0.152	1.40 (0.87, 2.25)	0.163	1.50 (0.92, 2.43)	0.103
DF	2.35 (1.31, 4.19)	**0.004**	1.96 (1.09, 3.56)	**0.026**	1.92 (1.06, 3.48)	**0.032**	1.87 (1.02, 3.43)	**0.043**	2.06 (1.11, 3.82)	**0.021**
RF	3.51 (2.11, 5.83)	**<0.001**	2.50 (1.45, 4.34)	**0.001**	2.40 (1.38, 4.17)	**0.001**	2.20 (1.25, 3.87)	**0.006**	2.29 (1.30, 4.03)	**0.004**
IF	6.51 (2.70, 15.68)	**<0.001**	4.49 (1.80, 11.19)	**0.001**	4.19 (1.67, 10.51)	**0.002**	3.22 (1.25, 8.32)	**0.015**	3.55 (1.37, 9.24)	**0.009**

95% CI, 95% confidence interval; DF, developing frailty; FTS5, Frailty Trait Scale 5; HR, hazard ratio; IF, increasing frailty; INF, improving to non-frailty; OR, odds ratio; RF, remaining frail; WNF, worsening from non-frailty.
In bold: *P* value < 0.05. Model 1: raw model. Model 2: Model 1 plus age and gender. Model 3: Model 2 plus MMSE. Model 4: Model 3 plus Charlson Index, Polypharmacy, and Katz Index. Model 5: Model 4 plus educational level.

any of the adverse outcomes, similar to the reference risk, *WNF*, which denoted the risk of people that remained robust along the follow-up. We did not find any particular additional risk in any of the categories of high risk, not allowing to ascribe a particular higher risk to any of the three trajectories with a poor prognosis.

Intermediate trajectories comparison and adverse outcomes

To study if similar baseline scores but with different evolution were associated with different risk, we repeated the analysis taking as reference each different trajectory.

When comparing with *INF*, subjects who were grouped in the *DF* had an increased risk of mortality of 1.81 [95% confidence interval (CI): 1.20–2.75] in the fully adjusted model, although not for the other adverse events. *MF* and *IF* trajectories had also a significant higher risk for death and hospitalization when *INF* was used as the reference category.

When *DF* was the reference, we found an increased risk for hospitalization for those subjects if belonging to *MF* (hazard ratio = 1.51; 95% CI = 1.10–2.08) or *IF* (HR = 1.81; 95% CI = 1.21–2.72).

Cross-sectionally assessed frailty and adverse outcomes

When we cross-sectionally assessed the association between frailty through FTS5 scores and the adverse outcomes, FTS5 showed a continuously increasing risk for developing any of the adverse outcomes (participant baseline characteristics according FTS5 score are shown in *Table S1*). This finding was consistent irrespective of the study wave at which the FTS5 score was selected as the exposure. When we split the score in FTS5 in five categories, we found a significant increased risk of death, incident, and worsening disability beyond a FTS5 ≥ 20, compared with FTS5 ≤ 10. In the case of hospitalization, the incremental risk was significant for values higher than 10, compared with 10 or lower, even after adjusting for potential confounders (*Table 3*).

Discussion

This work expands previous evidence linking frailty over time to adverse outcomes incidence in a population of community-dwelling older adults. Frailty is a continuum physiological construct that should be evaluated as a continuous identity, getting a proportional dose–effect relationship when risks adverse outcomes are associated with increasingly high FTS5 categories. Our results point to a dose–response association between frailty and an increased risk of death,

hospitalization and disability progression, with significant increases even for values well below the proposed FTS5 score thresholds for frailty.[8] However, although frailty burden tended to increase with age,[2] there could be variability in the rate of progression. According to our results, trajectories clearly show that reversing or improving frailty scores might be beneficial, obtaining the same risk than subjects with the lowest frailty scores over time. Our work does so by employing a novel methodological approach that overcomes important limitations of previous research. We identified five distinct trajectories of frailty, which supports the dynamic nature of this construct. Increasing frailty trajectories or those who maintained higher frailty scores over time had higher risk of death, hospitalization, and incident or worsening disability, than those who remained non-frail.

In fact, we have identified a trajectory in which those subjects with moderate frailty could reduce their frailty levels, what indicates that middle frailty burden could be reduced in community-dwelling older adults as it has been shown in other studies.[18] On the other hand, unexpectedly, we have not identified any trajectory in which those subjects with high frailty load reduced their frailty levels. This could confirm that high frailty load might be hard, but not impossible, to revert and probably point towards the need of tailored interventions to avoid frailty progression that may reduce the risk of developing adverse events. To do so, the early and accurate detection of frailty remains a need.[19,20] The clinical relevance of this finding supports assessing frailty levels to determine older adults health status and contributes to previous research indicating that the reduction of frailty load might be effective in lowering the burden of late-life adverse outcomes.

FTS5 includes objective functional measures (such as walking speed, grip strength, or balance test) and capture longitudinal frailty changes. These scales have been widely used in geriatric medicine to assess older adults' functional status. Sensitivity and positive predictive value of FTS5 rising score could permit recognize and stratify patients, supported by clinical judgement, with a reliable predictor of death or at risk of another adverse outcome (disability, first disability, or hospitalization) according to their frailty trajectory. Even including relevant cofounders, frailty trajectories have showed different adverse events risks according to frailty dynamics.

The Fried frailty phenotype[5] is largely the most frailty used tool.[9] It is based on the presence or absence of five domains to determine frailty (weight loss, gait speed, handgrip strength, physical activity, and fatigue) and identifies a very high (frail) and moderate (pre-frail) risk groups against adverse events.[5] Nevertheless, this tool is a categorical instrument, limiting, hence, the construction of different trajectories. Another commonly used tool is the Frailty Index (FI).[10] FI defines the amount of individual frailty based on the accumulation of deficits getting a proportion of physical, mental, and cognitive deficits present in an individual.[10,21]

Table 3 Multivariate regression models showing the association between FTS5 score (continuous or categorized) at Wave 2 on different adverse events

Death	Model 1 HR (95% CI)	Model 1 P value	Model 2 HR (95% CI)	Model 2 P value	Model 3 HR (95% CI)	Model 3 P value	Model 4 HR (95% CI)	Model 4 P value	Model 5 HR (95% CI)	Model 5 P value
FTS5 change in 1 point (continuous)	1.05 (1.03, 1.07)	**<0.001**	1.05 (1.03, 1.07)	**<0.001**	1.05 (1.03, 1.07)	**<0.001**	1.05 (1.02, 1.07)	**<0.001**	1.05 (1.03, 1.07)	**<0.001**
Reference (FTS5 ≤ 10)	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
FTS5 > 10 and ≤15	1.49 (0.90, 2.46)	0.121	1.25 (0.75, 2.08)	0.398	1.25 (0.75, 2.09)	0.389	1.22 (0.73, 2.04)	0.442	1.24 (0.74, 2.08)	0.404
FTS5 > 15 and ≤20	1.57 (0.94, 2.63)	0.084	1.45 (0.86, 2.45)	0.164	1.43 (0.84, 2.42)	0.184	1.44 (0.85, 2.44)	0.177	1.45 (0.85, 2.45)	0.172
FTS5 > 20 and ≤25	2.39 (1.46, 3.92)	**0.001**	2.10 (1.24, 3.56)	**0.006**	2.08 (1.22, 3.53)	**0.007**	2.01 (1.18, 3.43)	**0.011**	2.04 (1.20, 3.50)	**0.009**
FTS5 > 25	3.13 (1.92, 5.11)	**<0.001**	2.95 (1.71, 5.08)	**<0.001**	2.86 (1.65, 4.95)	**<0.001**	2.77 (1.58, 4.84)	**<0.001**	2.87 (1.64, 5.04)	**<0.001**
Hospitalization	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FTS5 change in 1 point (continuous)	1.03 (1.02, 1.05)	**<0.001**	1.04 (1.03, 1.06)	**<0.001**	1.04 (1.03, 1.05)	**<0.001**	1.04 (1.02, 1.05)	**<0.001**	1.04 (1.02, 1.05)	**<0.001**
Reference (FTS5 ≤ 10)	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
FTS5 > 10 and ≤15	1.54 (1.13, 2.11)	**0.007**	1.58 (1.15, 2.17)	**0.005**	1.58 (1.15, 2.17)	**0.005**	1.56 (1.13, 2.14)	**0.007**	1.55 (1.13, 2.14)	**0.007**
FTS5 > 15 and ≤20	1.48 (1.07, 2.06)	**0.018**	1.60 (1.15, 2.24)	**0.006**	1.58 (1.13, 2.22)	**0.007**	1.54 (1.10, 2.16)	**0.012**	1.54 (1.10, 2.16)	**0.013**
FTS5 > 20 and ≤25	2.10 (1.53, 2.88)	**<0.001**	2.34 (1.66, 3.29)	**<0.001**	2.32 (1.64, 3.27)	**<0.001**	2.23 (1.58, 3.16)	**<0.001**	2.23 (1.58, 3.16)	**<0.001**
FTS5 > 25	2.28 (1.64, 3.17)	**<0.001**	2.66 (1.85, 3.84)	**<0.001**	2.60 (1.79, 3.76)	**<0.001**	2.47 (1.69, 3.60)	**<0.001**	2.46 (1.69, 3.59)	**<0.001**
Worsening disability	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FTS5 change in 1 point (continuous)	1.06 (1.04, 1.08)	**<0.001**	1.05 (1.02, 1.07)	**<0.001**	1.05 (1.02, 1.07)	**<0.001**	1.04 (1.01, 1.06)	**0.004**	1.04 (1.01, 1.06)	**0.003**
Reference (FTS5 ≤ 10)	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
FTS5 > 10 and ≤15	1.50 (0.90, 2.51)	0.124	1.21 (0.71, 2.06)	0.482	1.22 (0.71, 2.07)	0.470	1.20 (0.70, 2.05)	0.511	1.22 (0.71, 2.10)	0.464
FTS5 > 15 and ≤20	1.59 (0.93, 2.70)	0.090	1.28 (0.73, 2.22)	0.387	1.23 (0.71, 2.15)	0.457	1.12 (0.64, 1.97)	0.690	1.12 (0.64, 1.98)	0.692
FTS5 > 20 and ≤25	3.02 (1.78, 5.11)	**<0.001**	2.14 (1.21, 3.80)	**0.009**	2.10 (1.18, 3.74)	**0.011**	1.96 (1.09, 3.52)	**0.025**	1.98 (1.10, 3.58)	**0.023**
FTS5 > 25	3.35 (1.93, 5.83)	**<0.001**	2.29 (1.23, 4.25)	**0.009**	2.15 (1.15, 4.01)	**0.016**	1.73 (0.91, 3.30)	0.095	1.81 (0.95, 3.46)	0.073
Incident disability	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FTS5 change in 1 point (continuous)	1.09 (1.06, 1.12)	**<0.001**	1.07 (1.04, 1.11)	**<0.001**	1.07 (1.04, 1.10)	**<0.001**	1.06 (1.03, 1.10)	**<0.001**	1.07 (1.03, 1.10)	**<0.001**
Reference (FTS5 ≤ 10)	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
FTS5 > 10 and ≤15	1.50 (0.88, 2.55)	0.134	1.23 (0.71, 2.12)	0.467	1.23 (0.71, 2.13)	0.458	1.24 (0.71, 2.15)	0.455	1.25 (0.72, 2.18)	0.434
FTS5 > 15 and ≤20	1.79 (1.04, 3.11)	**0.037**	1.48 (0.84, 2.61)	0.179	1.42 (0.80, 2.53)	0.228	1.33 (0.74, 2.39)	0.333	1.32 (0.73, 2.36)	0.355
FTS5 > 20 and ≤25	3.46 (1.99, 6.01)	**<0.001**	2.49 (1.37, 4.54)	**0.003**	2.44 (1.34, 4.45)	**0.004**	2.33 (1.26, 4.30)	**0.007**	2.36 (1.27, 4.37)	**0.006**
FTS5 > 25	5.16 (2.74, 9.73)	**<0.001**	3.46 (1.72, 6.95)	**0.001**	3.19 (1.57, 6.48)	**0.001**	2.71 (1.31, 5.64)	**0.007**	2.80 (1.34, 5.83)	**0.006**

95% CI, 95% confidence interval; FTS5, Frailty Trait Scale 5; HR, hazard ratio; OR, odds ratio.
In bold: P value < 0.05. Model 1: raw model. Model 2: Model 1 plus age and gender. Model 3: Model 2 plus MMSE. Model 4: Model 3 plus Charlson Index, Polypharmacy, and Katz Index. Model 5: Model 4 plus educational level.

FI has been shown to predict death equally well or better than the Fried phenotype[21] and some studies have studied frailty trajectories according to the FI.[22,23] However, FI is subject to measurement error due to self-reported health data, having a number of changeable items, which difficult its comparison, and would not allow for capturing improvements in frailty because the data on which it is based are mostly on long-term or irreversible deficits.[24] These two tools are supposed to measure the same construct, but using different domains and approaches. Because of that, some authors have raised the possibility that they can complement each other.[25] Notwithstanding, FTS5 may capture this construct with a better accuracy.[8] However, although FTS5 is a recent and promising scale, it should be validated in other cohorts.

Regarding the GBTM algorithm classification quality, the mean posterior probability of membership to each group is greater than 0.70, which is taken as a consistent indication that the modelled trajectories group individuals with similar patterns of change according to the outcome variable and discriminate between individuals with dissimilar patterns of change in a specific variable over time.[26]

Our findings regarding FTS5 trajectories and adverse events cannot be directly compared with previous studies due to the novelty of the scale and the identification of subgroups using GBTM. Although GBTM has been used by previous studies in order to explore the longitudinal evolution of subtypes[27] and factors related to frailty,[28] as physical activity,[29] we have only identified one study which used this method to explore frailty evolution with adverse outcomes.[30] This latter study examined patterns of cognition and frailty in 690 community-dwelling older adults and found that longitudinal declines in cognition had twice higher rates of hospitalization. According to disability, those with declines in cognition had higher rates of mobility disability, instrumental activities of daily living, but the dose–response association was especially accentuated for activities of daily living disability.[30]

Disablement process is not linear and could fluctuate in cycles of deterioration and recovery short time periods, and these fluctuations could be higher in late life.[22] Nevertheless, although disabled rates increase with ageing,[30] their evolution could depend on intraindividual variability in mobility limitation.[31] This finding supports frailty as a multidimensional measurement of health status and a sign of a loss of homeostasis with overall system vulnerability to estimate adverse event risk and an opportunity to anticipate disability.[1,5,8] Our results show that those trajectories of physical and functional decline are more likely to lead to disability or to a progress in their disability levels. Only those subjects who had moderate frailty scores and improved them (*improving to non-frailty*) have no statistically significant differences with respect to the reference trajectory. However, to date, no study has studied FTS5 fluctuations in shorter time intervals as a prognostic value to disability or mortality.

Frailty evolution has been previously associated with death. Buchman *et al.* analysed trajectories in a continuous frailty scale using gait speed, grip strength, body composition, and fatigue and found that baseline frailty and annual change in frailty were independently associated with mortality in a similar way of using a categorical frailty measure after adjustment for confounders. This approach reached also statistically results when the authors studied instrumental and basic activities of daily living incident disability, obtaining similar results to ours.[32] Rapid or moderate increases compared with those with stable frailty,[33] or those with higher fluctuations[22] in Frailty Index scores, were associated with higher mortality. Moreover, a 12 year follow-up study from the Canadian National Population Health Survey showed that the less frail individuals at baseline showed a healthier profile at follow-up, whereas frailer participants were more likely to die and utilized more healthcare services during the same period,[34] consistent with clinical experience and frailty constructs.[35]

Improvements in medicine jointly to other socio-economic facts have led to an extended lifespan but in many cases, accompanied by chronic health problems and disabilities associated with ageing.[35] According to some studies, current population cohorts are not only ageing, but they may also be frailer, especially in low-income individuals.[36] The surveillance of frailty status is paramount to predict older adults' future health[35] and public health burden and must be a priority for public health policies.[37] Our findings might support studies that indicate that the increase in life expectancy is associated with greater levels of frailty, leading to disability what may lead to greater costs for medical care, social services, and long-term care.[38]

Strengths and limitations

This study has many strengths, including the large population included, the excellent ascertainment of adverse events, and the inclusion of relevant confounders that might distort the associations.

We used GBTM, a novel powerful statistical tool to group subjects into patterns of evolution over age or time of a variable of interest according to the baseline score, magnitude, and direction of the change without using *ad hoc*, *ex ante* classification rules.[15,16] Nevertheless, it is inherently limited at capturing individual variability and may lead to overgrouping.[16] Because only two measurements were available to assess trajectories, the results should be interpreted with caution because the existing evidence suggests that studies with two time points cannot measure within-person change[39] but instead changes in terms of rank-order in the levels of a variable. Confirmation of our results in studies with more time points is therefore warranted.

Our study used two frailty assessments that were 5.04 years apart on average. Therefore, when clustering individuals, we could have failed at differentiating between rapid changes in frailty attending to an increasing individual vulnerability before death and more progressive changes related to ageing process. More frequent assessment might assist in reducing this bias.

Furthermore, discrepancies between how frailty is conceptualized, and the lack of a gold standard definition or tool limits our results extrapolation.

Future directions

Although works of frailty trajectories are a growing research area, more prospective works are necessary to confirm these results, analysing drivers and predicting trends in frailty states and ways to prevent and modify increases in frailty prevalence.

Older adults' health improvements and policies to promote them will potentially reduce costs incurred by an aged population. In not doing so, medical care, social services, and long-term care may lead to greater costs.[38] The better knowledge we have on how frailty changes over time, the better we could prevent it with rehabilitation, physical exercise, or nutritional programmes. Individualized programmes for older adults according to their frailty status are paramount in the clinical setting, especially in terms of functional outcomes.[40] In this regard and in the absence of a pharmacological approach for frailty, physical exercise has arisen as the unique contrasted alternative, with growing evidence in frail community dwellers, what have led some experts to question whether not prescribing it might be unethical.[41] Nevertheless, more research focusing on the intensity, timing of exercise and identification of the population who might benefit the most from those interventions are still necessary.

Conclusions

Our results support frailty as a continuum physiological construct with a proportional dose–effect relationship against adverse outcomes. Our study contributes to expand the notion of frailty dynamic nature and points towards the association of its load reduction and reduced risk of adverse events such as mortality, hospitalization, and disability. We

suggest that interventions tailored to the individual frailty status might positively impact the economic and public health burden of frailty.

Conflict of interest

Nothing to declare.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographic characteristics of the sample according to the FTS5 score.
Appendix S1. Frailty Trait Scale 5 (FTS5) score.

References

1. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a delphi method based consensus statement. The frailty operative definition-consensus conference project. *J Gerontol - Ser A Biol Sci Med Sci* 2013;**68**: 62–67.
2. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012;**60**: 1487–1492.
3. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a

dynamic process. *Gerontology* 2009;**55**: 539–549.

4. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K. Transitions between frailty states among community-dwelling older people: a systematic review and meta-analysis. *Ageing Res Rev* 2019;**50**:81–88.

5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**: M146–M156.

6. Welstead M, Jenkins ND, Russ TC, Luciano M, Muniz-Terrera G. A systematic review of frailty trajectories: their shape and influencing factors. *Gerontologist* 2020;**61**: e463–e475.

7. García-García FJ, Carcaillon L, Fernandez-Tresguerres J, Alfaro A, Larrion JL, Castillo C, et al. A new operational definition of frailty: the frailty trait scale. *J Am Med Dir Assoc* 2014;**15**:371.e7–371.e13.

8. García-García FJ, Carnicero JA, Losa-Reyna J, Alfaro-Acha A, Castillo-Gallego C, Rosado-Artalejo C, et al. Frailty trait scale-short form: a frailty instrument for clinical practice. *J Am Med Dir Assoc* 2020;**21**:1260–1266.e2.

9. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev* 2016;**26**:53–61.

10. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol - Ser A Biol Sci Med Sci* 2007;**62**: 722–727.

11. Garcia-Garcia FJ, Gutierrez Avila G, Alfaro-Acha A, Andres MA, Aparicio ME, Aparicio SH, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo study for healthy aging. *J Nutr Health Aging* 2011;**15**:852–856.

12. Katz S, Downs T, Cash H. Progress in development of the index of ADL—PubMed. *Gerontologist* 1970;**10**:20–30.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–383.

14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**: 189–198.

15. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010;**6**:109–138.

16. Nagin DS. Group-based trajectory modeling: an overview. In *Annals of Nutrition and Metabolism*, Vol. **65**. S. Karger AG; 2014. p 205–210.

17. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociol Methods Res* 2001;**29**:374–393.

18. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med* 2006;**166**:418–423.

19. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitja-Rabert M, Salvà A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014;**95**: 753–769.

20. Rodriguez-Mañas L, Laosa O, Vellas B, Paolisso G, Topinkova E, Oliva-Moreno J, et al. Effectiveness of a multimodal intervention in functionally impaired older people with type 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle* 2019;**10**: 721–733.

21. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol - Ser A Biol Sci Med Sci* 2007;**62**:738–743.

22. Stolz E, Mayerl H, Freidl W. Fluctuations in frailty among older adults. *Age Ageing* 2019;**48**:547–552.

23. Chamberlain AM, Rutten LJF, Manemann SM, Yawn BP, Jacobson DJ, Fan C, et al. Frailty trajectories in an elderly population-based cohort. *J Am Geriatr Soc* 2016;**64**:285–292.

24. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Rikkert MO, Nijhuis-Van der Sanden MW. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011;**10**:104–114.

25. Cesari M, Gambassi G, Abellan van Kan G, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 2014;**43**: 10–12.

26. Andruff H, Carraro N, Thompson A, Gaudreau P. Latent class growth modelling: a tutorial. *Tutor Quant Methods Psychol* 2009;**5**:11–24.

27. Huang S, Tange C, Otsuka R, Nishita Y, Peng LN, Hsiao FY, et al. Subtypes of physical frailty and their long-term outcomes: a longitudinal cohort study. *J Cachexia Sarcopenia Muscle* 2020;**11**:1223–1231.

28. Howrey BT, Al Snih S, Middleton JA, Ottenbacher KJ. Trajectories of frailty and cognitive decline among older Mexican Americans. *J Gerontol Ser A* 2020;**75**: 1551–1557.

29. Sanchez-Sanchez JL, Izquierdo M, Carnicero-Carreño JA, García-García FJ, Rodríguez-Mañas L. Physical activity trajectories, mortality, hospitalization, and disability in the Toledo Study of Healthy Aging. *J Cachexia Sarcopenia Muscle* 2020;**11**:1007–1017.

30. Liu Z, Han L, Gahbauer EA, Allore HG, Gill TM. Joint trajectories of cognition and frailty and associated burden of patient-reported outcomes. *J Am Med Dir Assoc* 2018;**19**:304–309.e2.

31. Lin J, Kelley-Moore JA. From noise to signal: the age and social patterning of intra-individual variability in late-life health. *J Gerontol B Psychol Sci Soc Sci* 2017;**72**:168–179.

32. Buchman AS, Wilson RS, Bienias JL, Bennett DA. Change in frailty and risk of death in older persons. *Exp Aging Res* 2009;**35**: 61–82.

33. Stow D, Matthews FE, Hanratty B. Frailty trajectories to identify end of life: a longitudinal population-based study. *BMC Med* 2018;**16**:171. https://doi.org/10.1186/s12916-018-1148-x

34. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *CMAJ* 2011;**183**:E487–E494.

35. Rodriguez-Mañas L, Fried LP. Frailty in the clinical scenario. *Lancet* 2015;**385**:e7–e9.

36. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. *J Epidemiol Community Health* 2015;**69**:316–321.

37. Rodríguez-Artalejo F, Rodríguez-Mañas L. The frailty syndrome in the public health agenda. *J Epidemiol Community Health* 2014;**68**:703–704.

38. Sirven N, Rapp T. The dynamics of hospital use among older people evidence for Europe using SHARE data. *Health Serv Res* 2017;**52**:1168–1184.

39. King KM, Littlefield AK, McCabe CJ, Mills KL, Flournoy J, Chassin L. Longitudinal modeling in developmental neuroimaging research: common challenges, and solutions from developmental psychology. *Dev Cogn Neurosci* 2018;**33**:54–72.

40. Romero-Ortuno R, Tiernan C, Cogan L. The impact of frailty on post-acute rehabilitation outcomes in older adults. *J Frailty Aging* 2014;**3**:234–237.

41. Izquierdo M, Rodriguez-Mañas L, Casas-Herrero A, Martinez-Velilla N, Cadore EL, Sinclair AJ. Is it ethical not to precribe physical activity for the elderly frail? *J Am Med Dir Assoc* 2016;**17**:779–781.

42. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the journal of cachexia, sarcopenia and muscle: update 2019. *J Cachexia Sarcopenia Muscle* 2019;**10**:1143–1145.