Archives of Gerontology and Geriatrics 95 (2021) 104401

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Transitions in frailty phenotype states and components over 8 years: Evidence from The Irish Longitudinal Study on Ageing

Roman Romero-Ortuno [a,b,c,#,*], Peter Hartley [a,b,d,#], James Davis [a,b], Silvin P. Knight [a,b], Rossella Rizzo [a,b], Belinda Hernández [a,b], Rose Anne Kenny [a,b,c], Aisling M. O'Halloran [a,b]

[a] The Irish Longitudinal Study on Ageing, Trinity College Dublin, Ireland
[b] Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Ireland
[c] Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland
[b] Department of Public Health and Primary Care, University of Cambridge, United Kingdom

ARTICLE INFO

Keywords:
Aged
Frailty
Longitudinal
Surveys
Transition

ABSTRACT

Aim: Fried's frailty phenotype (FP) is defined by exhaustion (EX), unexplained weight loss (WL), weakness (WK), slowness (SL) and low physical activity (LA). Three or more components define the frail state, and one or two the prefrail. We described longitudinal transitions of FP states and components in The Irish Longitudinal Study on Ageing (TILDA).

Methods: We included participants aged ≥50 years with FP information at TILDA wave 1 (2010), who were followed-up over four longitudinal waves (2012, 2014, 2016, 2018). Next-wave transition probabilities were estimated with multi-state Markov models.

Results: 5683 wave 1 participants were included (2612 men and 3071 women; mean age 63.1 years). Probabilities from non-frail to prefrail, and non-frail to frail were 27% and 2%, respectively. Prefrail had a 32% probability of reversal to non-frail, and a 10% risk of progression to frail. Frail had an 18% probability of reversal to prefrail and 31% risk of death. Probabilities of transitioning from not having to having a component were: 17% for LA, 11% for SL, 9% for EX, 7% for WL and 6% for WK. Probabilities of having a FP component and dying were: 17% for WL, 15% for WK, 14% for SL, 13% for EX, and 10% for LA. Probabilities of having a component and recovering at the next wave were: 59% for WL, 58% for EX, 40% for WK, 35% for LA and 23% for SL.

Conclusions: FP states and components are characterized by dynamic longitudinal transitions. Opportunities exist for reducing the probability of adverse transitions.

1. Introduction

In 2001, Fried *et al.* (Fried et al., 2001) developed and operationalized, in the US Cardiovascular Health Study (CHS), a frailty phenotype (FP) in older adults characterized by the following five components: unintentional weight loss, self-reported exhaustion, weakness (by grip strength), slow walking speed and low physical activity. According to this operationalization, prefrailty was defined, independently of age and sex, as a state defined by the presence of one or two criteria, and frailty as the state of having three or more (Fried et al., 2001).

Although individual FP components are equally considered in the computation of the FP score, it has been argued that each of them may have different weights in clinical practice (Hoogendijk et al., 2015). Indeed, there has been debate as to whether the FP should be considered as a unidimensional or a multidimensional construct (King-Kallimanis, Kenny, and Savva, 2014). Emerging evidence has suggested that the FP is not a homogeneous biological syndrome and that different combinations of the five FP components may have different metabolic and biomarker correlates (Liu et al., 2017) and implications for future morbidity (Huang et al., 2020), disability (Provencher et al., 2017), health outcomes including falls, emergency department visits, hospitalizations and institutionalizations (Liu et al., 2017), and mortality risk (Liu et al., 2017, Vidan et al., 2016, Romero-Ortuno, Scarlett, O'Halloran, and Kenny, 2019). A similar suggestion has been made as regards the association of individual FP components with different quality of life dimensions (Moreno-Aguilar et al., 2013). A call has been made for a

* Corresponding author at: Discipline of Medical Gerontology, 6th Floor, Mercer's Institute for Successful Ageing (MISA), St James's Hospital, Dublin 8, Ireland.
E-mail address: romeroor@tcd.ie (R. Romero-Ortuno).
# Authors contributed equally.

https://doi.org/10.1016/j.archger.2021.104401
Received 7 December 2020; Received in revised form 10 March 2021; Accepted 22 March 2021
Available online 26 March 2021

more differentiated approach to the FP bringing into consideration the specific influence of its components (Alves, Teixeira, Ribeiro, and Paul, 2020).

Since the seminal study by Gill *et al.* reporting for the first time transitions in FP states (i.e. non-fail, pre-frail, frail) (Gill, Gahbauer, Allore, and Han, 2006), research efforts have been dedicated to study patterns and determinants of those transitions, highlighting that they are dynamic over time (Kojima et al., 2019). Yet, in the face of increasing attention to individual FP components, there has been less work on the modelling of their longitudinal transitions. Our aim was to describe the 8-year longitudinal transitions of both FP states and components using data from a longitudinal study of ageing.

2. Methods

2.1. Design and setting

We analyzed data from a population-based longitudinal study that collects information on the health, economic and social circumstances from people aged 50 and over in Ireland (The Irish Longitudinal Study on Ageing: TILDA). Wave 1 of the study (baseline) took place between October 2009 and February 2011, and subsequent data was collected approximately 2-yearly over four longitudinal waves (wave 2: February 2012 to March 2013; wave 3: March 2014 to October 2015; wave 4: January to December 2016; wave 5: January to December 2018). An overview of the study is available on https://tilda.tcd.ie/about/where-are-we-now/. Waves 1 and 3 included a detailed health assessment conducted at a health centre. Waves 2, 4 and 5 were non-health centre waves. The full cohort profile has been described elsewhere (Donoghue et al., 2018, Kearney et al., 2011).

2.2. Sample

The baseline analytical sample included participants who had complete FP information at Wave 1. For subsequent waves, information was collected on transitions in FP states and components. Information was also collected on attrition due to deaths or missing data.

2.3. Frailty Phenotype measures

In each TILDA wave, the operationalization of the FP was conducted following the methodology of Fried *et al.* (Fried et al., 2001). Full details have been described elsewhere (O'Halloran et al., 2014, Peklar et al., 2015, Savva et al., 2013); in short, the FP was operationalized using population-specific cut-points owing to differences in the assessments of weakness (sex- and body mass index-adjusted grip strength measured with dynamometer on the dominant hand), physical activity (sex--adjusted kilocalories from the International Physical Activity Questionnaire-Short Form [IPAQ-SF] (Donoghue, O'Connell, and Kenny, 2016)), and walking speed (sex- and height-adjusted time in seconds to complete the Timed Up and Go [TUG] task). The IPAQ-SF asked respondents to indicate the number of days and typical time per day spent walking and doing physical activities of vigorous or moderate intensity during the last week. Weight loss was ascertained by the question "In the past year, have you lost 10 pounds (4.5 kg) or more in weight when you were not trying to?" Exhaustion was captured using 2 items from the 20-item Centre for Epidemiological Studies Depression (CES-D) scale (Orme, Reis, and Herz, 1986). Participants were asked how often they felt in the past week that "I could not get going" and "I felt that everything I did was an effort". A response of "moderate amount/all of the time" to either question was considered as exhaustion.

The original FP differed from the TILDA FP operationalization in that in the original FP, the physical activity criterion was based on the short version of the Minnesota Leisure Time Activity Questionnaire (in Kcals per week); slowness was based in time used to walk 15 feet at usual pace (rather than measured TUG); and maximal grip strength (kilograms) was measured in the dominant hand (3 measures averaged) using a Jamar hand-held dynamometer (in TILDA, two measures of handgrip strength were taken from the dominant hand with a Baseline Hydraulic Hand dynamometer, and the mean of these readings was calculated) (O'Halloran et al., 2014, TILDA 2010). In TILDA, the weight loss and the exhaustion items were defined in the same terms as in the original FP.

2.4. Other measures

Age was measured at baseline and each wave, and all the following were measured at baseline: sex (male = 0; female =1). Highest education level achieved at TILDA Wave 1 (primary or less = 1; secondary =2; third/higher =3). Number of chronic conditions counted from the following 27: hypertension; high cholesterol; angina; heart attack; heart failure; diabetes; stroke; TIA; heart murmur; heart rhythm problem; other cardiovascular disease; chronic lung disease; asthma; arthritis; osteoporosis; cancer or malignant tumor (excluding minor skin cancers); Parkinson's disease; emotional/nervous/psychiatric condition (depression or anxiety); alcohol or substance abuse; Alzheimer's disease, dementia or serious memory impairment; stomach ulcers; varicose ulcers; cirrhosis or serious liver damage; cataracts; glaucoma; and age-related macular degeneration. Number of self-reported difficulties in basic activities of daily living (ADL), counted from the following list: dressing, including putting on shoes and socks; walk across a room; bathing or showering; eating, such as cutting up food; getting in or out of bed; and using the toilet, including getting up or down (TILDA 2012). Polypharmacy, defined as regularly taking 5 or more medications (no = 0; yes =1). Living alone (no = 0; yes =1). Self-rated physical health (excellent = 1; very good = 2; good = 3; fair = 4; poor = 5).

2.5. Mortality

Regarding mortality, it was ascertained for all study participants at each follow-up wave. TILDA has approval from Ireland's Central Statistics Office to link survey respondents to their death certificate information held centrally by the General Register Office, where every death in the Republic of Ireland must be registered (Ward et al., 2020). Other than deaths, attrition at each wave was classified as 'missing'.

2.6. Statistical analyses

Descriptive statistics were computed with IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and given as mean with standard deviation (SD) and range, median with interquartile range (IQR), or proportion (%). To test for statistical association between baseline FP states (ordinal variable) and participant characteristics, the two-sided Spearman's rank correlation coefficient was used for continuous and ordinal variables, and the Chi-squared for trend test for dichotomous variables.

For the visualization of the longitudinal trajectories of the three FP states and five FP components, two alluvial charts were created using the R ggalluvial package (Bojanowski and Edwards, 2016). In each alluvial plot, the height of the stacked bars at each wave (which represent whether participants' status for the given frailty state or component was yes, no, missing or died) is proportional to the number of participants identified as belonging to this state at each wave. The thickness of the streams connecting the stacked bars between waves are proportional to the number of participants who have the state identified by both ends of the stream.

To estimate transition probabilities separately for FP states and components, we used multi-state Markov models using the R msm package, which allows a general multi-state model to be fitted to longitudinal data (Jackson, 2011). The multi-state Markov model is a way of describing a process in which individuals move through a series of states over time. In our design, each model had three states: a positive health characteristic (e.g. not exhausted), a negative health

Table 1
Proportions of FP states, components, and deaths at each wave.

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
Non-frail	64.1% (n=3645)	65.7% (n=3126)	59.9% (n=2126)	51.2% (n=1833)	47.6% (n=1551)
Prefrail	32.1% (n=1822)	30.5% (n=1453)	35.2% (n=1249)	42.1% (n=1507)	44.1% (n=1436)
Frail	3.8% (n=216)	3.7% (n=178)	4.9% (n=173)	6.7% (n=238)	8.3% (n=271)
Exhaustion	9.2% (n=520)	8.9% (n=463)	10.8% (n=510)	10.5% (n=454)	10.8% (n=418)
Unexplained weight loss	7.0% (n=395)	7.7% (n=404)	7.7% (n=370)	8.0% (n=351)	7.9% (n=308)
Weakness	12.4% (n=703)	6.8% (n=336)	10.0% (n=383)	9.3% (n=368)	10.9% (n=385)
Slowness	9.8% (n=558)	15.3% (n=780)	13.5% (n=564)	20.3% (n=813)	24.9% (n=899)
Low physical activity	14.4% (n=821)	14.2% (n=719)	19.5% (n=792)	32.0% (n=1300)	33.7% (n=1239)
Deaths	0.0% (n=0)	1.8% (n=102)	2.9% (n=165)	2.5% (n=140)	3.1% (n=176)

characteristic (e.g. exhausted), and death. All missing data were censored and considered missing completely at random. In addition, we conducted sensitivity analyses where missing data was modelled as an additional state in the models. We obtained matrices of estimated transition probabilities from wave x to wave x + 1 (with 95% confidence intervals [CIs]) for each FP state or component. We adjusted the multi-state Markov models for age and sex, as these non-modifiable factors have been associated with differences in incidence and determinants of the FP (Alexandre et al., 2018); education was also adjusted for as it has also been found to be an important determinant of the FP (Brigola et al., 2019). Multi-state Markov models handle confounders at baseline and subsequent waves. Whilst sex and education remained constant across waves, the age covariate was time-varying (i.e. increased for each wave); if participants missed a wave, age was imputed by adding 2 years from the preceding wave. Hazard ratios (HRs) and 95% CIs for the estimated covariate effects of age, sex and education were obtained. HRs were considered significant when their CIs did not include 1.

2.7. Ethics

Ethical approval for each wave was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, Ireland. All participants provided written informed consent prior to inclusion in the study.

3. Results

TILDA wave 1 recruited a total of 8504 participants, of whom 330 (3.9%) were aged less than 50 years. Among the remaining 8174, there were 5683 participants (69.5%) with complete FP information (2612 men and 3071 women). The mean (SD; minimum, maximum) age of wave 1 participants (n=5683) was 63.1 (9.2; 50-98) years; for wave 2 (n=5223): 65.0 (9.1; 52-97); for wave 3 (n=4806): 67.0 (8.8; 54-98); for wave 4 (n=4380): 68.8 (8.5; 56-101); and for wave 5 (n=3931): 70.3 (8.2; 58-103). The counts and proportions for FP states, components and deaths at each wave is presented in Table 1, and wave 1 cross-sectional associations between FP states and other characteristics are detailed in Table 2.

The alluvial plots are shown in Figures 1a (FP states) and 1b (FP components), and the transition numbers are detailed in Appendix 1. As expected, the cumulative proportion of deaths increased across waves. The proportion of missing data also tended to increase across waves, but more linearly so for the exhaustion and weight loss components. Appendix 2 details the proportions of baseline FP components (by Wave) in participants who improved their FP state (i.e. from prefrail to non-frail, frail to prefrail, or frail to non-frail) and participants whose FP state declined (i.e. from prefrail to frail, non-frail to frail, or non-frail to prefrail).

Table 3 shows, for FP states and components, the transition probabilities (with 95% CIs) of moving from one state to another over the course of one wave. Probabilities from non-frail to prefrail, and non-frail

Table 2
Baseline characteristics associated with frailty states.

	Non-frail (n=3645)	Prefrail (n=1822)	Frail (n=216)	P
Mean age (SD)	61.2 (7.9)	65.8 (10.1)	71.9 (11.3)	<0.001*
Female sex (%)	53.0	55.9	55.1	0.065^
Education level				<0.001*
-Up to primary	21.2	33.0	49.1	
-Secondary	42.2	39.5	35.2	
-Third/higher	36.6	27.6	15.7	
Median number of chronic conditions (IQR)	1.0 (2.0)	2.0 (3.0)	4.0 (3.0)	<0.001*
Median number of ADL difficulties (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (2.0)	<0.001*
Polypharmacy (%)	12.4	31.4	61.9	<0.001^
Living alone (%)	16.2	25.8	32.9	<0.001^
Self-rated physical health:				<0.001*
-Excellent	20.1	10.5	1.9	
-Very good	34.9	22.5	8.8	
-Good	32.0	34.5	15.3	
-Fair	11.6	25.0	39.4	
-Poor	1.3	7.4	34.7	
Exhaustion (%)	0.0	22.2	53.5	<0.001^
Unexplained weight loss (%)	0.0	16.5	43.7	<0.001^
Weakness (%)	0.0	30.6	68.9	<0.001^
Slowness (%)	0.0	21.6	78.5	<0.001^
Low physical activity (%)	0.0	34.9	85.6	<0.001^

SD: standard deviation; IQR: interquartile range; ADL: activities of daily living; * Spearman's rank correlation coefficient; ^ Chi-squared for trend.

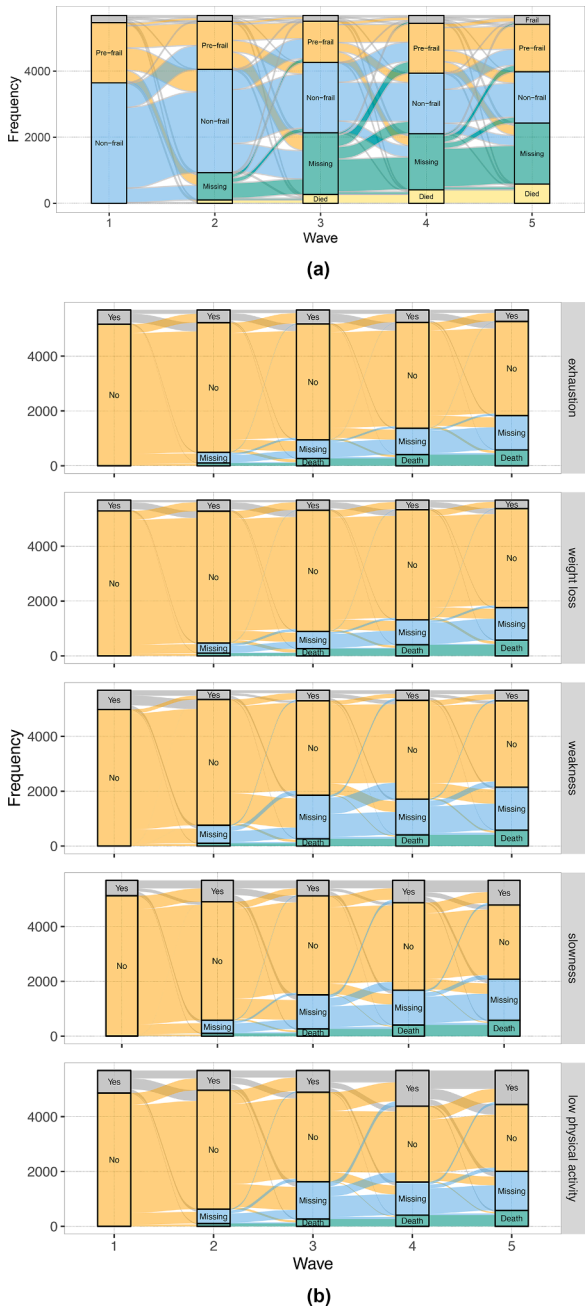

Figure 1. **a**. Alluvial chart of the longitudinal transitions of FP states in TILDA. **b**. Alluvial chart of the longitudinal transitions of FP components in TILDA.

to frail were 27% and 2%, respectively. Prefrail had a 32% probability of reversal to non-frail, and a 10% risk of progression to frail. Frail had a 6% probability of reversal to non-frail, an 18% probability of reversal to prefrail, and a 31% risk of death. Risks of death for non-frail and prefrail states were low (0% and 3%, respectively).

As regards FP components, probabilities of transitioning from not having to having a component were: 17% for low physical activity, 11% for slowness, 9% for exhaustion, 7% for weight loss and 6% for weakness. In terms of the probability of having a FP component and staying the same at the next wave, it was 63% for slowness, 56% for low physical activity, 45% for weakness, 29% for exhaustion, and 24% for weight loss. Probabilities of having an FP component and dying at the next wave were: 17% for weight loss, 15% for weakness, 14% for slowness, 13% for exhaustion, and 10% for low physical activity. Probabilities of having a component and recovering at the next wave were: 59% for weight loss, 58% for exhaustion, 40% for weakness, 35% for low physical activity and 23% for slowness. Probabilities for other transitions are shown in Table 3.

Appendix 3 shows a sensitivity analysis of the same multi-state Markov models where missing data was modelled as an additional state. As regards FP states, the probability of remaining missing was 60%, and there was an increasing probability gradient for transitioning to missing from non-frail (18%), prefrail (24%) and frail (32%) states. A similar pattern consistently occurred with the components, in that the most likely transitions were from missing to missing, but having the component had a higher probability of going missing than not having it (Appendix 3).

Table 4 shows the HRs and 95% CIs of the estimated covariate effects of sex, age and education (secondary and third compared to primary or less) in the multi-state Markov models. Based on the number of significant associations (depicted in bold in Table 4), results suggest that the effect of age was more influential than sex and education for many transitions.

Being older increased the risk of adverse state transitions from frail to death, from prefrail to frail, from non-frail to prefrail, and from non-frail to death. The opposite was suggested for favourable transitions from frail to prefrail, and prefrail to non-frail. Being older also increased the risk of adverse component transitions, from not having to having components, and from having components to dying at the next wave (Table 4). The opposite was true for transitions from having to not having components. As regards transitions from not having a component to death, higher age seemed to be implicated in exhaustion and weakness, but the opposite was suggested for physical activity (i.e. higher age seemed associated with reduced risk of transitioning from being physically active to death) (Table 4).

As regards sex, there were no significant associations with state transitions (Table 4). Being female increased the risk of adverse component transitions from no exhaustion to exhaustion, and no weight loss to weight loss; and decreased the risks from exhaustion to death, weight loss to death, slowness to death, and low physical activity to death. Female sex was also implicated in favourable component transitions from weakness to no weakness and slowness to no slowness (Table 4). In terms of education, there were trends in the expected direction with higher levels of baseline education being positively associated with favourable transitions and negatively associated to adverse transitions (Table 4). Notably, third-level education was consistently associated with reduced risk of not having to having FP components (Table 4).

4. Discussion

Using data from a population-based study of ageing spanning an 8-year period, we created alluvial plots to show that favorable and non-favorable longitudinal transitions in individual FP states and components are frequent. Using multi-state Markov models, we demonstrated that the probabilities of such transitions are different for different FP states and components, and that most are affected by age and some by sex and baseline education. Results paint a rather dynamic picture of longitudinal transitions in both FP states and components.

The general characterization of the FP states in our cohort (Table 2) is consistent with the original premise of the FP being an age-related syndrome driven by multimorbidity, with adverse psychosocial correlates, but representing a state of pre-disability (Fried et al., 2004) (i.e. low ADL burden), offering opportunities for interventions on modifiable factors that may delay or even reverse the disabling process (Travers, Romero-Ortuno, Bailey, and Cooney, 2019, Dent et al., 2019). While the risks of adverse progression from non-frail to prefrail, and prefrail to frail, were 27% and 10% respectively, favourable transitions from frail to prefrail, an especially prefrail to non-frail were also common (18% and 32%, respectively).

As regards reversibility in FP states, a previous systematic review (16

Table 3
Estimated transition probability (and 95% CI) matrix for each frailty phenotype state and component (from wave x to wave x + 1).

	STATE TO			
STATE FROM	**Non-frail**	**Prefrail**	**Frail**	**Death**
Non-frail	0.71 (0.70, 0.71)	0.27 (0.26, 0.27)	0.02 (0.02, 0.03)	0.00 (0.00, 0.01)
Prefrail	0.32 (0.31, 0.33)	0.55 (0.54, 0.57)	0.10 (0.09, 0.10)	0.03 (0.03, 0.04)
Frail	0.06 (0.05, 0.07)	0.18 (0.16, 0.20)	0.46 (0.43, 0.48)	0.31 (0.28, 0.33)
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)
	COMPONENT TO			
COMPONENT FROM	**Exhaustion**	**No Exhaustion**	**Death**	
Exhaustion	0.29 (0.27, 0.31)	0.58 (0.56, 0.61)	0.13 (0.10, 0.15)	
No Exhaustion	0.09 (0.08, 0.09)	0.90 (0.89, 0.90)	0.02 (0.02, 0.03)	
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	
	Weight loss	**No weight loss**	**Death**	
Weight loss	0.24 (0.22, 0.26)	0.59 (0.56, 0.61)	0.17 (0.16, 0.19)	
No weight loss	0.07 (0.07, 0.08)	0.91 (0.90, 0.91)	0.02 (0.01, 0.02)	
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	
	Weakness	**No weakness**	**Death**	
Weakness	0.45 (0.43, 0.48)	0.40 (0.37, 0.42)	0.15 (0.13, 0.17)	
No weakness	0.06 (0.06, 0.06)	0.92 (0.92, 0.93)	0.02 (0.01, 0.02)	
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	
	Slowness	**No slowness**	**Death**	
Slowness	0.63 (0.61, 0.65)	0.23 (0.22, 0.25)	0.14 (0.13, 0.15)	
No slowness	0.11 (0.11, 0.12)	0.88 (0.87, 0.88)	0.01 (0.01, 0.01)	
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	
	Physically inactive	**Physically active**	**Death**	
Physically inactive	0.56 (0.54, 0.57)	0.35 (0.33, 0.36)	0.10 (0.09, 0.11)	
Physically active	0.17 (0.16, 0.17)	0.82 (0.81, 0.83)	0.01 (0.01, 0.02)	
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	

CI: Confidence Interval.

studies) reported a 23.1% (18.8% - 27.6%) probability of transition from prefrail to non-frail, 3.3% (1.6% - 5.5%) from frail to non-frail, and 40.3% (34.6% - 46.1%) from frail to prefrail (Kojima et al., 2019). Our results are more optimistic for transitions from prefrail to non-frail (32%) and frail to non-frail (6%), but considerably less optimistic for improvement from frail to prefrail (18%). Based on our results, we agree with others (Dent et al., 2019, Sezgin, Liew, O'Donovan, and O'Caoimh, 2020) that prefrailty may be a better target than frailty for population-based interventions. Our results also agree with those from the Whitehall II cohort highlighting the importance of socioeconomic status (including education) in the risk of developing frailty (Dugravot et al., 2020), and with findings from the San Antonio Longitudinal Study of Aging that fewer years of education were an important predictor of progression in any frailty characteristic (Espinoza, Jung, and Hazuda, 2012). In our analyses, education referred to the level attained at baseline (Wave 1) and was a fixed variable for the computation of the Hazard ratios in the multi-state Markov models (Table 4).

At the level of the FP components, we saw large reversibility

Table 4
Hazard ratios and 95% CIs of the estimated covariate effects of sex, age and education in the multi-state Markov models.

From - To	Sex = Female	Age	Education = Secondary	Education = Third/Higher
Frail - Pre-frail	1.12 (0.84, 1.51)	**0.71 (0.61, 0.82)**	1.23 (0.88, 1.72)	**1.46 (1.00, 2.12)**
Frail - Non-frail	0.58 (0.00, 1.51×10^9)	0.34 (0.00, 1127.23)	1.30 (0.00, 2.87×10^7)	1.11 (0.00, 2.80×10^7)
Frail - Death	0.81 (0.65, 1.00)	**1.30 (1.13, 1.50)**	0.93 (0.71, 1.20)	1.10 (0.85, 1.43)
Pre-frail - Frail	0.91 (0.77, 1.07)	**2.01 (1.81, 2.22)**	0.85 (0.70, 1.03)	0.78 (0.64, 0.96)
Pre-frail - Non-frail	1.02 (0.91, 1.15)	**0.62 (0.58, 0.67)**	**1.23 (1.05, 1.43)**	**1.27 (1.09, 1.49)**
Pre-frail - Death	0.56 (0.15, 2.07)	0.42 (0.10, 1.83)	0.63 (0.12, 3.47)	0.09 (0.00, 11.31)
Non-frail - Frail	0.11 (0.00, 3.96)	0.12 (0.01, 1.88)	0.13 (0.00, 171.63)	0.96 (0.00, 872.11)
Non-frail - Pre-frail	1.05 (0.95, 1.16)	**1.40 (1.32, 1.49)**	0.94 (0.83, 1.06)	0.78 (0.69, 0.89)
Non-frail - Death	2.26 (0.02, 291.73)	**36.53 (2.60, 512.80)**	1.20 (0.01, 203.49)	0.68 (0.01, 69.32)
Exhaustion – No Exhaustion	1.04 (0.90, 1.20)	**0.87 (0.80, 0.93)**	**1.33 (1.12, 1.59)**	1.19 (0.99, 1.43)
Exhaustion - Death	**0.69 (0.50, 0.95)**	**1.95 (1.69, 2.24)**	0.84 (0.59, 1.20)	0.67 (0.44, 1.03)
No Exhaustion - Exhaustion	**1.29 (1.12, 1.49)**	**1.17 (1.07, 1.27)**	**0.79 (0.67, 0.94)**	**0.64 (0.54, 0.76)**
No Exhaustion - Death	0.58 (0.33, 1.02)	**5.56 (3.78, 8.18)**	0.99 (0.54, 1.82)	1.03 (0.55, 1.92)
Weight loss - No weight loss	1.13 (0.96, 1.33)	**0.87 (0.80, 0.95)**	**1.32 (1.09, 1.61)**	**1.40 (1.14, 1.72)**
Weight loss - Death	**0.60 (0.50, 0.73)**	**2.26 (2.01, 2.54)**	0.93 (0.74, 1.15)	0.93 (0.73, 1.20)
No weight loss - Weight loss	**1.17 (1.02, 1.34)**	**1.56 (1.46, 1.68)**	0.85 (0.72, 1.00)	**0.81 (0.68, 0.96)**
No weight loss - Death	0.78 (0.15, 3.99)	0.32 (0.06, 1.70)	0.48 (0.08, 3.01)	0.01 (0.00, 4.14)
Weakness – No weakness	**1.41 (1.19, 1.67)**	**0.61 (0.56, 0.67)**	0.96 (0.78, 1.19)	0.95 (0.76, 1.19)
Weakness - Death	0.90 (0.64, 1.26)	**2.10 (1.68, 2.63)**	0.78 (0.52, 1.16)	0.86 (0.56, 1.32)
No weakness - Weakness	0.99 (0.84, 1.16)	**2.12 (1.92, 2.33)**	0.82 (0.68, 1.00)	**0.69 (0.56, 0.85)**
No weakness - Death	0.71 (0.48, 1.04)	**2.53 (2.00, 3.21)**	0.72 (0.47, 1.12)	**0.52 (0.31, 0.88)**
Slowness – No slowness	**1.19 (1.01, 1.41)**	**0.59 (0.54, 0.65)**	**1.54 (1.26, 1.89)**	**1.34 (1.07, 1.67)**
Slowness - Death	**0.77 (0.64, 0.91)**	**1.66 (1.47, 1.86)**	0.86 (0.70, 1.05)	0.89 (0.71, 1.11)
No slowness - Slowness	0.98 (0.88, 1.09)	**2.30 (2.16, 2.45)**	0.91 (0.81, 1.03)	**0.72 (0.63, 0.82)**
No slowness - Death	0.57 (0.17, 1.93)	0.36 (0.12, 1.04)	0.41 (0.11, 1.53)	0.03 (0.00, 2.09)
Phys. inactive – Phys. active	0.92 (0.81, 1.05)	**0.69 (0.65, 0.74)**	0.99 (0.85, 1.16)	1.05 (0.89, 1.24)
Phys. inactive - Death	**0.74 (0.62, 0.88)**	**2.12 (1.92, 2.35)**	**0.77 (0.63, 0.94)**	0.80 (0.64, 1.00)
Phys. active – Phys. inactive	0.98 (0.89, 1.07)	**1.57 (1.49, 1.65)**	0.91 (0.81, 1.02)	**0.75 (0.67, 0.85)**
Phys. active - Death	0.31 (0.04, 2.24)	**0.27 (0.08, 0.93)**	0.21 (0.04, 1.00)	0.01 (0.00, 1.54)

CI: Confidence Interval. Significant associations (where the CI does not include 1.00) are depicted in bold.

proportions of around 60% for exhaustion and weight loss, 40% for weakness and physical inactivity, but only 20% for slowness. This is also mirrored by results in Appendix 2 showing that unexplained weight loss was present in 20.7 - 27.5% of 'improvers' but only 1.1 – 1.8% 'decliners'. Exhaustion was present in 27.0 – 31.7% of improvers and 1.9 – 3.5% decliners. This is consistent with previous TILDA results that exhaustion and weight loss (i.e. prefrailty 'type 1' items) were more common in the younger-old and perhaps more amenable to change, whereas the other components (i.e. prefrailty 'type 2' items) were more prevalent in the older-old, and may be more 'fixed' and carry poorer prognosis (Romero-Ortuno, Scarlett, O'Halloran, and Kenny, 2019). For example, data in Appendix 2 show that slowness was present at baseline in 13.2 - 31.8% of improvers, but a comparatively higher proportion (4.3 – 10.7%) of decliners. Analogously, baseline low physical activity was present in 4.0 – 14.4% decliners. However, baseline weakness (the third prefrailty 'type 2' component) seemed to have lower decliner proportions of 2.4 – 4.3% (Appendix 2). Performance-based items have more reproducibility than self-reported items; however, among the former, TUG repeated measures have shown lower coefficients of variation than handgrip strength measures (Alfonso-Rosa et al., 2014), and this could potentially explain lower decliner proportions associated with weakness.

The FP component with the highest risk of transitioning from being absent to present was low physical activity (17%). However, this component had the lowest risk of transitioning from being present to dying (10%). This could be interpreted in the light of increasing ageing-related sedentarism (Kandola, Stubbs, and Koyanagi, 2020) in a relatively healthy population-based sample. Indeed, research has suggested that in healthy groups, one may not find an increased risk of mortality associated with prolonged sitting, even among people who do not meet recommended physical activity guidelines (Theou, Blodgett, Godin, and Rockwood, 2017). However, in the Markov model, older age also seemed associated with reduced risk of transitioning from being physically active to death, and this could be interpreted in the light that the health gains from physical activity may be more pronounced in older than younger adults (Gulsvik et al., 2012, Hirsch et al., 2010, Hubbard et al., 2009).

Weight loss had the second lowest probability of transitioning from being absent to present (7%), but the highest risk of transitioning from being present to dying (17%). On the other hand, weight loss had the highest probability of transitioning from being present to absent (59%). Together, results suggest that the most frequent adverse transitions are not necessarily the riskiest. Results also suggest that some (but not other) components commonly improve, but when they do not, they may carry a poorer prognosis. For example, not all unintentional weight loss is harmful and in a majority of cases it may be short-lived; however, the increased mortality risk of the other causes of unintentional weight loss may be related to underlying disease with adverse prognosis (e.g. cancer) (Wijnhoven, van Zon, Twisk, and Visser, 2014). In the Women's Health and Aging Study II, Fried's group suggested that weakness may serve as a warning sign of increasing vulnerability in early frailty development, and weight loss and exhaustion may help to identify women most at risk for rapid adverse progression (Xue et al., 2008).

Overall, our findings challenge the theory (Fried et al., 2001) that the FP is a homogenous syndrome and support a more nuanced approach to the study of individual FP states and components, as regards their transition risks and prognostic implications. Clinically, closer individual attention to FP components may aid differential diagnosis (i.e. recognizing benign vs. serious causes) and allow more individualized and meaningful interventions in community-based prevention and rehabilitation programmes (Provencher et al., 2017).

The fact that weight loss was more strongly related to death than the other components could be interpreted in the light that it captured change over the preceding 1 year, whereas the time frame for self-report was one week for exhaustion and physical activity, and weakness and slowness were measured contemporaneously. Hence, there could have been more inter-wave fluctuations in exhaustion and physical activity, from combining at a given wave participants whose deficits had been persistent with participants with recent onset of symptoms. Potentially, the incidence of a component may have been more strongly related to mortality than the component itself, as the latter combines the trait and the state part of the characteristic; but unfortunately, such granularity was not available in our dataset.

Missing data limitations include that only 69.5% of wave 1 sample had FP information, which makes our findings not necessarily representative of the Irish population aged 50 or more. Wave 1 participants with missing FP data were overrepresented in the home health assessment group, which as previously described had a worse health profile than those attending the health assessment centre (Kearney et al., 2011). As expected, the proportions of missing data tended to increase across waves, but the increase in missingness seemed more linear for the exhaustion and weight loss components. Although one can expect longer questionnaires and performance-based measures to have more missing data than simple questions, the missingness patterns in our study may have more to do with how the data are captured in TILDA (Donoghue et al., 2018, Kearney et al., 2011) rather than an actual clinically relevant pattern of missingness. In our study, missingness patterns from health centre waves (Fried et al., 2001, King-Kallimanis, Kenny, and Savva, 2014) to non-health centre waves ((Hoogendijk et al., 2015, Liu et al., 2017)and (Huang et al., 2020)) seemed similar for weakness, slowness and low physical activity, but not for weight loss and exhaustion. This was reflected in the missingness pattern for FP states. For example, some wave 3 participants may have filled in the main questionnaire but didn't do the health centre assessment so had no slowness or weakness data, but this data was captured for them at waves 2, 4 or 5 in the home assessment.

Our study has further limitations. First, the FP operationalized in our study was slightly different from the original in the CHS (Fried et al., 2001), and criteria modifications may impact on their classification and predictive ability (Theou et al., 2015). In addition, for the mortality outcome, specific causes of death were not studied, and addressing this in future studies could shed further light into the biological differences between FP states and components. In a longitudinal study, the deaths of participants might introduce a selective survival bias, but this was managed by modelling death as a distinct state in the Markov models. However, death is a complex outcome that can be affected by numerous confounding variables including disease burden, physical function, and health behaviours. Therefore, the transition risks reported in our study cannot be considered as causal as associations may still be subject to potential confounders. As detailed in Appendix 1, the absolute numbers for some transitions were relatively low (e.g. frail to non-frail, n=25; non-frail to frail, n=77; non-frail to death, n=77), which as seen in Table 4, translated into very wide confidence intervals when age, sex and education were included as covariates.

In terms of the statistical approach based on multi-state Markov models, advantages include that they add probabilities to the state transitions seen in the alluvial plots and allow for adjustment for covariates. However, the models assume that the probabilities from one wave to the next are always the same, which may not be the case in real life. In addition, models censor missing data as missing completely at random, which again, may not reflect the true pattern of missingness. Indeed, the sensitivity analyses considering missing data as an additional state (Appendix 3) confirmed that those who were frailer at a given wave were more likely to have missing data at future waves. In the sensitivity analysis, the risks of adverse progression from non-frail to prefrail, and prefrail to frail, were slightly lower (21% and 7%, having been 27% and 10% respectively in the main analysis); and favourable transitions from frail to prefrail, and prefrail to non-frail were 18% and 27% (having been 18% and 32%, respectively). Overall, the sensitivity analysis yielded a similar pattern of results.

In future studies, it may be of interest to use statistical models that are not 'memoryless'. That is, the Markov Model assumption is that the

probability of moving to a future state depends purely on the present state, not the states before that. Hence, for example, we can predict the probability of moving from a state of exhaustion in wave 3 to a state of non-exhaustion in wave 4. However, we cannot predict the probability of moving into a state of non-exhaustion in wave 4 if in wave 1 to 3 the individual is in a state of exhaustion. In future studies, consideration will be given to more complex models such as joint frailty or latent transition analyses. In those, there will be scope to investigate additional predictors of transitions including specific diseases and health behaviours (Gil-Salcedo et al., 2020). Learnings from such models could offer clinicians a higher degree of precision as to how to manage FP components in individuals. In the meantime, clinicians should pay due attention to both FP states and components, systematically identify their medical and non-medical drivers through a comprehensive geriatric assessment, and promote, where individually relevant, evidence-based interventions such as physical activity (RoyChoudhury et al., 2014), nutrition optimization, and social engagement (Travers, Romero-Ortuno, Bailey, and Cooney, 2019, Dent et al., 2019).

Role of the funding source

This study was funded by a Grant from Science Foundation Ireland under Grant number 18/FRL/6188. TILDA is funded by Atlantic Philanthropies, the Irish Department of Health and Irish Life. The funders had no role in the conduct of the research and/or preparation of the article; in study design; in the collection, analysis and interpretation of data; in writing of the report; and in the decision to submit the paper for publication.

Author Contributions

All authors meet all 4 of the following authorship criteria:

Study conception and design (RRO, PH, AMO) and/or
Acquisition of data (RAK) and/or
Analysis and interpretation of data (RRO, PH, JD, SPK, RR, BH, RAK, AMO)
Drafting of manuscript (RRO, PH) and/or
Critical revision for important intellectual content (JD, SPK, RR, BH, RAK, AMO)
Final approval of the version to be submitted and any revision (RRO, PH, JD, SPK, RR, BH, RAK, AMO)

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors accept public responsibility for the report.

Sponsor's Role

This study is funded by a Grant from Science Foundation Ireland under Grant number 18/FRL/6188. TILDA is funded by Atlantic Philanthropies, the Irish Department of Health and Irish Life. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of competing interest

The authors have no competing interests to declare.

Appendix 1. Numbers of transitions for frailty phenotype states and components

	TO				
FROM	**Frail**	**Pre-frail**	**Non-frail**	**Death**	**Missing**
Frail	213	190	25	101	276
Pre-frail	406	2398	1652	176	1399
Non-frail	77	2377	6264	77	1935
Death	0	0	0	775	0
Missing	164	680	695	225	2627
FROM		**Exhaustion**	**No Exhaustion**	**Death**	**Missing**
Exhaustion		506	1144	101	196
No Exhaustion		1295	14890	351	1445
Death		0	0	775	0
Missing		42	220	128	1639
		Weight loss	**No weight loss**	**Death**	**Missing**
Weight loss		292	938	127	163
No weight loss		1086	15682	373	1393
Death		0	0	775	0
Missing		52	240	79	1532
		Weakness	**No weakness**	**Death**	**Missing**
Weakness		577	691	125	397
No weakness		711	13127	262	2514
Death		0	0	775	0
Missing		182	971	194	2206
		Slowness	**No slowness**	**Death**	**Missing**
Slowness		1306	622	198	589
No slowness		1528	12680	185	1852
Death		0	0	775	0
Missing		219	530	200	2048
		Physical inactive	**Physically active**	**Death**	**Missing**
Physical inactive		1646	1195	185	605
Physically active		2087	11026	217	1903
Death		0	0	776	0
Missing		313	589	180	2010

Appendix 2. Proportions of baseline FP components (by Wave) in participants who improved their FP state (i.e. from prefrail to non-frail, frail to prefrail, or frail to non-frail) and participants whose FP state declined (i.e. from prefrail to frail, non-frail to frail, or non-frail to prefrail)

	Improved state from W1 to W2	Worsened state from W1 to W2	Improved state from W2 to W3	Worsened state from W2 to W3	Improved state from W3 to W4	Worsened state from W3 to W4	Improved state from W4 to W5	Worsened state from W4 to W5
n	740	836	396	699	316	706	415	619
Exhaustion (%) at baseline Wave	207 (27.9%)	18 (2.2%)	112 (28.3%)	21 (3.0%)	100 (31.7%)	25 (3.5%)	112 (27.0%)	12 (1.9%)
Unexplained weight loss (%) at baseline Wave	153 (20.7%)	13 (1.6%)	109 (27.5%)	11 (1.6%)	75 (23.7%)	13 (1.8%)	91 (21.9%)	7 (1.1%)
Weakness (%) at baseline Wave	225 (30.4%)	36 (4.3%)	50 (12.6%)	17 (2.4%)	78 (24.7%)	27 (3.8%)	50 (12.1%)	24 (3.9%)
Slowness (%) at baseline Wave	98 (13.2%)	36 (4.3%)	126 (31.8%)	58 (8.3%)	61 (19.3%)	46 (6.5%)	108 (26.0%)	66 (10.7%)
Low physical activity (%) at baseline Wave	292 (39.5%)	42 (5.0%)	139 (35.1%)	28 (4.0%)	114 (36.1%)	44 (6.2%)	243 (58.6%)	89 (14.4%)

Appendix 3. Sensitivity analysis where missing data was considered as an additional state in the multi-state Markov models. Estimated transition probabilities (and 95% CIs) for each frailty phenotype state and component (from wave x to wave x + 1) are shown

	TO				
FROM	**Frail**	**Pre-frail**	**Non-frail**	**Death**	**Missing**
Frail	0.30 (0.27, 0.33)	0.18 (0.16, 0.20)	0.08 (0.07, 0.10)	0.13 (0.10, 0.15)	0.32 (0.28, 0.35)
Pre-frail	0.07 (0.06, 0.07)	0.40 (0.39, 0.42)	0.27 (0.26, 0.28)	0.02 (0.02, 0.02)	0.24 (0.23, 0.25)
Non-frail	0.02 (0.02, 0.02)	0.21 (0.20, 0.22)	0.59 (0.58, 0.60)	0.01 (0.01, 0.01)	0.18 (0.17, 0.19)
Death	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)
Missing	0.02 (0.01, 0.02)	0.18 (0.17, 0.19)	0.15 (0.14, 0.16)	0.06 (0.05, 0.06)	0.60 (0.59, 0.62)
FROM		**Exhaustion**	**No Exhaustion**	**Death**	**Missing**
Exhaustion		0.26 (0.25, 0.28)	0.56 (0.54, 0.59)	0.07 (0.06, 0.09)	0.10 (0.09, 0.12)
No Exhaustion		0.08 (0.07, 0.08)	0.83 (0.82, 0.83)	0.01 (0.01, 0.02)	0.08 (0.08, 0.09)
Death		0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)
Missing		0.02 (0.02, 0.03)	0.10 (0.09, 0.12)	0.10 (0.09, 0.12)	0.77 (0.75, 0.79)
		Weight loss	**No weight loss**	**Death**	**Missing**
Weight loss		0.21 (0.19, 0.23)	0.56 (0.54, 0.59)	0.12 (0.11, 0.14)	0.10 (0.09, 0.12)
No weight loss		0.06 (0.06, 0.07)	0.85 (0.84, 0.85)	0.01 (0.01, 0.02)	0.08 (0.07, 0.08)
Death		0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)
Missing		0.03 (0.02, 0.04)	0.12 (0.11, 0.14)	0.07 (0.05, 0.08)	0.78 (0.76, 0.80)
		Weakness	**No weakness**	**Death**	**Missing**
Weakness		0.33 (0.31, 0.35)	0.38 (0.35, 0.40)	0.06 (0.04, 0.08)	0.24 (0.22, 0.26)
No weakness		0.04 (0.04, 0.05)	0.79 (0.78, 0.80)	0.01 (0.01, 0.01)	0.16 (0.15, 0.16)
Death		0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)
Missing		0.05 (0.04, 0.06)	0.26 (0.25, 0.27)	0.08 (0.07, 0.09)	0.61 (0.59, 0.63)
		Slowness	**No slowness**	**Death**	**Missing**
Slowness		0.49 (0.47, 0.51)	0.22 (0.21, 0.24)	0.06 (0.05, 0.07)	0.23 (0.21, 0.24)
No slowness		0.09 (0.09, 0.10)	0.78 (0.77, 0.79)	0.01 (0.01, 0.01)	0.11 (0.11, 0.12)
Death		0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)
Missing		0.07 (0.06, 0.08)	0.17 (0.16, 0.18)	0.08 (0.07, 0.09)	0.68 (0.66, 0.69)
		Physical inactive	**Physically active**	**Death**	**Missing**
Physical inactive		0.46 (0.44, 0.47)	0.32 (0.31, 0.34)	0.04 (0.04, 0.05)	0.17 (0.16, 0.19)
Physically active		0.14 (0.13, 0.14)	0.72 (0.72, 0.73)	0.01 (0.01, 0.01)	0.13 (0.12, 0.13)
Death		0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)
Missing		0.10 (0.09, 0.11)	0.18 (0.17, 0.19)	0.08 (0.07, 0.09)	0.64 (0.63, 0.66)

CI: Confidence interval.

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