RESEARCH ARTICLE

Frailty index transitions over eight years were frequent in The Irish Longitudinal Study on Ageing [version 1; peer review: 3 approved, 1 approved with reservations]

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Abstract

Background: The frailty index (FI) is based on accumulation of health deficits. FI cut-offs define non-frail, prefrail and frail states. We described transitions of FI states in The Irish Longitudinal Study on Ageing (TILDA).
Methods: Participants aged ≥50 years with information for a 31-deficit FI at wave 1 (2010) were followed-up over four waves (2012, 2014, 2016, 2018). Transitions were visualized with alluvial plots and probabilities estimated with multi-state Markov models, investigating the effects of age, sex and education.
Results: 8174 wave 1 participants were included (3744 men and 4430 women; mean age 63.8 years). Probabilities from non-frail to prefrail, and non-frail to frail were 18% and 2%, respectively. Prefrail had a 19% probability of reversal to non-frail, and a 15% risk of progression to frail. Frail had a 21% probability of reversal to prefrail and 14% risk of death. Being older and female increased the risk of adverse FI state transitions, but being female reduced the risk of transition from frail to death. Higher level of education was associated with improvement from prefrail to non-frail.
Conclusions: FI states are characterized by dynamic longitudinal transitions and frequent improvement. Opportunities exist for reducing the probability of adverse transitions.

Keywords

Aged, Frailty, Longitudinal, Surveys, Transition, Multi-state

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This article is included in the TILDA gateway.

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Companion paper

This article is based on methodology first reported in Roman Romero-Ortuno, Peter Hartley, James Davis, Silvin P. Knight, Rossella Rizzo, Belinda Hernández, Rose Anne Kenny, Aisling M. O'Halloran, *Transitions in frailty phenotype states and components over 8 years: Evidence from The Irish Longitudinal Study on Ageing*, Archives of Gerontology and Geriatrics, Volume 95, 2021, https://doi.org/10.1016/j.archger.2021.104401[1].

What is new?

- We described longitudinal transitions in frailty index states.
- Transition probabilities were estimated with multi-state models.
- Frail had a 21% probability of reversal to prefrail and 14% risk of death.
- Frailty index transitions are dynamic and include improvement.
- Opportunities exist for reducing the probability of adverse transitions.

Introduction

As populations get older, the association between chronological age and health status becomes increasingly variable, to the extent that for a large sector of the older population, chronological age is not a relevant marker for understanding the experience of ageing[2]. To describe this heterogeneity in health status as we age, the concept of frailty has been proposed[3–5].

The frailty index (FI) methodology was introduced by Rockwood and colleagues[6,7] as a way to quantify the accumulation of people's health 'deficits' (i.e. symptoms, clinical signs, medical conditions and disabilities) at a given chronological age. As per published standard procedure[8], a FI can be constructed on any suitable health database by considering a minimum of 30 deficits that need to satisfy the following criteria: (a) be associated with health status, and not simply attributes (e.g. hair graying); (b) cover a range of systems; (c) not saturate too early (e.g. presbyopia is nearly universal by age 55); and (d) their prevalence must increase with age (excluding survivor effects); in addition, in repeated assessments the FI construction must be the same[8].

Since FI deficits must increase with age, the FI has a statistically significant association with chronological age[9]. However, on account of the above-mentioned population heterogeneity, the effect size of this association has been found to be small[10,11]. The sex-specific properties of the FI have also been studied. A systematic review and meta-analysis[12] consistently showed that women have higher FI scores than males at all ages. However, whilst women tend to accumulate more deficits than men of the same age, their risk of mortality tends to be lower[6]. Socioeconomic status, including education, has also been reported to explain variation in FI within individuals of the same chronological age[13].

Frailty in older adults can be improved and even reversed with appropriate medical and non-medical interventions[14]. However, despite abundant research to the contrary, non-specialist clinicians and the general public often believe that frailty is a 'fixed' state with little potential to change over time[15]. Previous works have shown that the FI is longitudinally dynamic[16–21], but Irish data on FI transitions was lacking and few studies have employed long follow-up periods. Our aim was to describe the eight-year longitudinal transitions of FI states using data from The Irish Longitudinal Study on Ageing.

Methods

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 two-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 full cohort profile has been described elsewhere[22,23].

Sample

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

Construction of the FI

As previously published[24], a 31-item FI was constructed using self-reported health measures available in TILDA's Computer-Assisted Personal Interview (CAPI) questionnaire conducted at wave 1. The selection of deficits was consistent with the standard FI requirements[8], including that deficits are any symptom, sign, disease or disability associated with age and adverse outcomes, are present in at least 1% of the population, cover several organ systems, and have under 5% missing data[24]. The components of this 31-item FI are in Appendix 1 (see *Extended data*)[25]. Deficits with more than two categories (i.e. no=0 or yes=1) were coded as a proportion of the number and order of responses; for example, five-answer categories for the deficit 'Self-rated physical health': *Excellent*, *Very good* and *Good* were coded as 0 (no deficit); *Fair* was coded as 0.5 (partial deficit); and *Poor* was coded as 1.0 (full deficit). Analyses from diverse datasets have suggested that variables included in an FI can be coded either as dichotomous or ordinal, with negligible impact on the performance of the index in predicting mortality[26].

In keeping with previous literature[27], the following cut-offs were applied at each wave for the definition of the three FI states: FI < 0.10: non-frail; FI ≥ 0.25: frail; and the rest:

prefrail. As conducted by others[28], and as a sensitivity analysis, we categorized the FI based on baseline quartiles.

Other measures

Age was measured at baseline and each wave, and the following were measured at baseline: sex (male = 0; female = 1); and highest education level (primary or less = 1; secondary = 2; third/higher = 3).

Mortality

Mortality 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[29]. Other than deaths, attrition at each wave was classified as 'missing'.

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 or proportion (%).

For the visualization of the longitudinal trajectories of FI states, an alluvial chart was created using the R ggalluvial package[30]. In the alluvial plot, the height of the stacked bars at each wave (which represent whether participants' status for the given frailty state 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. As a supplementary visualization, alluvial charts were created for two age subsamples: less than 75 and 75 or more at baseline. As a further supplementary visualization, alluvial charts were created for each of the individual 31 FI items on the total sample.

To estimate transition probabilities for the FI states, we used multi-state Markov models using the R msm package, which allows a general multi-state model to be fitted to longitudinal data[31]. The multi-state Markov model is a way of describing a process in which individuals move through a series of states over time. 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 FI state. We adjusted the multi-state models for age, sex and education. Multi-state 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). 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.

Ethics

Ethical approval for each wave was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, Ireland: Wave 1: "The Irish Longitudinal Study on Ageing (granted 2 May 2008)"; Wave 2: "The Irish Longitudinal Study on Ageing (granted 19 October 2011)"; Wave 3: "Main Wave 3 Tilda Study (granted 9 June 2014)"; Wave 4: "Ref: 150506"; and Wave 5: "Ref: 170304". Prior to inclusion in the study, all participants provided written informed consent for participation and utilisation of collected data for scientific publications.

Results

TILDA wave 1 recruited a total of 8504 participants, of whom 330 (3.9%) were aged less than 50 years. The remaining 8174 had complete FI information (3744 men and 4430 women). The mean (SD; minimum, maximum) age of wave 1 participants (n=8174) was 63.8 (9.8; 50–105) years; for wave 2 (n=6994): 65.5 (9.5; 52–97); for wave 3 (n=6249): 67.5 (9.2; 54–98); for wave 4 (n=5571): 69.2 (8.9; 56–101); and for wave 5 (n=4874): 70.6 (8.5; 58–103). Overall, 6832 (83.6%) participants were aged <75 and 1342 (16.4%) 75 or more. The counts and proportions for FI states and deaths at each wave is presented in Table 1.

The alluvial plot for the FI states in the total sample is shown in Figure 1, and Appendices 2 and 3 (see *Extended data*) show the alluvial plots for age groups (<75 versus 75 and more), and each of the 31 FI items in the total sample, respectively. As expected, the cumulative proportions of deaths and missing data increased across waves. Numbers of FI state transitions in the total sample are detailed in Appendix 4 (see *Extended data*)[25].

Table 2 shows the probabilities of transition (with 95% confidence intervals) in frailty states from one wave to the next. Figure 2 visually shows the transition probabilities. In the age subanalyses presented in Appendix 5 (see *Extended data*)[25],

Table 1. Proportions of frailty index states and deaths at each wave.

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
Non-frail	55.5% (n=4540)	52.5% (n=3667)	50.9% (n=3179)	50.1% (n=2794)	46.6% (n=2273)
Prefrail	30.7% (n=2508)	32.4% (n=2262)	34.3% (n=2140)	35.0% (n=1952)	36.7% (n=1790)
Frail	13.8% (n=1126)	15.2% (n=1061)	14.9%(n=928)	14.8%(n=826)	16.6%(n=810)
Deaths	0.0% (n=0)	2.5% (n=208)	3.8% (n=309)	3.2% (n=259)	3.4% (n=275)

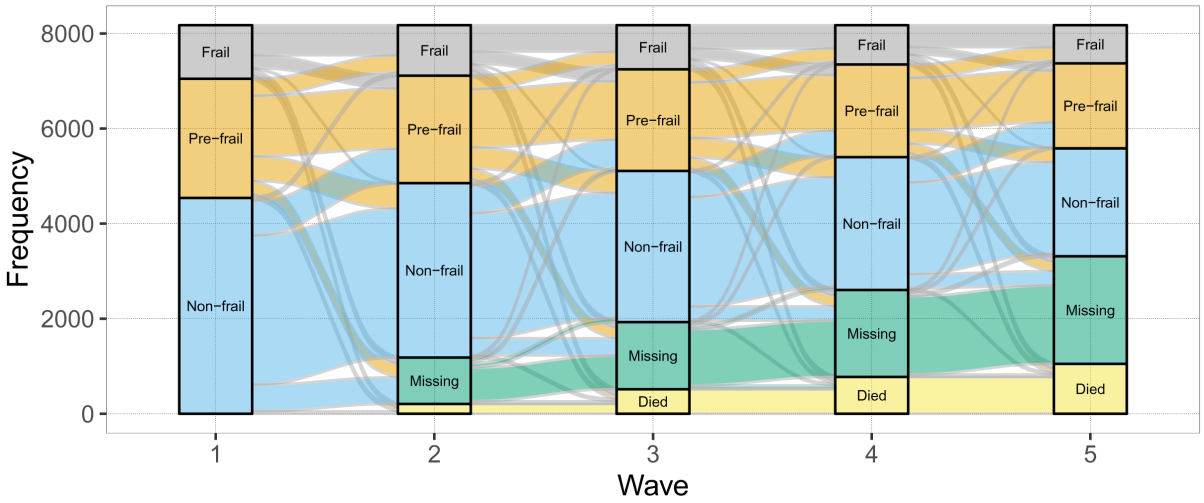

Figure 1. Alluvial chart of the longitudinal transitions of frailty index states in The Irish Longitudinal Study on Ageing (n=8174).

Table 2. Estimated transition probability (and 95% CI) matrix for each frailty index state (from wave x to wave x + 1) in the total sample (n=8174).

	STATE TO			
STATE FROM	**Non-frail**	**Prefrail**	**Frail**	**Death**
Non-frail	0.79 (0.78, 0.79)	0.18 (0.17, 0.19)	0.02 (0.02, 0.02)	0.01 (0.01, 0.01)
Prefrail	0.19 (0.18, 0.20)	0.62 (0.60, 0.63)	0.15 (0.15, 0.16)	0.04 (0.03, 0.05)
Frail	0.03 (0.03, 0.04)	0.21 (0.20, 0.22)	0.62 (0.60, 0.63)	0.14 (0.13, 0.16)

CI: confidence interval.

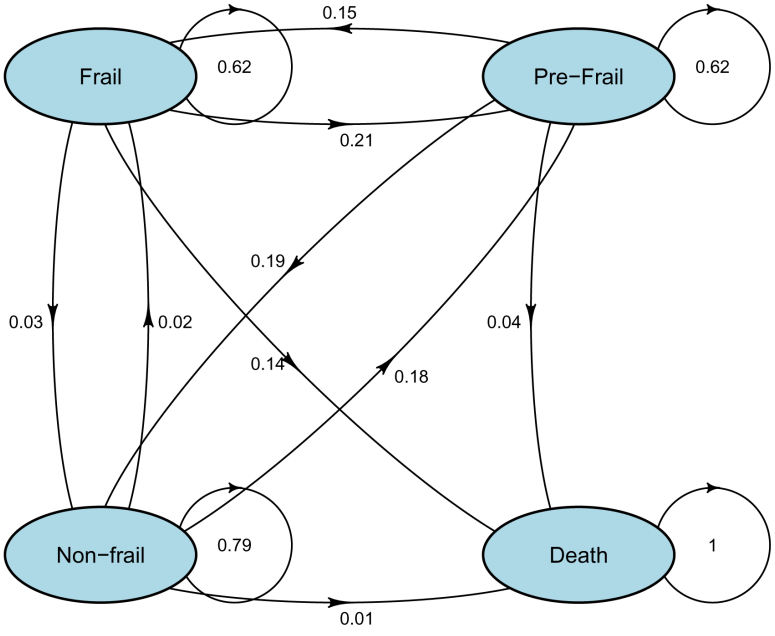

Figure 2. Estimated transition probability for each frailty index state (from wave x to wave x + 1) in the total sample (n=8174).

in those age 75 or more, the risk of death from a frail state was 67%, and the probabilities of improvements from frail to prefrail and prefrail to non-frail were 12% and 6%, respectively.

Appendix 6 (*Extended data*)[25] shows the transition probabilities based on FI quartiles at baseline in the total sample. According to this FI categorization, severe frailty had a 25% risk of death, a 22% probability of transition to moderate frailty and a 6% probability of improvement to mild frailty. The probability of improvement from moderate to mild frailty was 26%, and the probability of improvement from mild frailty to fit state was 22%. Other transition probabilities according to the FI quartiles categorization are shown in Appendix 6 (see *Extended data*)[25].

Appendix 7 (*Extended data*)[25] shows a reanalysis modelling missing data as a fourth state. Table 3 shows the effects of sex, age and education in the multi-state models. Being older increased the risk of adverse state transitions from frail to death, from prefrail to frail, and from non-frail to prefrail. The opposite was suggested for favourable transitions from frail to prefrail, and prefrail to non-frail.

As regards sex, being female increased the risk of adverse transitions from non-frail to prefrail, and prefrail to frail; however, it reduced the risk of transition from frail to death. Being female reduced the risk of favourable transitions from pre-frail to non-frail and frail to prefrail. In terms of education, there were trends in the expected direction with higher levels of education being positively associated with the favourable transition from prefrail to non-frail and negatively associated to adverse transitions (Table 3).

Discussion

Using Irish data from a large population-based study of ageing spanning eight years, we corroborated that FI states are dynamic and many transitions are affected by age, sex, and education, in the expected directions. Indeed, frailty is not all steady state and progression, but reversion is also common[32]. Our study adds value to previous research by reporting a long follow-up period in an Irish sample and offers some new insights on the dynamics of the FI in relation to chronological age. Indeed, our age subanalyses suggested that the FI dynamics are not the same in older groups, with frailer people aged 75 or more having higher mortality and less reversibility than people aged less than 75. This agrees with previous research suggesting that chronological age and the FI may be complementary in predicting health outcomes[33,34]. Specifically about sex, our results are in keeping with the known fact that whilst women tend to accumulate more deficits than men of the same age, their risk of mortality tends to be lower[6]. Our results also agree with previous observations that sociodemographic factors (e.g. education) are related to changes in FI status[16]. The age-sex-education effects are consistent with previous research and we did not model other time-varying covariates such as physical activity or polypharmacy[17]. However, in our FI operationalization, items related to physical activity difficulties and polypharmacy were included as defining FI deficits (Appendix 1, *Extended data*)[25]. On the other hand, the efficient statistical handling of additional covariates would have probably required a larger sample size, judging by some of the wide CIs obtained in Table 3 for transitions with a relatively low number of events (Appendix 4, *Extended data*)[25]. Even though we broke the FI into three categories utilizing a previously reported scheme and performed sensitivity analysis based on quartiles, the FI is continuous in nature and concern remains as to its optimal categorization[27].

Our study has further limitations. For the mortality outcome, specific causes of death were not studied, and addressing this in future studies could shed light into specific biological risks associated with FI states. Another limitation is that missing

Table 3. Hazard ratios and 95% CIs of the estimated covariate effects of sex, age and education in the multi-state models.

From - To	Sex = Female	Age	Education = Secondary	Education = Third/Higher
Frail - Prefrail	**0.83 (0.72, 0.95)**	**0.97 (0.97, 0.98)**	1.00 (0.86, 1.17)	1.19 (1.00, 1.42)
Frail - Non-frail	0.79 (0.00, 1259.15)	0.94 (0.62, 1.42)	1.01 (0.00, 4101.10)	1.51 (0.00, 19123.09)
Frail - Death	**0.64 (0.44, 0.93)**	**1.14 (1.11, 1.17)**	0.98 (0.62, 1.56)	1.55 (0.96, 2.52)
Prefrail - Frail	**1.32 (1.17, 1.49)**	**1.04 (1.04, 1.05)**	**0.69 (0.60, 0.79)**	**0.61 (0.53, 0.71)**
Prefrail - Non-frail	**0.84 (0.76, 0.93)**	**0.97 (0.96, 0.98)**	1.04 (0.91, 1.18)	**1.23 (1.08, 1.40)**
Prefrail - Death	0.60 (0.27, 1.36)	1.06 (1.01, 1.11)	1.31 (0.39, 4.40)	0.39 (0.05, 2.96)
Non-frail - Frail	1.73 (0.07, 45.67)	0.79 (0.61, 1.01)	0.89 (0.00, 950.30)	0.19 (0.00, 270.39)
Non-frail - Prefrail	**1.22 (1.12, 1.32)**	**1.05 (1.05, 1.06)**	**0.76 (0.68, 0.85)**	**0.68 (0.60, 0.76)**
Non-frail - Death	0.32 (0.01, 6.93)	1.13 (0.99, 1.29)	0.44 (0.00, 119.96)	1.37 (0.03, 65.28)

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

data was censored as missing completely at random. However, analyses in Appendix 7, *Extended data*[25], suggested that frailer individuals were not more likely to have missing data at future waves (11% for all frailty states).

Another limitation of the use of an FI that was based on self-report is measurement error or misclassification. As visually suggested by the individual-deficit alluvial plots in Appendix 3 (see *Extended data*)[25], some items showed implausible favourable transitions (i.e. from having history of a medical condition at one wave, to not reporting history of that same medical condition at the following wave). However, Appendix 8 (*Extended data*)[25] shows, for example, that implausible transitions from having to not having history of heart attack, diabetes, osteoporosis, cancer, and stroke/TIA, were less frequent (n = 155 to 657) than transitions from other deficits where improvement could be more plausible (e.g. self-rated health, daytime sleepiness, self-rated memory, and difficulties rising from a chair or carrying weights, n = 1946 – 4060). Research from other longitudinal studies has shown that self-reported health questions are prone to significant biases[35], and TILDA is not free of those.

As a limitation to the extrapolation of the study and its external validity, it is important to note that the operationalization of frailty does not have a universal consensus, and we here opted for the FI model. Hence, our results cannot be extrapolated to other frailty models such as the frailty phenotype[5]. In the latter case, polypharmacy is not included in the definition of frailty; hence, the frailty phenotype may be more suited for the study of that covariate than the FI. However, the frailty phenotype would be less suited for the study of physical activity because that item is included in the frailty definition.

In summary, given the importance of FI states transition information in planning public health interventions, there is a need to support data collection and projects that measure frailty trajectories and transitions between different levels of frailty severity[36], in a way that non-specialist clinicians and the general public can easily understand. We believe that it is important to create a body of international evidence that consistently supports the important public health message that frailty is dynamic over a long period of time, throughout which there is potential and opportunities for improvement. In future work, it would be possible to adapt more advanced methodologies[37,38] to explore the main clusters or groupings of factors that determine different trajectories to identify the best opportunities for reducing the probability of adverse frailty transitions.

Data availability

Underlying data

The data underlying the results cannot be shared due to ethical and data protection issues. Requests to access this data can be made directly to TILDA (tilda@tcd.ie) and will be considered on a case-by-case basis. The first four waves of TILDA data are available from the Irish Social Science Data Archive (ISSDA) at www.ucd.ie/issda/data/tilda/. To access the TLDA survey data, please complete an ISSDA Data Request Form for Research Purposes, sign it, and send it to ISSDA by email (issda@ucd.ie).

Extended data

Figshare: Extended data.docx. https://doi.org/10.6084/m9.figshare.14681292.v1[25].

This project contains the following extended data:

- Appendix 1 (31-item Frailty Index (FI): items and scoring of individual items)
- Appendix 2 (Alluvial charts by age groups)
- Appendix 3 (Alluvial charts for each of the 31 FI items in the total sample)
- Appendix 4 (Numbers of transitions for FI states in the total sample)
- Appendix 5 (Sensitivity analysis of transition probabilities by age groups)
- Appendix 6 (Sensitivity analysis of transition probabilities on the total sample categorised by FI quartiles at baseline)
- Appendix 7 (Sensitivity analysis where missing data was considered as an additional state in the multi-state models)
- Appendix 8 (Implausible transitions from having to not having history of medical conditions were less frequent than transitions from other deficits where improvement would be more plausible)

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Version 1

Reviewer Report 03 September 2021

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✔ **Mario Ulises Pérez Zepeda**
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I enjoyed very much reading this article and its companion paper. There is no doubt that that the field of frailty needs to advance into the direction of longitudinal analyses and in particular of the meaning of the trajectories. In this work, the authors show how these transitions and trajectories of frailty, and depicted with the frailty index, change over time and how some factors are associated with this change, mainly sex, age and education. In addition, in their ancillary analyses, show how different arranges bring light into for example age (age stratified analysis) or the dynamics of the deficit accumulation. Methods are described in detail, and authors make their best to address methodological/analytical problems that are common when doing research on frailty index with data sets. I missed that the authors did not discuss the difference/similarity of the phenotype with their results with the FI. They already have one work on this matter with the phenotype, an opinion on how do this two tools compare would be mostly appreciated by the 'frailty community' It is true that the index and the phenotype are different, as authors acknowledge, however, they live under the same semantic umbrella, frailty; and that should not be overlooked. Even if the authors think they are measuring different conditions (for example the phenotype could be a great tool for measuring sarcopenia); would be interesting to read their thoughts on that. As they iteratively comment, there is scarce evidence on this matter, and having first hand the opinion from researchers that had the opportunity to address the phenomenon both with the index and the phenotype will certainly enrich the discussion. Furthermore, what would they think these trajectories will look like with other tools? Maybe this is too far from their objective, but a brief comment might increase interest and raise more interesting questions. Just a technical problem, I did not find the alluvial graphs for each deficit.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Geriatrics, frailty, geriatric syndromes, geriatric epidemiology, sarcopenia

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 27 August 2021

https://doi.org/10.21956/hrbopenres.14461.r29644

Danielle Ni Chroinin
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Thank you for the opportunity to review this paper, which details transitions in frailty with time over an 8 year period as part of the Irish TILDA project. The study includes adults in later middle age through to old age (50+ years, mean 63.8 years at recruitment; >80% aged <75), with >8000 participants included in Wave 1, and data available for 4874 by wave 5. The authors highlight that a companion paper, which adopted different focus and definitions of frailty, exists and was published elsewhere.

Overall, the paper is clearly written, and the diagrams and tables present what could be very complicated data in an accessible fashion. Follow-up rates are slightly disappointing, but perhaps not unexpected. The rate of death is low (and as sourced from the central register, shouldn't be influenced by 'missing' data'), but the population is not very old, which may explain that figure. Data regarding activities and interventions which might have been associated with frailty transitions (in either direction) are not included, which is a pity, although the authors note that analysing more covariates was beyond the scope of the paper/sample size. The findings add to the evidence base supporting the concept of frailty as a dynamic condition, over a longer (8-year) follow up period, and in an Irish context. Transitions were affected by age, sex and (early) educational attainment, but these are fixed. For clinicians, I think the real key will be identifying

what we can do to influence trajectories.

Further comments:
The Introduction gives a clear explanation of frailty and the FI tool, which will be helpful to the uninitiated reader. The authors note that frailty may be reversible and is dynamic. The lack of Irish data and long follow up are highlighted. It would be helpful to know where existing data hail from, and if certain ethnicities/cultural backgrounds are under- or over-represented in the available data, and if/how the Irish population differ from these.

Methods:
Design and setting were outlined concisely, and a link to further information about the TILDA project was included. Construction of the FI is clearly outlined, and the specific data-points collected are included in Appendix 1.

The cut-offs applied are perhaps slightly arbitrary and non-age-adjusted, based on those used by the first author in an earlier publication, but this is a reasonably pragmatic approach to use of a continuous scale, and quartiles were analysed in a secondary analysis. The authors helpfully included death data from the General Register Office (rather than other maybe less-accurate data sources). Models were adjusted for age, sex and education, but not SES per se.

Results:
Data were available for 4874 of the original 8174 by the end of the final wave (5), with 3% reported dead at the end of 8 year follow up- low by geriatric standards, but maybe not given the relative youth of the recruitees.

It might have been nice if distribution of deficits in FI (Appendix 1) were included within the Appendix (e.g. proportions with polypharmacy, IHD, DM, stroke, etc, and 5-point distribution for 'self-rated memory' etc).

The baseline rate of frailty/pre-frailty in the cohort aged <75 is not insubstantial.

Unsurprisingly, likelihood of death in older frail patients was high, and those with severe frailty were at highest risk. While there were transitions in both directions, those with severe frailty rarely reversed to 'fit' or 'mild[ly] frail' levels, and women more often experienced adverse transitions.

The alluvial plots are helpful for visual representation, the tables are easy to understand, and the Appendices give additional detail.

Discussion:
While the opening line is perhaps a little underwhelming in stating that the authors 'corroborate that FI states are dynamic', agree better this than over-interpretation.

While the authors acknowledge that they did not 'model other time-varying covariates such as physical activity or polypharmacy', changes in activity, geriatric/multidisciplinary team intervention, changes in polypharmacy/medication burden and acute hospitalisations would have been helpful to have known, and I believe that the TILDA dataset would include some of this info (e.g. in the companion paper, info regarding physical activity is captured using the IPAQ-SF). While the authors note that 'statistical handling of additional covariates would have probably required a

larger sample size', some indication of how these might have related to changes in frailty trajectory would be of interest, especially to clinicians. This is noted in the paper's concluding line, but the authors have quite a wealth of information within TILDA, and may be able to explore this further in their own dataset.

A small point: In relation to implausible transitions, I wonder if cognitive impairment might have accounted for some of these. While they were not common, I was unclear as to whether the authors performed additional sensitivity analyses where 'implausible transitions' were reanalysed with the original status carried through (e.g. positive 'history stroke' in wave 1 extended to all subsequent waves, even if the patient changed their answer to negative in subsequent waves).'

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Geriatric medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 August 2021

https://doi.org/10.21956/hrbopenres.14461.r29817

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Dorly J. H. Deeg
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Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

This is a companion paper to 'Transitions in frailty phenotype status and components of frailty over 8 years' (2021), as stated in the preliminaries. The difference is that a different definition of frailty is now used, i.e., the Frailty Index (FI), which is conceived of as a continuous index, rather than an index with two or three states as is the case with the frailty phenotype (FP). In the current paper, socio-demographic correlates of transitions are assessed. In the companion paper, an emphasis was on transitions in the five components of the FP. As the FI is conceived of as a continuous measure, the wisdom of distinguishing states (and transitions between them) might need some argumentation.

The argument leading up to the aim of the paper is rather technically phrased: Irish data on FI transitions are not available yet, and few studies have employed longer follow-ups. However, why would additional (i.e., Irish) data on transitions be useful? And why would a longer follow-up be useful? I would have expected a more substantial argument for a study of transitions. The only statement that comes close to an argument is that 'non-specialist clinicians and the general public often believe that frailty is a "fixed state"'. But the authors also state that there is 'abundant research to the contrary', so what does the current study add to the existing research findings? The bullets listed under 'What is new?' are not really 'new'. I know that as a reviewer, I am not asked to comment on novelty or interest of the paper, but a proper argumentation is indispensable.

I do see merits in this study. It includes a large number of participants, which allows the study of less-frequent transitions. The relatively large number of time intervals across which the transitions are observed, also helps the study of less frequent transitions. That said, for some calculations, the number of transitions still is too low, as apparent from the huge confidence intervals for the association of secondary and higher education with the transition frail-nonfrail and nonfrail-frail (Table 3). Therefore, I would recommend to dichotomise, instead of trichotomise, education.

Apparently, the main interest of the authors is in back-transitions ('favourable' transitions), as they tend to report the risk of death and the probability of improvement, omitting report of risks of 'adverse' transitions. The average age of the initial sample is rather young at 64 years; only 16% are older than 74. From Appendix 5, one can observe that the frailty states are much less stable at ages 75+ than at younger ages; in particular, the probability of adverse transitions is much higher, especially to the state of death. As in clinical practice, the majority of frailty cases have ages 75+, the findings in this age group are especially useful. When reporting the results for the full sample, however, the emphasis on favourable transitions suggests that these apply to all ages. This suggestion should be avoided, for example by showing Appendix 5 in the main text and distinguishing older ages in the discussion of the results.

The cut-point between 'fit' and 'pre-frail' is chosen as 0.10, referring to a previous publication by the same author(s) (reference 27). However, this article proposes to use age-specific cut-points. Therefore, this article does not support the current cut-off. Other studies use as a criterion for 'fit' having a maximum of 4-5 deficits, or – as the authors state – use quartiles. An argument to support the cut-point of 0.10 is needed.

The alluvial chart nicely illustrates the various transitions, including transitions to missing. Incidentally, it would be more logical to have the categories 'dead' and 'missing' stacked at the top

rather than at the bottom. From Appendix 7, it can be observed that there are transitions from missing back to having available data or death. Regardless, missing is the most stable state at probability 0.82. Are they all alive at the end of the study? In their Discussion, the authors mention that all frailty states had similar transition probabilities to 'missing'. How does this reflect on their assumption of MCAR?

Because frailty is, by definition, an unstable state, many changes can happen within the 2-year interval between waves. This should be commented on in the Discussion, including the consequences for the transition probabilities found. Are they under- or overestimated?

Table 2 should include the absolute numbers, as now provided in Appendix 4 only – which then can be omitted. The absolute numbers should be available in the main text. The same goes for Appendix 5. Please also state the total number of transitions, not only the initial number of participants. The three states presented in this table appear highly stable, with probabilities of staying in the same state as 0.79, 0.62, and 0.62, respectively. How is it possible that in Appendix 5, the age-specific probabilities of staying in the same state are so much lower?

The authors mention in the Discussion that 5 of the 31 items, all self-reported chronic diseases, show implausible favourable transitions. This 'recovery' should indeed be considered as a measurement error, which can be corrected by proper longitudinal cleaning of the data. I recommend that the authors clean their data longitudinally and then recalculate the FI transition probabilities.

Details:

- In Table 1, the last row should read 'Deaths since previous wave'.
- Appendix 5 is not a 'sensitivity analysis' as stated in its header, but a sub-analysis, as stated in the main text.
- In the very last sentence of the Discussion, it would be good to insert 'frailty' before 'trajectory'.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of ageing; longitudinal studies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 21 July 2021

https://doi.org/10.21956/hrbopenres.14461.r29766

Daniel Kam Yin Chan
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The study is well designed and the paper is well written. An excellent study.

The only query (not criticism) is whether intervention data (medical or non-medical) are being collected, and if yes, are they available? If not available, it would be good to indicate it in the paper, such as under the section "other measures", as I cannot find it there. This would be of interest to indicate if such interventions improve the reversibility in different stages of Frailty Index.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Geriatrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.