An alternative method for Frailty Index cut-off points to define frailty categories

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Abstract

Purpose—the Frailty Index (FI) is a popular operationalization of frailty. FI cut-off points have been proposed to define, regardless of age, frailty categories with increasing risk. Here, an alternative method is described that takes age into account.

Subjects and methods—29,905 participants aged $\geq$ 50 from the first wave of the Survey of Health, Ageing and Retirement in Europe. The mean follow-up for mortality was 2.4 years. Curve estimation procedures were carried out between age and a FI, and 50% Confidence Intervals (CI) for the regression mean were derived. As opposed to the usual method (FI $\leq$ 0.08: non-frail; FI $\geq$ 0.25: frail; rest: pre-frail), the alternative method defines as 'fit for their age' those with a FI below the lower 50% CI; 'frail for their age' those with a FI above the upper 50% CI; the rest as 'average for their age'. Using both methods, the prevalence of the frailty categories and their associated mortality rates were compared for each age group.

Results—The best fit between age the FI was by cubic regression ($R^2 = 0.174$, $P < 0.001$). Among those in their 50s, 5% were frail by the usual method (mortality: 5%) and 14% by the alternative (mortality: 2%). Among those in their 90s, 64% were frail by the usual method (mortality: 43%) and 41% by the alternative (mortality: 48%).

Conclusion—the alternative method may be more sensitive in younger ages and more specific in older ages. This may have implications for population screening.

Keywords

Frail Elderly; Severity of Illness Index; Longitudinal Study; Mortality; Validation studies

Introduction

Frailty in older adults is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime (1). Although there is no international consensus on a definition of frailty (2, 3), two popular operationalizations are the Frailty *Index* (FI) and the frailty *phenotype* (4, 5).

According to the phenotypic approach, frailty is defined as a clinical syndrome consisting of *unintentional weight loss*, self-reported *exhaustion*, *weakness*, *slow walking speed*, and *low*

physical activity (6, 7). Fried *et al*. operationalized these criteria in the Cardiovascular Health Study and defined three frailty categories: *frail* (i.e. three or more criteria present), *pre-frail* (i.e. one or two criteria present) and *non-frail* (i.e. none of the criteria present) (6).

The Frailty Index (FI) sees frailty in relation to the *accumulation of health deficits*. The FI is measured by comparing the ratio of health deficits present within an individual to possible health deficits, using a pre-specified list of 30 or more deficits (4). A deficit can be any symptom, sign, disease, disability, or laboratory abnormality that is associated with age and adverse outcomes, present in at least 1% of the population, covers several organ systems and has no more than 5% missing data (8). Age is not included as a deficit, but the FI increases exponentially with age (9).

While the construct validity of the FI is examined through its relationship to chronological age, its criterion validity is examined in its ability to predict adverse outcomes, including mortality (10). The latter has been the focus of many epidemiological studies (11–13).

Rockwood *et al*. have proposed FI cut-off points to define phenotypical population subgroups with increasing levels of frailty. For example, in one of their studies they proposed FI ≤ 0.08 as 'non-frail', FI ≥ 0.25 as 'frail', and the rest as 'pre-frail' (14). In another of their studies, they proposed FI ≤ 0.03 as 'relatively fit', 0.03 < FI ≤ 0.10 as 'less fit', 0.10 < FI ≤ 0.21 as 'least fit', 0.21 < FI ≤ 0.45 as 'frail', and FI ≥ 0.45 as 'most frail' (15). These cut-offs were proposed *regardless* of age; thus, for example, a 50 year-old and an 80 year-old with a FI = 0.4 would be, according to their scheme, equally frail. This is illustrated in Figure 2, Panel A.

A potential problem with the usual FI cut-off method is that it does not take age into account, especially given the fact that the FI increases exponentially with age (9). In real clinical life, practitioners often operate within a framework of 'fit for his/her age' or 'frail for his/her age'. For example, a FI of 0.1 measured in a 50 year-old could be, at that young age, regarded as unusually high and trigger aggressive interventions to delay the onset of adverse outcomes in that vulnerable young person. On the other hand, a nonagenarian with a FI of 0.1 could be regarded as fitter and more resilient than the majority of his/her peers at that age. Therefore, a FI of 0.1 may not mean the same to people of different ages.

The aim of the present paper was to explore the properties of an alternative method for FI cut-off points that takes into account age and the exponential association between age and the FI. This is a theoretical paper exemplified with real data from the *Survey of Health, Ageing and Retirement in Europe* (SHARE), a large longitudinal population-based survey.

Methods

Setting

The present study is based on the *Survey of Health, Ageing and Retirement in Europe* (SHARE, http://www.share-project.org/). SHARE is a multidisciplinary and cross-national panel database of micro data on health, socio-economic status and social and family networks. Based on probability samples in all participating countries, SHARE represents the non-institutionalised population aged 50 and older. Spouses were also interviewed if they were younger than 50 but here they were excluded from the analyses. The first wave data collection was carried out between 2004 and 2005.

FI

This study uses a previously validated 40-item FI based on the first wave of SHARE (16). Each of the 40 deficit variables was scored such that 0 = deficit absent and 1 = deficit

present. The scores were added and divided by the total number of deficits evaluated (i.e. 40), to produce a FI between 0.0 (no deficits present) and 1.0 (all deficits present). For the full information on the FI deficit variables and cut-off points, please see the original validation study (16).

Mortality data (i.e. dead, alive or missing) was collected during the second wave of the study (2005 – 2006). The mean follow up period between wave 1 and wave 2 was 2.4 years.

Statistical analyses were conducted with IBM SPSS 20.0. Automatic curve estimation procedures were used to assess the relative fit of non-linear (i.e. quadratic, cubic) regression models. For the best fitting regression model, predicted values and 50% prediction intervals (upper and lower bounds) were saved.

The alternative cut-off method defines as 'fit for their age' those with a FI below the lower 50% CI for the regression. 'Frail for their age' are those with FI above the upper 50% CI. The rest are 'average for their age'. To compare the usual (0.08 as 'non-frail', FI 0.25 as 'frail', and the rest as 'pre-frail') and the alternative method, the sample was divided into age categories (i.e. 50s, 60s, 70s, 80s and 90+) and for each age category, the prevalence and the associated mortality rate of the frailty categories were compared.

Results

The first wave of SHARE included 29,905 participants aged 50+ from 12 countries (Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, and Israel). Overall, the mean (standard deviation: SD) age was 64.6 (10.1) years, and 54.2% were females.

The results of the curve estimation procedure are shown in Figure 1. The best fit between age and the FI was shown by the cubic model ($R^2 = 0.174$, $P < 0.001$). As per cubic regression, the mean FI (50% CI) was 0.08 (0.01 – 0.16) for those aged 50; 0.10 (0.03 – 0.17) for those aged 60; 0.14 (0.07 – 0.22) for those aged 70; 0.21 (0.13 – 0.28) for those aged 80; 0.30 (0.23 – 0.38) for those aged 90; and 0.43 (0.36 – 0.51) for those aged 100. The Appendix 1 shows the predicted FI values (with 50% CIs) for all ages. Figure 2 (Panel B) visually shows the alternative cut-off approach. Those with a FI below the lower 50% CI for the cubic regression are 'fit for their age'. Those with a FI above the upper 50% CI are 'frail for their age'. The rest are 'average for their age'.

Table 1 shows the sizes and mortality rates of the sample subgroups. Among those in their 50s, 5% were frail by the usual method (mortality: 5%) and 14% by the alternative (mortality: 2%). Among those in their 60s, 8% were frail by the usual method (mortality: 5%) and 15% by the alternative (mortality: 5%). Among those in their 70s, 19% were frail by the usual method (mortality: 12%) and 19% by the alternative (mortality: 11%). Among those in their 80s, 37% were frail by the usual method (mortality: 19%) and 26% by the alternative (mortality: 21%). Among those in their 90s, 64% were frail by the usual method (mortality: 43%) and 41% by the alternative (mortality: 48%).

Discussion

The aim of the present study was to explore the properties of an alternative method for FI cutoff points that takes into account age and the known exponential association between age and the FI. According to the usual method, those with FI 0.08 were 'non-frail', those with FI 0.25 'frail', and the rest 'pre-frail'. The alternative method defined as 'fit for their age' those with a FI below the lower 50% CI for the cubic regression, 'frail for their age' those with a FI above the upper 50% CI, and the rest as 'average for their age'. Naturally, the

scheme chosen here to illustrate the usual (i.e. age-independent) cut-off method is one of the many proposed (14, 15). On the other hand, the 50% choice for the regression CI was arbitrary, although visually it seems reasonable *vis-à-vis* the usual method (Figure 2). The results of the exercise suggest that, for the purpose of frailty screening, the alternative (i.e. age-specific) method may have higher sensitivity in younger groups and higher specificity in older groups.

Age-specific cut-off points have been previously proposed for population screening purposes. For example, the serum prostate-specific antigen (PSA, a marker of prostate cancer in men) is directly associated with age, so rather than rely on a single reference range for men of all age groups, age-specific reference ranges have been proposed which have the potential to make the test a more discriminating marker for detecting clinically significant disease in the old (i.e. increasing specificity) and to find more potentially curable disease in the young (i.e. increasing sensitivity) (17). In that light, the use of age-specific PSA reference ranges has been widely welcome (18–22). However, some have argued that the use of age-specific PSA ranges runs the risk of missing clinically significant cancers in older men and augmenting the rate of unnecessary invasive procedures (and potential complications) in younger men (23). In frailty screening, similar risks could apply.

Population screening does not exist without dilemmas and the trade-off between benefit and harm is crucial in health screening recommendations (24), in which a delicate balance exists between the benefit *for the population* and the benefit *for the individual* (25). Furthermore, in addition to the ethical precepts of autonomy, nonmaleficence, and equity (26), population screening in areas of geriatric relevance must avoid age discrimination (27). Indeed, although the association between age and the FI is statistically significant, the variance explained by age is small, owing to the fact that at a population level the association between chronological age and health status is extremely variable (28). The FI addresses the cumulative deficits in health leading to adverse outcomes, regardless of age. Age was not included as a deficit in the FI presented in this manuscript, but it is known that the FI increases exponentially with age (9). Therefore, given the known association between age and the FI, the question is whether cutting off the FI into 'phenotypical' categories should take age into account or not.

Based on SHARE, the frailty phenotype has been previously operationalized using modified Fried's criteria (29). The operationalization of frailty by modified Fried's criteria in SHARE did not establish age-specific cut-offs for the definition of frailty, so the alternative cut-off system exemplified here using the FI can also be applied to Fried's approach. Indeed, the modified Fried phenotypes in SHARE were also associated with age (29).

Potentially, an age-specific screening approach may facilitate the prevention of frailty in the longer term. This is so because when frailty is identified via screening in an individual, the next step should be the provision of a Comprehensive Geriatric Assessment (CGA) to the individual to establish the causes and potential interventions to avoid or delay the onset of adverse outcomes. It has been said that because of greater risk of death than for the non-frail state and greater likelihood of regression than for the frail state, the pre-frail state may be an optimal target for intervention (30). Therefore, it is possible that lowering the threshold for CGA at younger ages (i.e. considering a greater number of younger people as pre-frail) may offer more opportunities for long-term prevention (i.e. and in turn reduce the prevalence of frailty in older ages). However, the value of doing this is not yet proven.

At present, it is not clear whether the use of age-specific reference ranges for the phenotypic diagnosis of frailty could be more appropriate than the usual cut-off approach for population

screening purposes. This theoretical paper will stimulate debate and further research in the area.

Acknowledgments

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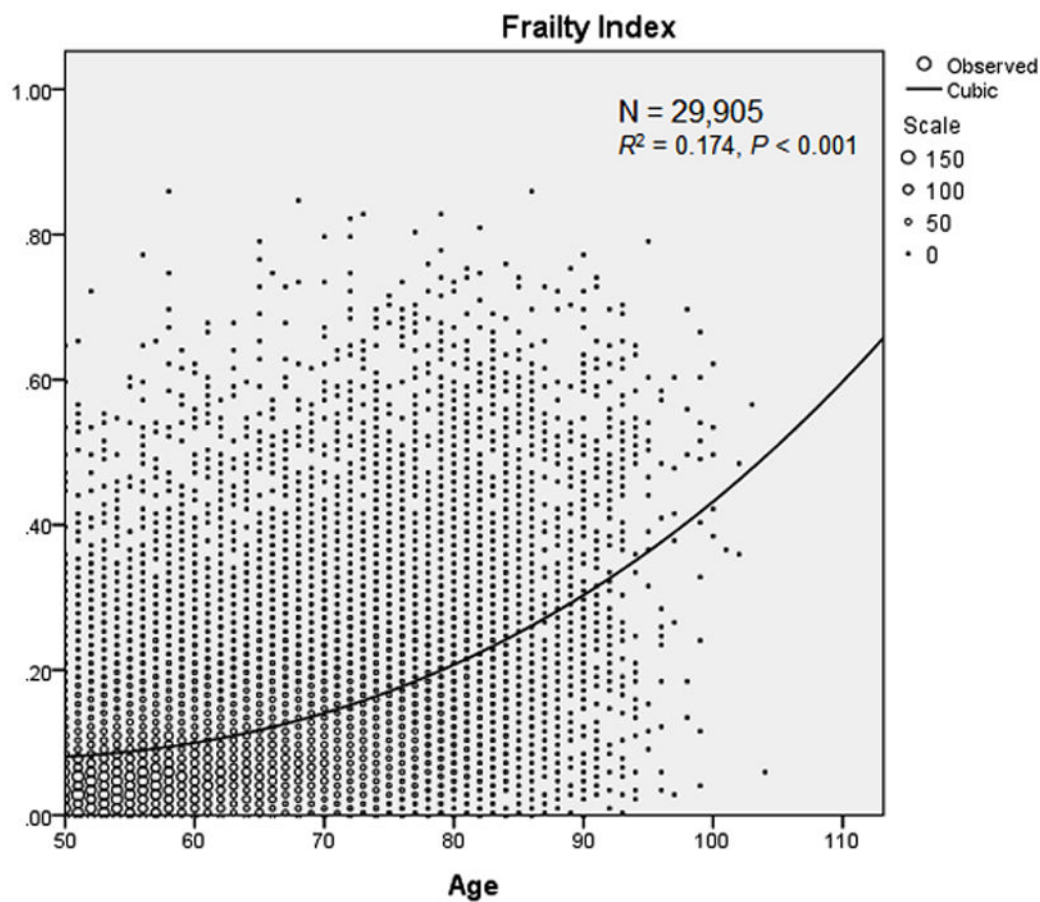
Figure 1.
Cubic regression between age and the FI.
Equation:

$$f(x) = A^* x^3 + B^* x^2 + C^* x + D$$

Coefficients:

$A = 6.102 * 10^{-7}$

$B = 0$

$C = -0.004$

$D = 0.187$
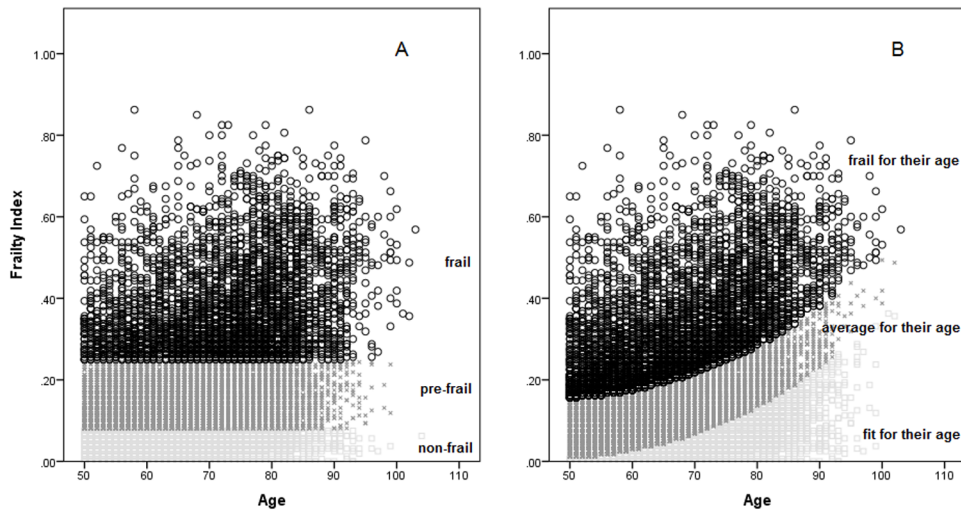
Figure 2.
Visual representation of the usual (Panel A) and alternative (Panel B) FI cut-off methods. According to the usual method, those with FI ≤ 0.08 are non-frail, those with FI ≥ 0.25 are frail, and the rest are pre-frail. The alternative method defines as 'fit for their age' those with a FI below the lower 50% CI for the cubic regression, 'frail for their age' those with a FI above the upper 50% CI, and the rest as 'average for their age'.

Table 1

Comparison between the usual and the alternative cut-off methods: prevalence and associated mortality rate of the frailty categories.

Age group	Usual cut-off	N	N%	N dead	Dead %	Alternative cut-off	N	N%	N dead	Dead %
50–59	Non-frail	4177	57	18	0.4	below 50% CI	903	12	1	0.1
	Pre-frail	2814	38	24	0.9	within 50% CI	5445	74	33	0.6
	Frail	359	5	16	4.5	above 50% CI	1002	14	24	2.4
60–69	Non-frail	2873	45	26	0.9	below 50% CI	1402	22	10	0.7
	Pre-frail	3015	47	68	2.3	within 50% CI	4037	63	66	1.6
	Frail	527	8	28	5.3	above 50% CI	976	15	46	4.7
70–79	Non-frail	1261	30	19	1.5	below 50% CI	1475	35	25	1.7
	Pre-frail	2212	52	87	3.9	within 50% CI	1978	46	82	4.1
	Frail	798	19	94	11.8	above 50% CI	818	19	93	11.4
80–89	Non-frail	240	16	10	4.2	below 50% CI	621	40	37	6.0
	Pre-frail	730	47	59	8.1	within 50% CI	525	34	61	11.6
	Frail	575	37	111	19.3	above 50% CI	399	26	82	20.6
90+	Non-frail	19	9	1	5.3	below 50% CI	76	37	10	13.2
	Pre-frail	56	27	10	17.9	within 50% CI	46	22	17	37.0
	Frail	133	64	57	42.9	above 50% CI	86	41	41	47.7

Appendix 1

Predicted FI values (with 50% CIs) according to the cubic model (all ages).

Age	Predicted FI value	Lower 50% CI	Upper 50% CI
50	0.08	0.01	0.16
51	0.08	0.01	0.16
52	0.08	0.01	0.16
53	0.08	0.01	0.16
54	0.09	0.01	0.16
55	0.09	0.01	0.16
56	0.09	0.02	0.16
57	0.09	0.02	0.17
58	0.09	0.02	0.17
59	0.10	0.02	0.17
60	0.10	0.03	0.17
61	0.10	0.03	0.18
62	0.11	0.03	0.18
63	0.11	0.04	0.18
64	0.11	0.04	0.19
65	0.12	0.04	0.19
66	0.12	0.05	0.20
67	0.13	0.05	0.20
68	0.13	0.06	0.20
69	0.14	0.06	0.21
70	0.14	0.07	0.22
71	0.15	0.07	0.22
72	0.15	0.08	0.23
73	0.16	0.08	0.23
74	0.16	0.09	0.24
75	0.17	0.10	0.24
76	0.18	0.10	0.25
77	0.18	0.11	0.26
78	0.19	0.12	0.27
79	0.20	0.12	0.27
80	0.21	0.13	0.28
81	0.22	0.14	0.29
82	0.22	0.15	0.30
83	0.23	0.16	0.31
84	0.24	0.17	0.32
85	0.25	0.18	0.33
86	0.26	0.19	0.34

Age	Predicted FI value	Lower 50% CI	Upper 50% CI
87	0.27	0.20	0.35
88	0.28	0.21	0.36
89	0.29	0.22	0.37
90	0.30	0.23	0.38
91	0.31	0.24	0.39
92	0.33	0.25	0.40
93	0.34	0.26	0.41
94	0.35	0.28	0.43
95	0.36	0.29	0.44
96	0.38	0.30	0.45
97	0.39	0.32	0.46
98	0.40	0.33	0.48
99	0.42	0.34	0.49
100	0.43	0.36	0.51