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ORIGINAL RESEARCH

Longitudinal trajectories of frailty are associated with short-term mortality in older people: a joint latent class models analysis using 2 UK primary care databases

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Abstract

Objectives: Frailty is a dynamic health state that changes over time. Our hypothesis was that there are identifiable subgroups of the older population that have specific patterns of deterioration. The objective of this study was to evaluate the application of joint latent class model in identifying trajectories of frailty progression over time and their group-specific risk of death in older people.

Study Design and Setting: The primary care records of UK patients, aged over 65 as of January 1, 2010, included in the Clinical Practice Research Datalink: GOLD and AURUM databases, were analyzed and linked to mortality data. The electronic frailty index (eFI) scores were calculated at baseline and annually in subsequent years (2010-2013). Joint latent class model was used to divide the population into clusters with different trajectories and associated mortality hazard ratios. The model was built in GOLD and validated in AURUM.

Results: Five trajectory clusters were identified and characterized based on baseline and speed of progression: low−slow, low−moderate, low−rapid, high−slow, and high−rapid. The high−rapid cluster had the highest average starting eFI score; 7.9, while the low−rapid cluster had the steepest rate of eFI progression; 1.7. Taking the low−slow cluster as reference, low−rapid and high−rapid had the highest hazard ratios: 3.73 (95% CI 3.71, 3.76) and 3.63 (3.57-3.69), respectively. Good validation was found in the AURUM population.

Conclusion: Our research found that there are vulnerable subgroups of the older population who are currently frail or have rapid frailty progression. Such groups may be targeted for greater healthcare monitoring.

Keywords: Older people; Longitudinal; Frailty; Electronic frailty index; Mortality; Joint latent class models; Joint models

Disclaimer: This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The views, interpretations, and conclusions expressed are those of the authors and not necessarily those of the NHS, National Institute for Health and Care Research or the Department of Health and Social Care.

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Plain Language Summary

Frailty is a condition of increased vulnerability to changes in health and is common in older age, affecting around 10% of those over 65. It is characterized by gradual deterioration in body systems and loss of inbuilt reserves such as muscle strength.

People with frailty are at increased risk of falls, disability, loneliness, and therefore hospitalization and nursing home admission. These reduce quality of life and are costly for medical and social care.

Recently a screening tool: the electronic frailty index score has been developed for use in primary care to help identify older people living with frailty, to better target packages of care. The electronic frailty index score will change over time, and our study aims to identify different groups of older people with frailty based on how quickly or slowly their score changes. For example, a rapidly increasing score might suggest that a person needs extra medical or social services support.

We identified 5 distinct groups and found that groups of older people who are currently frail or deteriorating rapidly were at higher risk of death. We recommended research over longer periods so general practitioners (GPs) can timely identify those groups. This can then allow us to further support GPs to target older people with frailty who are at higher risk of worsening health, compared to those whose health is more stable. This information will help GPs target the limited resources available to those most in need.

1. Introduction

Frailty can be defined as a loss of biological reserve leading to vulnerability to adverse outcomes. These include unplanned hospitalization, admission to long-term care, and death [1−4]. At an individual level, identification of those with increased frailty for targeted interventions including Comprehensive Geriatric Assessment, enhancing physical activity, nutritional support, and psychological support could result in a reduction in the rate of adverse outcomes [5,6]. Further, knowledge of the extent of frailty at a population level would be important for health and social care planning.

The electronic frailty index (eFI) was developed to support targeted frailty care and population planning based on the identification in the primary care electronic health records (EHRs) [7] of the presence of 36 specified deficits. Data extracted from those records were used to calculate the eFI score as a cumulative proportion of those 36 that had been recorded. People were divided into categories (fit, mild, moderate, and severe frailty) based on these scores. These categories were predictive of subsequent mortality, emergency hospital and nursing home admission [7]. As a consequence, eFI has now been widely adopted by the National Health Service (NHS) in England to support routine frailty identification [8].

While eFI score was found to be associated with mortality on the population level, using a cross-sectional value had poor predictive performance on the individual level even if calculated only 3 months before the patient's death [9]. Frailty is not a static phenomenon. Available evidence indicates that the number of health deficits on average double between the ages of 50 and 80 [10]. In their analysis of data from four surveys for people aged 65+ from Europe and the United States, Stolz et al applied joint modeling to assess the association between frailty trajectory over time and the risk of death and found that an increasing trend of frailty was a good predictor of mortality, independent of baseline value [11].

Frailty also does not progress to the same extent in different individuals. In a study of over 12,000 older residents using a reference standard frailty index, three different trajectories of frailty were identified [12]. Other studies found similar results; varying distinct frailty trajectories exist in older people with different characteristics and/or near death [13,14]. The methods employed to identify such distinct trajectories included traditional and machine-learning longitudinal clustering. These methods, while providing important tools to analyze longitudinal data, either require a uniform number of data points or fail to account for the nonrandom dropouts, often occurring due to death in such an old population.

The objective of the current study was therefore to address whether, by applying joint latent class models (JLCMs), we were able to identify distinct trajectories of eFI that have different mortality risk profiles. Such trajectories could then be used as a more robust indicator, over a single baseline score, to target interventions.

2. Materials and methods

2.1. Summary of design

A longitudinal cohort study using EHR of two large national primary care databases of individuals aged over 65, the first for ascertaining trajectories in frailty, the second to validate these. Based on eFI, we identified the proportions who were 'fit' or had 'mild', 'moderate,' or 'severe' frailty at baseline and determined the transitions over the next 4 years. Next, we attempted to derive clusters based on the trajectories of the eFI and their associated risk for

What is new?

Key findings

- We identified 5 subgroups of older people with different frailty progression patterns and associated risk of death. These subgroups had distinct patterns of frailty progression over 4 years based on the changes in electronic frailty index (eFI) score.

What this adds to what is known?

- eFI is being used in UK primary care to identify vulnerable older people using one cross-sectional value. Our research has shown that both high starting eFI score and rapid progression over 4 years were associated with a higher risk of mortality.

What is the implication and what should change now?

- We identified patients who are currently frail or have rapid frailty progression, and are at a higher risk of mortality. This allows health providers to target interventions and treatment packages toward these vulnerable groups of the older population.

mortality. Lastly, the emerging clusters were validated in the second dataset.

2.2. Data source

Primary data for building the models were extracted using the Clinical Practice Research Datalink (CPRD), a UK primary care data provider. We used CPRD 'GOLD' to build the trajectory clusters and CPRD 'AURUM' to evaluate the resultant clusters. Both these databases comprised anonymized patients' records and demographic data including socioeconomic status, smoking and alcohol consumption, and body mass index information. These databases record also the reasons for all consultations in primary care plus information on laboratory tests, other assessments, diagnoses, and prescriptions [15] that permit calculation of eFI. The 2 databases use different electronic recording systems and cover different areas of the UK. Further details about GOLD and AURUM can be found elsewhere [15,16]. The CPRD data were linked to Office for National Statistics for mortality data.

2.3. Population

Patients aged over 65 and alive on January 1, 2010, (start date) from both GOLD and AURUM were eligible for inclusion if they have been registered in an ''up-to-standard'' practice [15] for at least 1 year before start date. Duplicate patients belonging to both databases were removed from CPRD AURUM.

2.4. Exposure and outcome

The main exposure was the eFI score. Full details of the eFI and its ascertainment are provided elsewhere [7]. This index is a cumulative count based on the presence or absence of 36 'deficits' in the primary care electronic records. The baseline eFI was calculated based on counts of deficits recorded any time before December 31, 2009. If an individual did not have recorded consultations for any of the deficits, then eFI score was entered as zero. The eFI was recalculated at the end of each follow-up year or the patient's study exit date, whichever comes first. All previous deficits—except for polypharmacy, which was calculated annually - were carried forward. eFI was then derived for the next 4 years until December 31, 2013. Deaths were defined as death recorded in Office for National Statistics and/or CPRD.

2.5. Statistical analysis

Patients exited the study at the earliest of the following: practice last collection date, patient transfer-out of practice date, death date [17] or study end date. The base demographic and individual eFI deficits were extracted and compared between the 2 cohorts: GOLD and AURUM. Study participants were allocated to 1 of the 4 categories of frailty based on the original eFI scoring system [7]: 'fit' (eFI score/36: 0-0.12), 'mild' ($>$0.12-0.24), 'moderate' ($>$0.24-0.36), and 'severe' ($>$0.36) at baseline and at their last observation time point. We examined the transition between these four states over the follow-up period to gain an overall sense of the underlying pattern.

We used joint modeling to ascertain the shape of eFI slope during follow-up and the covariate structure between the longitudinal (eFI) and time-event (all-cause mortality) parts [18]. The joint model assumes a homogenous population with an average trajectory. After choosing the preferred methods to model eFI, we attempted to see if there were clusters of discrete patterns of eFI change and whether these allocations had distinct risk profiles. For this, we applied JLCMs, an extension to joint modeling. JLCM has 2 submodels: longitudinal and time-to-event submodels. It assumes a heterogeneous population and uses latent class modeling to divide the population into subgroups (clusters) with different average slopes [19]. The advantage of using this method in contrast to the traditional clustering methods is that it accounts for censored data: patients who died before the end of the observation period. Age and sex were accounted for in the derivation of clusters in both longitudinal and time-to-event models. Two- to 6-cluster models were fitted; the optimum number of clusters was based on Bayesian Information Criterion, convergence, and clinical plausibility.

2.5.1. Model validation

We assessed the performance of the emergent best fit cluster model (derived from GOLD) in the validation of

AURUM sample. Good validation performance was defined as the cluster-specific average posterior probabilities of belonging to the predefined clusters being ≥0.7 for at least half (50%) of each cluster's members. The threshold of 0.7 indicates clear classification of people into clusters [20]. We calculated the hazard ratios (HRs) for mortality of the clusters identified in the AURUM sample and compared them to the original model.

As a final step in assessing the face and content validity of the model, the demographic and clinical characteristics were compared between the resultant clusters. We also examined the contribution of the individual deficits within the eFI and their change in determining cluster membership.

3. Results

3.1. Model building in CPRD GOLD

3.1.1. Study population

There were 475,503 patients in CPRD GOLD database eligible for the analysis. Table 1 describes the baseline characteristics. Mean age was 75.1 (SD 7.4) and majority of the patients were in the "Fit" eFI category, 305,946 (64.3%).

3.1.2. Transition in frailty category

During the 4 years of observation 114,218 (24.4%) patients transitioned to a worse eFI category with 3748 (<0.1%) transitioning to a better frailty category. Most transitions 72,298 (15.2%) were from fit to mild, with 33,158 (7.0%) mild to moderate, and 5086 (1.1%) moderate to severe transitions, while 3676 (<0.1%) crossed more than 1 frailty category (Table 2).

3.1.3. Joint latent class modeling

Median follow-up was 4 years (IQR 2.5-4 years), with 68,977 (14.5%) dying during the observation period. Linear shape was chosen based on the joint modeling analysis, which have also confirmed an association between eFI progression and an increased risk of death (Table S1 in the Appendix). We used the latent class analysis to identify clusters of trajectories of eFI and how these impacted on survival. After testing models with up to 6 clusters, the 5-cluster model emerged as the preferred model based on statistical and clinical plausibility; it had the lowest Bayesian Information Criterion before the models stopped converging. Table S2 in the Appendix describes the models tested. We describe the 5 clusters based on the shape of their trajectories as follows.

- Low−slow (intercept = 2.0, slope = 0.2): individuals who had low eFI value (mostly in the eFI 'fit-mild' categories) at the start of the follow-up and had a very slow progression
- Low−moderate (intercept = 2.1, slope = 0.8): individuals who had low eFI value at the start of the follow-up and had a moderate progression

Table 1. Baseline characteristics of each cluster (GOLD)

Cluster	Overall population	Low−slow	Low−moderate	Low−rapid	High−slow	High−rapid
N	475,503 (100%)	338,029 (71.1%)	69,794 (14.7%)	12,869 (2.7%)	45,707 (9.6%)	9104 (1.9%)
Gender = Male (*n* (%))	211,751 (44.5%)	153,144 (45.3%)	30,393 (43.5%)	5790 (45.0%)	18,695 (40.9%)	3729 (41.0%)
Age (mean (SD))	75.1 (7.4)	74.3 (7.2)	76.5 (7.3)	79.1 (7.2)	77.0 (7.5)	78.2 (7.1)
Visits to primary care[a] (median [IQR])	4 [2, 8]	4 [2, 7]	4 [2, 8]	5 [2, 9]	8 [5, 13]	10 [6, 15]
Socioeconomic status (*n* (%))						
1 (least deprived)	81,714 (17.2%)	58,709 (17.4%)	12,041 (17.3%)	2171 (16.9%)	7263 (15.9%)	1530 (16.8%)
2	93,243 (19.6%)	66,758 (19.7%)	14,154 (20.3%)	2428 (18.9%)	8269 (18.1%)	1634 (17.9%)
3	95,679 (20.1%)	69,018 (20.4%)	14,961 (21.4%)	2698 (21.0%)	7523 (16.5%)	1479 (16.2%)
4	100,448 (21.1%)	71,733 (21.2%)	13,149 (18.8%)	2506 (19.5%)	10,913 (23.9%)	2147 (23.6%)
5 (most deprived)	104,419 (22.0%)	71,811 (21.2%)	15,489 (22.2%)	3066 (23.8%)	11,739 (25.7%)	2314 (25.4%)
BMI (mean (SD))	27.2 (5.7)	27.0 (5.4)	27.1 (6.2)	26.8 (5.5)	28.3 (6.0)	28.4 (6.0)
eFI score[a] (mean (SD))	3.8 (2.9)	3.1 (2.1)	3.3 (2.2)	3.9 (2.4)	9.4 (2.1)	9.7 (2.2)
eFI score[a] (median [IQR])	3 [2, 6]	3 [1, 5]	3 [1, 5]	4 [2, 6]	9 [8, 10]	9 [8, 11]
Frailty category[a,b] (*n* (%))						
Fit	305,946 (64.3%)	248,982 (73.7%)	49,124 (70.4%)	7839 (60.9%)	0	1 (0.0%)
Mild	133,543 (28.1%)	87,935 (26.0%)	20,066 (28.8%)	4619 (35.9%)	17,997 (39.4%)	2926 (32.1%)
Moderate	33,342 (7.0%)	1112 (0.3%)	604 (0.9%)	410 (3.2%)	25,630 (56.1%)	5586 (61.4%)
Severe	2672 (0.6%)	0	0	1 (0.0%)	2080 (4.6%)	591 (6.5%)

BMI, body mass index; eFI, electronic frailty index.
Proportion of missing data was 6.1% for smoking, 26.6% for drinking, and 32.3% for BMI in GOLD.
[a] Baseline: calculated on December 31, 2009.
[b] Frailty categories are fit (mean eFI/36: 0-0.12), mild (>0.12-0.24), moderate (>0.24-0.36), and severe (>0.36).

Table 2. Transitions between frailty categories in GOLD

Baseline	Last observation				
Frailty category[a,b]	Fit	Mild	Moderate	Severe	Total
Fit	230,528 (48.5%)	72,298 (15.2%)	3096 (0.7%)	24 (<0.1%)	305,946 (64.3%)
Mild	3104 (0.7%)	96,725 (20.3%)	33,158 (7.0%)	556 (0.1%)	133,543 (28.1%)
Moderate	0	585 (0.1%)	27,671 (5.8%)	5086 (1.1%)	33,342 (7.0%)
Severe	0	0	59 (<0.1%)	2613 (0.6%)	2672 (0.6%)
Total	233,632 (49.1%)	169,608 (35.7%)	63,984 (13.5%)	8279 (1.7%)	475,503 (100%)

[a] Baseline category: calculated on December 31, 2009.
[b] Frailty categories are fit (mean eFI/36: 0-0.12), mild (>0.12-0.24), moderate (>0.24-0.36), and severe (>0.36).

- Low−rapid (intercept = 2.4, slope = 1.7): individuals who had low eFI value at the start of the follow-up and had a rapid progression
- High−slow (intercept = 7.4, slope = 0.3): individuals who had high eFI value (mostly in the eFI 'mild-moderate' categories) at the start of the follow-up and had a very slow progression
- High−rapid (intercept = 7.9, slope = 1.0): individuals who had high eFI value at the start of the follow-up and had a rapid progression in their frailty

Figure 1 shows the trajectories of each of these 5 clusters and their associated mortality risk profiles. Table S3 reports the estimates for each cluster.

There was a concordance between the 5 trajectories and their mortality risks. Taking low−slow cluster as the reference, low−rapid and high−rapid had the highest HR; 3.73 (95% CI: 3.71, 3.76) and 3.63 (3.57-3.69), respectively. Followed by the high−slow cluster; 2.80 (2.74-2.85). The low−moderate cluster had the lowest HR after low−slow; 1.24 (1.13 to 1.37). Median follow-up, yearly visits to primary care, deaths and eFI scores are reported in Table S4.

Table 1 describes the distribution of the GOLD cohort between these 5 groups. Most of the included patients belonged to the low−slow (71.1%) and low−moderate (14.7%) clusters with only 4.6% in the 2 rapidly progressive groups combined. The 2 rapid clusters had the highest mean age.

Table S5 in the Appendix shows the prevalence of individual deficits at the start and end of study for each cluster. Deficits such as polypharmacy, hypertension, ischemic heart disease, and osteoporosis were already common at baseline for all clusters and their prevalence was elevated by the end of observation. There were no obvious differences between the clusters in which the new deficits appeared during follow-up.

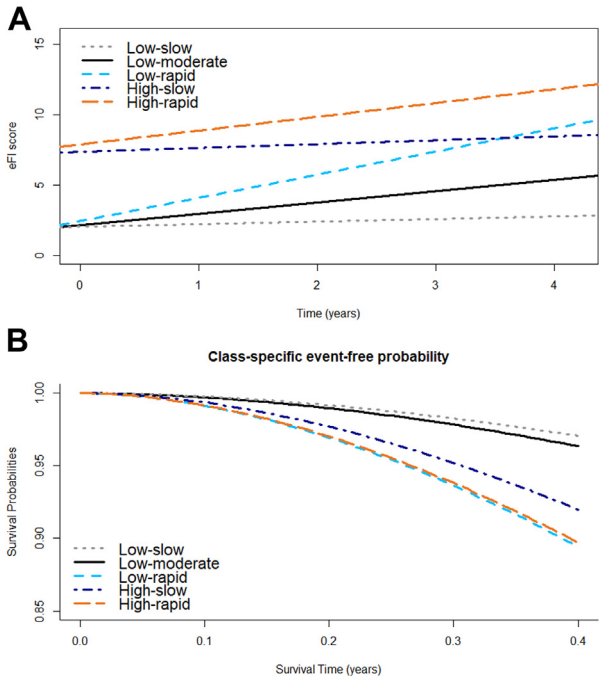

Figure 1. Results of the 5-cluster model (A) intercept and slope of each cluster (B) Survival curve of each cluster.

3.2. Model validation in CPRD AURUM

3.2.1. Study population

We included 390,204 patients from AURUM. Table 3 describes the baseline characteristics for this population. The distributions of age, gender, and socioeconomic status were almost identical between GOLD and AURUM. Unexpected was the difference in eFI score between these 2 otherwise nationally representative populations. At baseline, the AURUM cohort had on average a higher eFI score and their distribution of frailty category was shifted toward a more severe score. We considered whether there were specific deficits that were more prevalent in the AURUM cohort compared to GOLD in Appendix Table S6 and found that a few deficits had a higher prevalence in AURUM including arthritis, hypertension, and visual impairment.

3.2.2. Transition in frailty category and resultant clusters

Compared to the GOLD population, slightly higher proportion of 107,376 (27.5%) patients transitioned to worse eFI category in AURUM, with 2911 (0.7%) transitioning to a better frailty category. Most transitions 53,674 (13.8%) were from fit to mild, with 36,411 (9.3%) mild

Table 3. Baseline of each cluster for the validation dataset (CPRD AURUM)

Cluster	Overall population	Low−slow	Low−moderate	Low−rapid	High−slow	High−rapid
N	390,204 (100%)	225,598 (57.8%)	54,171 (13.9%)	9464 (2.4%)	81,314 (20.8%)	19,657 (5.0%)
Gender = Male (*n* (%))	173,854 (44.6%)	103,260 (45.8%)	23,893 (44.1%)	4262 (45.0%)	34,464 (42.4%)	7975 (40.6%)
Age (mean (SD))	75.0 (7.4)	73.8 (7.0)	76.0 (7.2)	79.0 (7.2)	76.6 (7.6)	78.5 (7.1)
Socioeconomic status (*n* (%))						
1 (least deprived)	71,057 (18.2%)	43,959 (19.5%)	9707 (17.9%)	1372 (14.5%)	13,260 (16.3%)	2759 (14.0%)
2	70,429 (18.1%)	42,844 (19.0%)	9665 (17.8%)	1488 (15.7%)	13,533 (16.6%)	2899 (14.7%)
3	76,085 (19.5%)	44,919 (19.9%)	10,618 (19.6%)	1676 (17.7%)	15,391 (18.9%)	3481 (17.7%)
4	85,591 (21.9%)	47,546 (21.1%)	11,980 (22.1%)	2367 (25.0%)	18,747 (23.1%)	4951 (25.2%)
5 (most deprived)	87,042 (22.3%)	46,330 (20.5%)	12,201 (22.5%)	2561 (27.1%)	20,383 (25.1%)	5567 (28.3%)
BMI (mean (SD))	27.3 (10.3)	26.9 (10.1)	27.2 (9.9)	27.2 (14.5)	28.2 (10.7)	28.4 (7.9)
eFI[a] (mean (SD))	4.8 (3.4)	3.1 (2.0)	3.8 (2.0)	4.5 (2.3)	9.0 (2.4)	10.3 (2.9)
eFI (median [IQR])	4 [2, 7]	3 [2, 5]	4 [2,5]	5 [3, 6]	9 [7, 10]	10 [8, 12]
Frailty category[a,b] (*n* (%))						
Fit	201,865 (51.7%)	163,732 (72.6%)	33,478 (61.8%)	4634 (49.0%)	14 (0.0%)	7 (0.0%)
Mild	132,767 (34.0%)	61,755 (27.4%)	20,528 (37.9%)	4457 (47.1%)	40,226 (49.5%)	5801 (29.5%)
Moderate	44,433 (11.4%)	111 (0.0%)	165 (0.3%)	369 (3.9%)	33,954 (41.8%)	9834 (50.0%)
Severe	11,139 (2.9%)	0	0	4 (0.0%)	7120 (8.8%)	4015 (20.4%)

BMI, body mass index, eFI, electronic frailty index.
Proportion of missing data was 4.7% for smoking, 15.9% for drinking, and 15.7% for BMI in AURUM.
[a] Baseline category: calculated on December 31, 2009.
[b] Frailty categories are fit (mean eFI/36: 0-0.12), mild (>0.12-0.24), moderate (>0.24-0.36), and severe (>0.36).

to moderate, and 12,496 (3.2%) moderate to severe transitions, while 4795 (1.2%) crossed more than 1 frailty category (Table 4).

In the AURUM population, the median follow-up was 4 years (IQR 3.9-4 years), and 62,500 (16.0%) died during the observation period.

The fit of the population to the clusters was good in AURUM: 84.1% of patients had a posterior probability ≥0.7. Table S7 in the Appendix describes the proportion of patients in each cluster with different posterior probability cut-offs.

Similar to GOLD, the fit−rapid and frail−rapid clusters had the steepest survival curves, followed by the frail−moderate cluster. With the low−slow cluster being the reference, low−rapid and high−rapid had the highest HR; 3.69 (95% CI: 3.57−3.81) and 3.31 (3.22-3.41), respectively. Followed by the high−slow cluster; 2.92 (2.87-2.98). Low−moderate cluster had the lowest HR after low−slow; 1.15 (1.12-1.18).

Low−slow had the highest proportion of patients (57.8%), followed by the high−slow cluster (20.8%), instead of the low−moderate cluster (13.9%) which was the second highest in CPRD GOLD. Table 3 describes the population belonging to each cluster. Table S8 in the Appendix describes the prevalence of individual deficits in each cluster at baseline and at the end of observation.

4. Discussion

We identified 5 clusters of frailty trajectories over 4 years in older patients. In addition to the statistical considerations discussed above, the emergent 5 cluster model was

Table 4. Transitions between frailty categories in AURUM

Baseline	Last observation				
Frailty category[a,b]	Fit	Mild	Moderate	Severe	Total
Fit	145,451 (37.3%)	53,674 (13.8%)	2660 (0.7%)	80 (<0.1%)	201,865 (51.7%)
Mild	2140 (0.6%)	92,161 (23.6%)	36,411 (9.3%)	2055 (0.5%)	132,767 (34.0%)
Moderate	0	615 (0.2%)	31,322 (8.0%)	12,496 (3.2%)	44,433 (11.4%)
Severe	0	0	156 (<0.1%)	10,983 (2.8%)	11,139 (2.9%)
Total	147,591 (37.8%)	146,450 (37.5%)	70,549 (18.1%)	25,614 (6.6%)	390,204 (100%)

[a] Baseline category: calculated on December 31, 2009.
[b] Frailty categories are fit (mean eFI/36: 0-0.12), mild (>0.12-0.24), moderate (>0.24-0.36), and severe (>0.36).

clinically plausible and the resultant clusters had distinct eFI patterns (baseline and trajectories).

Three groups started from a low eFI value and progressed at different slopes over time. Two started from an elevated eFI value and progressed slowly or at a rapid slope over time. The risk analysis showed that those who progressed at a faster rate and/or had high eFI starting value were at higher risk of death compared to the other clusters. These groups were generally older, in agreement with previous studies which showed that older age is linked to worse frailty levels [21−24]. Findings from Chamberlain et al and others—including those focusing on terminal frailty—were similar: steeper trajectories and older age groups had higher risk of mortality [12,14,25]. High-frailty baseline value was found to be associated with higher 1-, 3- and 5-year mortality risk in Clegg et al and other previous studies [4,7,26]. Evaluation metrics, that is, high posterior probability value and similar HR trends in AURUM, suggest good performance of the model.

Interestingly, inspection of the clusters did not reveal that the trajectories were based on the accrual of specific individual deficits. The implication was that monitoring an overall frailty score could be acceptable without a deeper dive into the contributing morbidities. Another option could have been to model transitioning between categories. However, our method allowed to detect the small changes/accumulations over the study period.

The advantage of using eFI, based on recorded deficits in the EHR is that it is directly derived from routinely collected data. Using routinely collected data makes conducting longitudinal studies like this one more feasible and generalizable; the same patients can be monitored over an extended period, and the study sample is representative of the wider population [16]. However, the accuracy of the deficits recording depends on whether or not there is missing information, the length of a patient's registration with their GP, individual systems, and coding/data-entry practices as we are making secondary use of the data collected for practice management and not for clinical research [15,27,28]. Nonetheless, external validation and early pilot studies on eFI found that it had good discrimination and clinical validity in identifying frailty [26,29]. This makes eFI an attractive pragmatic screening tool; it offers simplicity and practicality as a trade-off for granularity.

Traditional clustering methods require complete observations, leading to the use of relatively healthier groups [30]. The use of joint modelling and JLCM was a particular strength in this study, as they allowed us to account for those who were censored before the end of the study. Thus, we included all available patients and minimized the risk of bias.

There are some cautions in interpreting these results. Firstly, we only followed up the cohort for a relatively short time. Although this 4-year period was long enough to observe distinct trajectory clusters, longer follow-up might show different relationships with mortality. The challenge of a longer follow-up is the potential that other confounders become more relevant in influencing mortality risk. Secondly, we modeled frailty on calendar years, not chronological age. While accounting for age in the models allowed for characterizing the association of age with frailty levels and trajectories, age-specific frailty models can offer more clinical value.

Despite the good model performance in AURUM, compared to GOLD, the extracted sample of AURUM had higher baseline eFI values, although the 2 populations were derived from primary care practices contributing to the 2 databases. This has led to small differences in the proportion of AURUM population belonging to each cluster. These differences are likely to occur when running studies on different EHR systems where different code lists are used.

The main implication of this study is that monitoring frailty over time is a better approach to identifying older people at higher risk of death than relying on a cross-sectional measure. Our results have shown that both baseline value and trajectory of frailty progression over time were associated with higher mortality risk. An important group for health providers to monitor is the low-rapid group, where patients started from a seemingly healthy state and deteriorated quickly within 4 to 5 years. While frailty usually has worsening trends, a small proportion (15%-23%) of the older population's frailty state improves over time [31,32]. Exploring in detail age-specific frailty patterns over longer periods, how stable they are, and whether there are inflexion points to identify the rapidly deteriorating groups would aid in tailoring preventive treatment packages for the old, frail population.

5. Conclusion

This study provides a novel approach to model frailty over time. We confirmed that there are subgroups within the population who are currently frail or have rapid frailty progression and need more healthcare monitoring and resources. Future research looking into the generalizability of these subgroups, considering longer frailty monitoring periods and different patterns of morbidities is recommended.

Patient and public involvement

Age UK organized a patient and public involvement event in January 2020 to engage with a number of older people and ascertain their views on frailty and the current composition of the eFI model based on the list of deficits. The attendance comprised AS and AC, all members of Age UK's lay panel team, and eight members of the pubic

who were older people with pre-existing health problems. The aim of the event was to identify what aspects of health problems reported from GP records are considered relevant for older individuals in terms of their general health perceptions, with a focus on frailty.

Data sharing

Data were obtained from CPRD under the Oxford University CPRD license. Direct data sharing is not allowed. Data access can be obtained from CPRD, conditional on Independent Scientific Advisory Committee approval.

CRediT authorship contribution statement

Leena Elhussein: Writing − review & editing, Writing − original draft, Project administration, Methodology, Formal analysis. **Danielle E. Robinson:** Writing − review & editing, Formal analysis, Conceptualization. **Antonella Delmestri:** Writing − review & editing, Data curation, Conceptualization. **Andrew Clegg:** Writing − review & editing, Formal analysis, Conceptualization. **Daniel Prieto-Alhambra:** Writing − review & editing, Supervision, Formal analysis, Conceptualization. **Alan Silman:** Writing − review & editing, Writing − original draft, Funding acquisition, Formal analysis, Conceptualization. **Victoria Y. Strauss:** Writing − review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2024.111442.

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