Age and Ageing 2019; **49:** 39–45
doi: 10.1093/ageing/afz129
Published electronically 11 November 2019

RESEARCH PAPER

Is phenotypical prefrailty all the same? A longitudinal investigation of two prefrailty subtypes in TILDA

Roman Romero-Ortuno[1,2], Siobhan Scarlett[2], Aisling M. O'Halloran[2], Rose Anne Kenny[1,2]

[1]Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland
[2]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland

Address correspondence to: Roman Romero-Ortuno, Discipline of Medical Gerontology, 6th floor, Mercer's Institute for Successful Ageing, St James's Hospital, Dublin 8, Ireland. Tel: (+353) 1 896 3555; Fax: (+353) 1 896 3407. Email: romeror@tcd.ie

Abstract

Background: Fried's frailty phenotype is defined by five criteria: exhaustion, unexplained weight loss, weakness, slowness and low physical activity. Prefrailty (PF) meets one or two criteria. PF is of interest as a target for preventative interventions, but it is not known if it is a homogenous syndrome.
Objective: to compare the longitudinal trajectories of two PF groups: one defined by exhaustion and/or unexplained weight loss (PF1) and one defined by one or two of the following: weakness, slowness, low physical activity (PF2).
Design and setting: population-based longitudinal study of ageing.
Subjects: One-thousand four-hundred seventy-six PF participants aged ≥50 years from wave 1 of the study (2010), followed 2-yearly over four longitudinal waves (2012, 2014, 2016, 2018).
Methods: generalised estimating equations (GEEs) were used to assess the effect of PF type across waves to predict cumulative mortality and disability in basic activities of daily living (ADL) and independent ADL (IADL), adjusting for baseline characteristics (age, sex, education, living alone, self-rated health, comorbidity, body mass index).
Results: in wave 1, there were 503 PF1 and 973 PF2 participants. By wave 5, 38 (7.6%) PF1 and 145 (14.9%) PF2 participants had died. In PF1 participants, mean numbers of ADL and IADL disabilities both increased from 0.1 to 0.2 from wave 1 to wave 5, whilst in PF2 increases were from 0.2 to 0.5. Adjusted GEE models suggested significantly divergent trajectories of IADL disability by wave 2, ADL disability by wave 3 and mortality by wave 3.
Conclusion: PF may not be a homogenous biological syndrome.

Keywords: disability, frailty, longitudinal studies, mortality, older people, phenotype

Key points

- Fried's frailty phenotype is defined by five criteria; PF meets one or two.
- We defined PF1 as exhaustion and/or unexplained weight loss.
- We defined PF2 as one or two of the following: weakness, slowness, low physical activity.
- Over 8-year follow-up, PF1 and PF2 had divergent trajectories of mortality and disability.
- PF may not be a homogenous biological syndrome.

Introduction

In 2001, Fried *et al*. [1] developed and operationalised in the US Cardiovascular Health Study (CHS), a phenotype of frailty in older adults characterised by the following criteria: unintentional weight loss, self-reported exhaustion, weakness (by grip strength), slow walking speed and low physical activity. According to this physical phenotype theory, frailty is related to, but distinct from, comorbidity and disability [2]. The frailty phenotype has been shown to be predictive of mortality, disability and adverse health outcomes in many epidemiological studies [3–5] and has been proposed as a tool to identify vulnerable adults in routine healthcare settings [6, 7].

In 2006, Bandeen-Roche *et al*. [8] delineated the frailty phenotype measure in the US Women's Health and Ageing Studies and, using latent class analysis, evaluated whether criteria composing the measure aggregated into a syndrome, concluding that the CHS frailty definition showed internal construct validity *vis à vis* a medical syndrome. This was also suggested by Romero-Ortuno *et al.* [9], who developed a frailty phenotype measure based on latent class analysis using data from the Survey of Health, Ageing and Retirement in Europe (SHARE).

Also using SHARE data and through a confirmatory factor analysis approach, King-Kallimanis et al. [10] reported in 2014 that although the five items of the frailty phenotype conformed to an underlying single latent factor that seemed consistent across European countries, there was a significant residual correlation between the exhaustion and appetite loss components. The authors suggested that an alternative two-dimensional model also seemed to be supported by the data, where exhaustion and weight loss could be indicative of one dimension and slowness, weakness and low physical activity of a different dimension.

According to the frailty phenotype operationalisation, prefrailty (PF) is defined as the presence of one or two criteria, whilst frailty is identified when three or more criteria are present [1]. PF is attracting increasing interest as the preferred target for preventative interventions that may help delay or reverse the disabling process [11–13]. However, if the frailty phenotypes were not a unidimensional construct, this would have implications for the definition of PF as the latter can be made up of different combinations of the five criteria. For example, taking into account the two-dimensional suggestion by King-Kallimanis et al. [10], PF can be defined by exhaustion and/or unexplained weight loss and also by the presence of one or two amongst slowness, weakness and low physical activity. The original frailty phenotype operationalisation would not differentiate these two possible PF types; yet, they may have different characteristics and prognoses and require different preventative strategies. No studies had previously operationalised these two PF types and compare their long-term trajectories.

The aim of this study was to compare the long-term longitudinal trajectories of two mutually exclusive PF groups: one defined by exhaustion and/or unexplained weight loss (PF type 1 [PF1]) and one defined by one or two of the following: weakness, slowness, low physical activity (PF type 2 [PF2]). Using data from a longitudinal study of ageing, we compared their baseline characteristics and their 8-year mortality and disability trajectories.

Methods

Design and setting

We analysed 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/. The cohort profile has been described in detail elsewhere [14, 15].

Subjects

In wave 1 of the study, we operationalised two mutually exclusive PF groups: one defined by exhaustion and/or unexplained weight loss, in the absence of weakness, slowness and low physical activity (PF type 1: PF1) and one defined by one or two amongst weakness, slowness and low physical activity, in the absence of exhaustion and unexplained weight loss (PF type 2: PF2). The operationalisation of the frailty phenotype in our study was the same as in the CHS, except for the physical activity criterion, for which we used the short form of the International Physical Activity Questionnaire [16]; the CHS used the Minnesota Leisure Time Activity questionnaire [1].

Measures

Baseline characteristics between the two PF groups were compared across the following measures: age (years); sex (1: male, 2: female); self-rated health score (1: poor, 2: fair, 3: good, 4: very good, 5: excellent); attainment of third or higher level education (yes/no); living alone (yes/no); mean number of chronic diseases (counted from the following list: heart attack or heart failure or angina, cataracts, hypertension, high cholesterol, stroke, diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer and hip fracture [17]); body mass index (BMI, Kg/m^2); and mean number of self-reported difficulties in basic activities of daily living (ADL) and independent ADL (IADL), counted from the following list [18]:

- ADLs (six items): 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.
- IADLs (six items): preparing a hot meal; doing household chores (laundry, cleaning); shopping for groceries; making telephone calls; taking medications; and managing money such as paying bills and keeping track of expenses.

As regards longitudinal outcomes, mortality in all study participants was ascertained at each wave follow-up. 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 must be registered. Data on ADL and IADL difficulties were obtained at each wave.

Methods

All statistical analyses were computed with IBM® SPSS® Statistics version 25 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$ throughout.

Descriptive statistics was given as mean with standard deviation (SD) or proportion (%). Cumulative mortality was expressed in each wave as proportion (%) in respect of wave 1. Bivariate comparisons between PF groups were conducted with the independent samples Mann–Whitney *U* test (continuous variables) and the two-sided Chi-square test (dichotomous variables). For the graphical representation of the PF trajectories, means were plotted with error bars representing 1 standard error (SE).

Generalised estimating equations (GEEs) were used to assess the effect of PF type across waves (modelled as interaction PF type × study wave) to predict cumulative mortality, ADL and IADL disability, whilst adjusting for baseline characteristics (age, sex, education, number of chronic diseases, living alone, self-rated health and BMI). The unique participant number (common across waves) was specified as subject effect, and the study wave was specified as within-subject effect. For mortality, the binary logistic model was used. For ADL and IADL, a Poisson distribution with log function was used. As well as the interactions PF type × study wave and confounders, models included the main effects of PF type and study wave, and intercept. Statistics were based on complete case analysis, and no statistical weights were applied. For sensitivity analyses, GEE models were repeated with multiple imputation of missing data.

Ethical approval

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.

Results

Of 8,172 participants aged 50 or more years in wave 1 of the study, Fried's physical frailty phenotype information was available in 5,697 (69.7%). Amongst the latter, 3,873 (68.0%) were non-frail, 1,660 (29.1%) prefrail (PF) and 164 (2.9%) frail. Amongst the 1,660 PF participants, 503 (30.3%) had PF1 and 973 (58.6%) PF2. On-hundred eighty-four (11.1%) PF participants had mixed PF1 and PF2 features and were excluded (31 with exhaustion and weakness, 27 with exhaustion and slowness, 52 with exhaustion and low physical activity, 23 with weight loss and weakness, 23 with weight loss and slowness, and 28 with weight loss and low physical activity). Of the 503 PF1 participants, 262 (52.1%) had exhaustion only, 199 (39.6%) weight loss only and 42 (8.3%) exhaustion and unexplained weight loss. Of the 973 PF2 participants, 272 (27.9%) had weakness only, 166 (17.1%) had slowness only, 366 (37.6%) had low physical activity only, 60 (6.2%) had weakness and slowness, 45 (4.6%) had weakness and low physical activity and 64 (6.6%) had slowness and low physical activity.

The comparison of the baseline characteristics of the two PF types are shown in Table 1. PF1 was significantly younger; more likely to be female; have higher education; be less comorbid as regards hypertension, diabetes, arthritis; more likely to have osteoporosis; have lower BMI and report lower number of ADL difficulties in wave 1.

As regards longitudinal outcomes, mortality data was complete, and attrition numbers for disability are shown in Table 1. By wave 5, 38 (7.6%) PF1 and 145 (14.9%) PF2 participants in wave 1 had died. In PF1 participants, mean numbers of ADL and IADL difficulties both increased from 0.1 to 0.2 from wave 1 to wave 5, whilst in PF2 increases were from 0.2 to 0.5 (Table 1). Figure 1 illustrates these trajectories.

The results of the adjusted GEE models showing the effects of the interactions PF × study wave are presented in Table 2. Results suggested significantly divergent trajectories of IADL disability by wave 2, ADL disability by wave 3 and mortality by wave 3. Sensitivity analyses with multiple imputation of missing data did not significantly change these results. The full results of the GEE models are shown in the Supplementary Data appendix.

Discussion

Using data from a longitudinal study of ageing spanning an 8-year period, we found evidence that two PF operationalisations may have different longitudinal trajectories of mortality and disability. Our findings challenge the theory [1] and previous cross-sectional evidence [8, 9] that the frailty phenotype is a homogenous, one-dimensional syndrome and support a previous empirical suggestion [10] that there may be more than one dimension underlying the syndrome. Our findings need to be placed in the context that mortality and disability having been the main outcomes against which the frailty phenotype has been validated [3–5, 19]. Our GEE models took into account the recognised associations between age, sex [20], comorbidity [2] and the frailty phenotype; accordingly, we adjusted by those and other variables, but this did not seem to attenuate the differences in PF trajectories.

Table 1. Comparison between PF type 1 and type 2: baseline (wave 1 characteristics) and longitudinal outcomes

Participants' characteristics and outcomes	Prefrail (total) $n = 1476$	Prefrail type 1 $n = 503$	Prefrail type 2 $n = 973$	P (type 1 versus 2)
Baseline (wave 1) characteristic				
Age (years): mean (SD)	65.7 (10.4)	61.0 (7.9)	68.2 (10.7)	<0.001[a]
Female sex (%)	54.1	63.4	49.2	<0.001*
Self-rated health score: mean (SD) (1: poor; 5: excellent)	3.4 (1.0)	3.3 (1.1)	3.4 (1.0)	0.152[a]
Third/higher education (%)	27.8	34.8	24.2	<0.001*
Living alone (%)	25.3	22.9	26.5	0.126*
Number of chronic diseases: mean (SD)	2.1 (1.5)	1.9 (1.5)	2.1 (1.6)	0.036[a]
History of cancer (%)	6.8	7.0	6.7	0.840*
History of hypertension (%)	42.7	39.2	44.5	0.049*
History of angina (%)	7.7	7.8	7.7	0.975*
History of heart attack (%)	7.0	6.0	7.5	0.272*
History of diabetes (%)	10.8	8.5	11.9	0.048*
History of stroke (%)	2.2	2.2	2.2	0.971*
History of lung disease (%)	5.2	5.6	5.0	0.664*
History of osteoporosis (%)	10.4	12.9	9.1	0.025*
History of arthritis (%)	34.9	30.0	37.4	0.005*
BMI: mean (SD)	29.2 (5.4)	28.4 (5.1)	29.7 (5.5)	<0.001[a]
Number of ADL difficulties: mean (SD)	0.18 (0.60)	0.14 (0.50)	0.20 (0.60)	0.038[a]
Number of IADL difficulties: mean (SD)	0.14 (0.60)	0.12 (0.44)	0.15 (0.62)	0.876[a]
Longitudinal outcomes				
Number dead by wave 2 (cumulative %)	38 (2.6)	9 (1.8)	29 (3.0)	0.171*
Number dead by wave 3 (cumulative %)	94 (6.4)	23 (4.6)	71 (7.3)	0.042*
Number dead by wave 4 (cumulative %)	141 (9.6)	29 (5.8)	112 (11.5)	<0.001*
Number dead by wave 5 (cumulative %)	183 (12.4)	38 (7.6)	145 (14.9)	<0.001*
Number of ADL difficulties: mean (SD) wave 2 (n participants)	0.16 (0.70) (1329)	0.12 (0.44) (456)	0.19 (0.76) (873)	0.589[a]
Number of ADL difficulties: mean (SD) wave 3 (n participants)	0.20 (0.80) (1188)	0.10 (0.53) (422)	0.26 (0.91) (766)	<0.001[a]
Number of ADL difficulties: mean (SD) wave 4 (n participants)	0.24 (0.86) (1055)	0.15 (0.67) (391)	0.29 (0.95) (664)	0.003[a]
Number of ADL difficulties: mean (SD) wave 5 (n participants)	0.38 (1.05) (805)	0.23 (0.85) (295)	0.46 (1.15) (510)	<0.001[a]
Number of IADL difficulties: mean (SD) wave 2 (n participants)	0.23 (0.80) (1329)	0.11 (0.43) (456)	0.29 (0.94) (873)	0.001[a]
Number of IADL difficulties: mean (SD) wave 3 (n participants)	0.27 (0.99) (1188)	0.13 (0.61) (422)	0.35 (1.14) (766)	0.005[a]
Number of IADL difficulties: mean (SD) wave 4 (n participants)	0.28 (1.01) (1055)	0.12 (0.60) (391)	0.38 (1.18) (664)	<0.001[a]
Number of IADL difficulties: mean (SD) wave 5 (n participants)	0.36 (1.16) (930)	0.21 (0.82) (356)	0.45 (1.31) (574)	0.014[a]

[a]Independent samples Mann–Whitney U test. *Two-sided Chi-square test.

Without a long follow-up period, some differences in trajectories may not have been noticeable, especially taking into account the relative small sample sizes of the PF groups under study. Indeed, whilst divergent IADL trajectories were already evident after only 2 years, ADL and mortality differences became evident at 4 years. The increasing time required to detect trajectory differences is consistent with the natural history of the disabling process, with difficulties in higher level functions appearing first and evolving in time into difficulties in personal care and ultimately death [21]. Our findings illustrate the benefit of long-term follow-up in longitudinal studies of ageing.

Fried's group previously suggested the existence of the two PF components that we studied here. Indeed, in the Women's Health and Ageing Study II, they found that despite significant heterogeneity, occurrence of weakness, slowness and low physical activity tended to precede exhaustion and weight loss in women who were non-frail at baseline. However, our findings disagree with their suggestion that weight loss and exhaustion may help to identify women most at risk for rapid adverse progression to disability and death [22].

The InCHIANTI investigators commented that the frailty phenotype seemed to have a suboptimal capacity to identify older people at risk of functional decline, concluding that more studies were needed to identify instruments with better prognostic capacity in terms of the prediction of disability trajectories [23]. In addition, another study could not identify a specific skeletal muscle phenotype of PF [24]. As suggested by our findings, had those studies considered the underlying phenotype components separately, their results might have been different.

Our findings suggest that the frailty phenotype component with a better ability to predict future disability may be related to sarcopenia (e.g. low handgrip strength, low gait speed [25]). Indeed, it has been suggested that the level of physical activity, weakness and slow gait speed are the items that most influence the determination of frailty [26]. Another study aimed to estimate the weight of each frailty phenotype component in terms of age-related deficit accumulation, concluding that of the five components of the phenotype, slow gait speed seemed to be the key indicator of frailty [27].

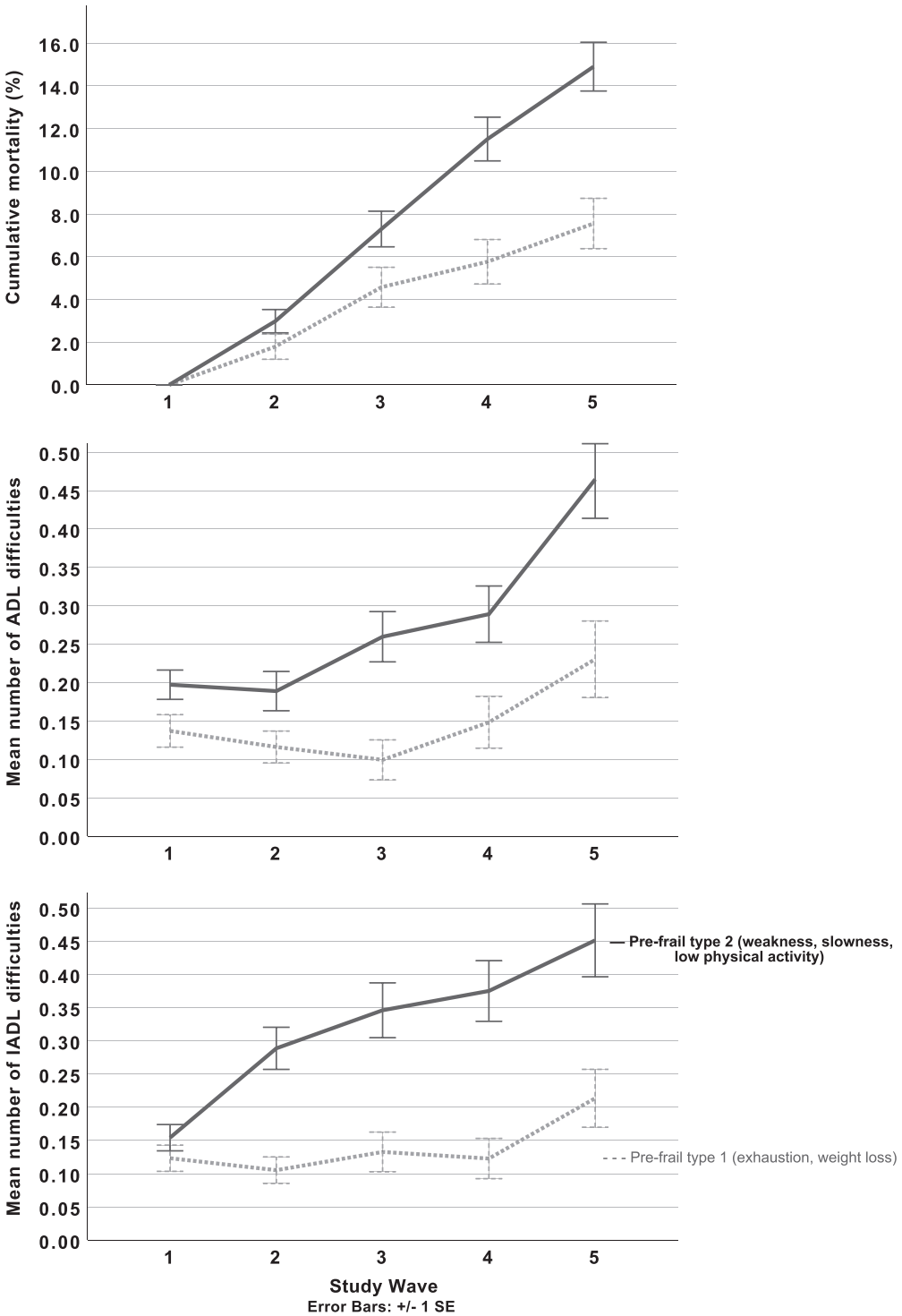

Figure 1. Mortality and disability trajectories of PF type 1 ($N = 503$) and type 2 ($N = 973$).

In terms of the implications of our findings for the design of preventative strategies, it has been argued that trying to predict different disability trajectories may be useful for the care of older people in order to promote individualised interventions to reduce the burden of disabilities and their consequences [23]. The characteristics of PF1 and PF2 groups seem consistent with previous findings from the Mexican Study of Nutritional and Psychosocial Markers of Frailty suggesting that weight loss and exhaustion could be more (but not only) related to the mental component of health-related quality of life, whilst gait speed and grip strength may be more (but not only) related to the physical component

Table 2. Results of the GEEs models showing the effects of the interaction term between PF type and study wave. Each model is adjusted for baseline characteristics (age, sex, third/higher level education, number of chronic conditions BMI, self-rated health, living alone). In the models: PF1 = 1; PF2 = 2. The full results of the GEE models including the effects of all variables are shown in Models 1, 2 and 3 of the Supplementary Data appendix. Sensitivity analyses with multiple imputation of missing data are shown in Models 1a, 2a and 3a of the Supplementary Data appendix

Model	Regression coefficient	SE	95% Wald confidence interval		*P*
			Lower	Upper	
Model 1. Cumulative mortality (*N* = 7,097 observations)					
PF type × study wave 5	1.716	0.555	0.629	2.804	**<0.001**
PF type × study wave 4	2.264	0.598	1.091	3.437	**<0.001**
PF type × study wave 3	1.314	0.512	0.311	2.317	**0.010**
PF type × study wave 2	1.346	0.531	0.045	2.412	0.110
PF type × study wave 1 (reference)	.	.	.	.	.
Model 2. ADL disability (*N* = 5,847 observations)					
PF type × study wave 5	0.655	0.176	0.311	1.000	**<0.001**
PF type × study wave 4	0.508	0.184	0.149	0.868	**0.006**
PF type × study wave 3	0.733	0.198	0.345	1.120	**<0.001**
PF type × study wave 2	0.115	0.187	−0.251	0.481	0.538
PF type × study wave 1 (reference)	.	.	.	.	.
Model 3. IADL disability (*N* = 5,972 observations)					
PF type × study wave 5	0.852	0.182	0.496	1.207	**<0.001**
PF type × study wave 4	1.103	1.978	0.715	1.491	**<0.001**
PF type × study wave 3	0.833	0.191	0.459	1.208	**<0.001**
PF type × study wave 2	0.794	0.198	0.407	1.182	**<0.001**
PF type × study wave 1 (reference)	.	.	.	.	.

Bold values denote statistical significance. "." means reference category.

[28]. Although natural heterogeneity in populations may never allow for clear-cut approaches, the identification of PF1 (after ruling out, where appropriate, serious underlying diseases such as cancer or consumptive disease) may benefit from mental and/or psychosocial approaches to optimisation. On the other hand, the identification of PF2 may be facilitated by the objective assessment of sarcopenia, which has different preventative and therapeutic targets including physical activity and nutrition [29]. Of utmost importance for daily clinical practice is the understanding that even the identification of more homogeneous PF subtypes does not provide a substitute for a comprehensive geriatric assessment, to diagnose the cause/s of any frailty at an individual level.

Our study has limitations. First, the frailty phenotype operationalised in our study was slightly different from the original in the CHS [1], and criteria modifications may impact on its classification and predictive ability [30]. As regards ADL and IADL difficulties, another potential limitation is their self-reported nature, as opposed to being based on objective disability assessments. 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 PF1 and PF2. Despite the sensitivity analyses, the findings of our study do not aim to be population representative and should be interpreted in the light of a sub-cohort within a longitudinal study of ageing on which complete case analyses were performed.

In conclusion, not all PF may be biologically the same, and further research is required to understand differential mechanisms and opportunities for intervention.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

Declaration of Funding: The Irish Longitudinal Study on Ageing is funded by the Irish Department of Health, the Atlantic Philanthropies and Irish Life. The financial sponsors played no role in the design, execution, analysis and interpretation of data, or writing of the study.

References

1. 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: M146–56.
2. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: omplications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004; 59: 255–63.
3. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. Eur J Intern Med 2016; 31: 3–10.
4. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospec-

tive analysis of 493 737 UK biobank participants. Lancet Public Health 2018; 3: e323-32.
5. Aguilar-Navarro S, Gutierrez-Robledo LM, Garcia-Lara JM, Payette H, Amieva H, Avila-Funes JA. The phenotype of frailty predicts disability and mortality among Mexican community-dwelling elderly. J Frailty Aging 2012; 1: 111–7.
6. Dent E, Lien C, Lim WS, Wong WC, Wong CH, Ng TP *et al.* The Asia-Pacific clinical practice guidelines for the management of frailty. J Am Med Dir Assoc 2017; 18: 564–75.
7. Bieniek J, Wilczynski K, Szewieczek J. Fried frailty phenotype assessment components as applied to geriatric inpatients. Clin Interv Aging 2016; 11: 453–9.
8. Bandeen-Roche K, Xue QL, Ferrucci L, Walston J, Guralnik JM, Chaves P, *et al.* Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 2006; 61: 262–6.
9. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary care: Findings from the survey of health, ageing and retirement in Europe (SHARE). BMC Geriatr 2010; 10: 57.
10. King-Kallimanis BL, Kenny RA, Savva GM. Factor structure for the frailty syndrome was consistent across Europe. J Clin Epidemiol 2014; 67: 1008–15.
11. Travers J, Romero-Ortuno R, Bailey J, Cooney MT. Delaying and reversing frailty: a systematic review of primary care interventions. Br J Gen Pract 2019; 69: e61–9.
12. Serra-Prat M, Sist X, Domenich R, Jurado L, Saiz A, Roces A, *et al.* Effectiveness of an intervention to prevent frailty in pre-frail community-dwelling older people consulting in primary care: a randomised controlled trial. Age Ageing 2017; 46: 401–7.
13. Fairhall N. Physical, nutritional, cognitive and combination interventions reduce frailty in community-dwelling prefrail and frail older people. Evid Based Med 2016; 21: 142.
14. Donoghue OA, McGarrigle CA, Foley M, Fagan A, Meaney J, Kenny RA. Cohort profile update: The Irish longitudinal study on ageing (TILDA). Int J Epidemiol 2018; 47: 1398–l.
15. Kearney PM, Cronin H, O'Regan C, Kamiya Y, Savva GM, Whelan B *et al.* Cohort profile: The Irish longitudinal study on ageing. Int J Epidemiol 2011; 40: 877–84.
16. Donoghue O, O'Connell M, Kenny RA. 2016. Walking to Wellbeing: Physical Activity, Social Participation and Psychological Health in Irish Adults Aged 50 Years or Older. Available at https://tilda.tcd.ie/publications/reports/pdf/Report_PhysicalActivity.pdf (accessed 6 April 2019).
17. Richardson K, Moore P, Peklar J, Galvin R, Bennett K, Kenny RA. 2012. Polypharmacy in Adults Over 50 in Ireland: Opportunities for Cost Saving and Improved Healthcare. Available at: <https://tilda.tcd.ie/publications/reports/pdf/Report_Polypharmacy.pdf> (accessed 6 April 2019).
18. Kamiya Y, Murphy C, Savva GM, Timonen V. 2012. Profile Of Community-Dwelling Older People With Disability and Their Caregivers in Ireland. Available at: https://tilda.tcd.ie/publications/reports/pdf/Report_CaregiversProfile.pdf? (accessed 6 April 2019).
19. Romero-Ortuno R, O'Shea D, Kenny RA. The SHARE frailty instrument for primary care predicts incident disability in a European population-based sample. Qual Prim Care 2011; 19: 301–9.
20. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. Age Ageing 2014; 43: 222–8.
21. Kingston A, Collerton J, Davies K, Bond J, Robinson L, Jagger C. Losing the ability in activities of daily living in the oldest old: a hierarchic disability scale from the Newcastle 85+ study. PLoS One 2012; 7: e31665.
22. Xue QL, Bandeen-Roche K, Varadhan R, Zhou J, Fried LP. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's health and aging study II. J Gerontol A Biol Sci Med Sci 2008; 63: 984–90.
23. Costanzo L, Cesari M, Ferrucci L, Bandinelli S, Antonelli Incalzi R, Pedone C. Predictive capacity of frailty phenotype toward patterns of disability identified using latent class analysis. J Am Med Dir Assoc 2019; 20: 1026–1031.
24. St-Jean-Pelletier F, Pion CH, Leduc-Gaudet JP, Sgarioto N, Zovile I, Barbat-Artigas S, *et al.* The impact of ageing, physical activity, and pre-frailty on skeletal muscle phenotype, mitochondrial content, and intramyocellular lipids in men. J Cachexia Sarcopenia Muscle 2017; 8: 213–28.
25. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, *et al.* Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 16–31.
26. Silva SL, Neri AL, Ferrioli E, Lourenco RA, Dias RC. [Phenotype of frailty: The influence of each item in determining frailty in community-dwelling elderly - the Fibra study]. Cien Saude Colet 2016; 21: 3483–92.
27. Hoogendijk EO, van Kan GA, Guyonnet S, Vellas B, Cesari M. Components of the frailty phenotype in relation to the frailty index: results from the Toulouse frailty platform. J Am Med Dir Assoc 2015; 16: 855–9.
28. Moreno-Aguilar M, Garcia-Lara JM, Aguilar-Navarro S, Navarrete-Reyes AP, Amieva H, Avila-Funes JA. The phenotype of frailty and health-related quality of life. J Frailty Aging 2013; 2: 2–7.
29. Afilalo J. Conceptual models of frailty: the sarcopenia phenotype. Can J Cardiol 2016; 32: 1051–5.
30. Theou O, Cann L, Blodgett J, Wallace LM, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the survey of health, ageing, and retirement in Europe. Ageing Res Rev 2015; 21: 78–94.

Received 9 April 2019; editorial decision 3 September 2019