# Development and validation of an electronic frailty index using routine primary care electronic health record data

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## Abstract

**Background:** frailty is an especially problematic expression of population ageing. International guidelines recommend routine identification of frailty to provide evidence-based treatment, but currently available tools require additional resource.

**Objectives:** to develop and validate an electronic frailty index (eFI) using routinely available primary care electronic health record data. **Study design and setting:** retrospective cohort study. Development and internal validation cohorts were established using a randomly split sample of the ResearchOne primary care database. External validation cohort established using THIN database. **Participants:** patients aged 65–95, registered with a ResearchOne or THIN practice on 14 October 2008.

**Predictors:** we constructed the eFI using the cumulative deficit frailty model as our theoretical framework. The eFI score is calculated by the presence or absence of individual deficits as a proportion of the total possible. Categories of fit, mild, moderate and severe frailty were defined using population quartiles.

Outcomes: outcomes were 1-, 3- and 5-year mortality, hospitalisation and nursing home admission.

**Statistical analysis:** hazard ratios (HRs) were estimated using bivariate and multivariate Cox regression analyses. Discrimination was assessed using receiver operating characteristic (ROC) curves. Calibration was assessed using pseudo- $R^2$  estimates.

**Results:** we include data from a total of 931,541 patients. The eFI incorporates 36 deficits constructed using 2,171 CTV3 codes. One-year adjusted HR for mortality was 1.92 (95% CI 1.81–2.04) for mild frailty, 3.10 (95% CI 2.91–3.31) for moderate frailty and 4.52 (95% CI 4.16–4.91) for severe frailty. Corresponding estimates for hospitalisation were 1.93 (95% CI 1.86–2.01), 3.04 (95% CI 2.90–3.19) and 4.73 (95% CI 4.43–5.06) and for nursing home admission were 1.89 (95% CI 1.63–2.15), 3.19 (95% CI 2.73–3.73) and 4.76 (95% CI 3.92–5.77), with good to moderate discrimination but low calibration estimates.

**Conclusions:** the eFI uses routine data to identify older people with mild, moderate and severe frailty, with robust predictive validity for outcomes of mortality, hospitalisation and nursing home admission. Routine implementation of the eFI could enable delivery of evidence-based interventions to improve outcomes for this vulnerable group.

Keywords: frailty, primary care, electronic frailty index, electronic health record, cumulative deficit, older people

### Background

Frailty is an especially problematic expression of population ageing. It is a condition characterised by loss of biological reserves across multiple organ systems and vulnerability to physiological decompensation after a stressor event [1]. Older people with frailty are at increased risk of adverse outcomes including disability, hospitalisation, nursing home admission and mortality [2, 3].

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There is evidence that frailty may be modifiable and it is considered to have greater reversibility than disability [1, 4]. The UK and international consensus guidance has recommended identification of frailty as part of routine clinical encounters, or wider population screening, to facilitate the planning and delivery of services for older people [5, 6]. However, there are several current obstacles to these recommendations, including additional clinical resource required and inaccuracy of simple tools [7].

The cumulative deficit model identifies frailty on the basis of a range of variables that include symptoms, signs, diseases, disabilities and abnormal laboratory values, collectively referred to as deficits [8]. The original model was based on 92 variables, but subsequent work has shown that this can be reduced to a more manageable 30 or so without loss of predictive validity [9]. The variables can be used to calculate a frailty index (FI) score, which is a simple calculation of the presence or absence of each variable as a proportion of the total. The core criteria for variable inclusion into the FI are: (i) biologically plausible; (ii) accumulates with age; and (iii) does not saturate too early (i.e. the prevalence of the deficit does not reach 100% before older age) [10]. This makes the FI very adaptable as a conceptual approach.

Primary care EHR systems in the UK use Read codes to categorise and log multiple patient characteristics, including symptoms, signs, laboratory test results, diseases, disabilities and information about social circumstances [11]. Similar coding schemes (IPCP and ICD-10) are used in primary care EHR systems in other countries [12]. EHR systems therefore provide a potentially simple yet powerful mechanism for identifying cumulative deficits to recognise and grade the severity of frailty as part of routine care.

#### **Objectives**

The objective of this study was to develop and validate an electronic frailty index (eFI) that is automatically populated from routinely collected data contained within the primary care EHR.

#### **Methods**

#### Study design

We conducted a retrospective cohort study using anonymised primary care electronic health record data contained in the ResearchOne [13] and The Health Improvement Network (THIN) [14] databases from 14 October 2008 to 14 October 2013.

ResearchOne is a health and care research database consisting of de-identified clinical and administrative data drawn from the electronic health records of around six million patients currently held on the TPP SystmOne clinical system [15]. The THIN database contains longitudinal anonymised EHRs from over 500 UK primary care practices using the Vision clinical computer system [16] and has linked secondary care data for approximately 160 of these practices. We used the ResearchOne database to establish development and internal validation cohorts using a randomly split sample approach. We then used the THIN database to establish an independent external validation cohort.

#### **Participants**

Patients aged 65–95 years and registered at a ResearchOne or THIN practice on 14 October 2008 were eligible. Patients not permanently registered at the practice were excluded.

#### **Development cohort**

We used the cumulative deficit model of frailty as our theoretical framework. We followed published guidance on creating an FI using the cumulative deficit model in a randomly split sample of the ResearchOne database [10]. As previous frailty indexes have been validated using non-weighted methods [8], our approach to development of the eFI was based on improper linear modelling techniques, whereby the weights of the predictor variables were assumed to be equal [17].

We ran a series of searches to identify Clinical Terms Version 3 (CTV3) Read codes for inclusion. The first search used terms based on the Canadian Study of Health and Aging (CSHA) FI [18] to identify potential text and numeric codes. We then ran a second search by calculating regression coefficients for code prevalence against increasing age between 65 and 95 years to identify individual codes that increase in prevalence with age.

Two independent researchers then hand searched all potential codes to identify those with face validity for inclusion. Codes were then categorised by an organ system to ensure a range of deficits were considered, consistent with the cumulative decline in multiple physiological systems that characterises frailty [1]. Codes identifying physical disability and social vulnerability were categorised separately. Any disagreements were settled by consensus. Cut-points for numeric data were defined by reported laboratory reference ranges and international standard diagnostic criteria. An expert frailty panel then constructed the eFI by grouping codes into deficits to ensure that the first criterion for inclusion (biologically plausible) was met [10].

Prevalence of putative deficits was plotted against age and linear regression coefficients and  $r^2$  values were calculated. To ensure that the second criterion for inclusion (increased prevalence with age) was met, only deficits with a population prevalence >0.5%, a positive regression coefficient and an  $r^2$  value of >0.30 were included. To satisfy the third criterion for inclusion (does not saturate too early), deficits that reached 100% prevalence by age 65 were excluded.

Categories of fit, mild frailty, moderate frailty and severe frailty were defined by eFI quartiles using the 99th centile as the upper limit.

#### Internal validation cohort

Validation of the eFI was by investigation of predictive validity as a method of criterion validation and the measure of primary clinical interest in frailty. The main outcomes of interest were: (i) all-cause mortality; (ii) unplanned hospitalisation; and (iii) nursing home admission. All-cause mortality was identified by date of death, which is reliably recorded in the electronic health record; practices were included after the date of acceptable mortality recording [19]. Unplanned hospitalisation was identified using coded evidence of a hospital admission/discharge (using Read codes or outcome field in medical file). Nursing home admission was identified using Read coded evidence of nursing home admission, or by change of residence to nursing home address, using the Care Quality Commission list of registered UK nursing homes.

Hazard ratios (HRs) at 1, 3 and 5 years were estimated for outcomes of mortality, hospitalisation and nursing home admission using bivariate and multivariate Cox regression analyses, with the eFI as the independent variable and age and gender as covariates.

We assessed for discrimination using receiver operating characteristic (ROC) curves to estimate areas under the curve (AUC) and associated c statistics for the eFI for mortality, unplanned hospitalisation and nursing home admission at 1, 3 and 5 years. To assess how much variability in these outcomes (mortality, hospitalisation, nursing home admission) was explained by the eFI, we tested calibration using pseudo- $R^2$  estimates. Higher values indicate more variation is explained. We used R (version 3.0.2) [20] for all analyses.

#### **External validation cohort**

The individual eFI deficits (predictors) of interest were mapped from CTV3 (used in SystmOne/ResearchOne practices) to Read version 2 (used in Vision/THIN practices) using a standard mapping table, available from the Technology Reference data Update Distribution website [21], and validated by researchers and clinicians with expertise in clinical coding.

HRs at 1, 3 and 5 years were estimated for the outcome of mortality using bivariate and multivariate Cox regression analyses, with the eFI as the independent variable and age and gender as covariates. In THIN, hospitalisation was identified by linked hospital data using the Hospital Episode Statistics (HES) database, which records UK information on hospital admissions, outpatient appointments and Accident & Emergency Department attendances. One- and 3-year HRs were estimated for the outcome of hospitalisation using HES linked data, measured between 14 October 2008 and 30 March 2012. It was not possible to estimate 5-year HRs, because there is a delay to routine data linkage between HES and THIN. Admission rates per 1,000 person-years and bed-days per admission for those identified as fit, mild frailty, moderate frailty and severe frailty were also estimated. It was not possible to identify nursing home admission in THIN.

We assessed for discrimination using ROC curves and associated c statistics for the eFI for mortality at 1, 3 and 5 years, and hospitalisation at 1 and 3 years. We tested eFI calibration using pseudo- $R^2$  estimates for these timepoints. We

used Stata (version 12) for analysis of the external validation cohort [22].

#### Results

Anonymised data from a total of 931,541 patients aged 65– 95 were included (207,814 in the development cohort, 207,720 in the internal validation cohort, 516,007 in the external validation cohort). A total of 213,064 patients in the external validation cohort had HES linkage for the estimation of hospitalisation, admission rates and bed-day usage.

Baseline characteristics for the development, internal validation and external validation cohorts are presented (Table 1). The mean eFI score was 0.14 (SD 0.09) for the development and internal validation cohorts and 0.15 (SD 0.10) for the external validation cohort. The mean eFI score was slightly higher for females in all three cohorts (see Table 1) and increased with age for both females and males.

There was a right-skewed population distribution to the eFI in all three cohorts, consistent with the usual FI distribution reported in epidemiological studies (Supplementary data, Figure S1, available in *Age and Ageing* online). There was a negative correlation between the eFI and social deprivation,

Table I. Baseline characteristics

Characteristic	Development cohort ( <i>n</i> = 207,814)	Internal validation cohort ( <i>n</i> = 207,720)	External validation cohort $(n = 516,007)$
•••••			
Age (years)	75.0 (7.2)	75.0 (7.3)	75.0 (7.3)
Gender			
Male	45%	45%	44%
Female	55%	55%	56%
FI score: mean (SD)	0.14 (0.09)	0.14 (0.09)	0.15 (0.10)
Males: mean (SD)	0.13 (0.09)	0.13 (0.09)	0.14 (0.10)
Females: mean (SD)	0.15 (0.10)	0.15 (0.10)	0.16 (0.10)
FI score 99th centile	0.49	0.49	0.42
Frailty category <sup>a</sup>			
Fit	50%	50%	43%
Mild	35%	35%	37%
Moderate	12%	12%	16%
Severe	3%	3%	4%
Number of comorbidities	2.1 (1.2)	2.2 (1.1)	2.3 (1.3)
Number of medications	8 (8.0)	8 (8.1)	9 (6.8)
Townsend quintile (so	ocial deprivation) <sup>b</sup>		
1 (least deprived)	28%	28%	27%
2	18%	18%	24%
3	23%	23%	20%
4	16%	16%	16%
5	15%	15%	11%

All values are mean (SD) unless otherwise stated. Comorbidities defined using Health Survey for England definition (cardiovascular disease; diabetes; cancer; chronic lung disease; asthma; arthritis; osteoporosis; Parkinson's disease; any emotional, nervous or psychiatric disease).

FI, frailty index.

<sup>a</sup>FI scores of 0-0.12 = fit; >0.12-0.24 = mild frailty; >0.24-0.36 = moderate frailty; >0.36 = severe frailty.

<sup>b</sup>2% missing data on social deprivation in external validation cohort.

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measured using the index of nultiple deprivation (IMD) (Supplementary data, Figure S2, available in *Age and Ageing* online).

#### **Development cohort**

Thirty-six deficits, constructed using 2,171 CTV3 codes, met our inclusion criteria (Box 1). Polypharmacy was defined on the basis of the presence of  $\geq$ 5 prescribed medications, using chapters 1–15 of the British National Formulary.

The prevalence of individual deficits is presented in Supplementary data, Table S2, available in *Age and Ageing* online. The mean eFI score was 0.14 (SD 0.09). The 99th centile eFI score was 0.49. Therefore, patients with an eFI score of 0–0.12 were defined as fit; >0.12–0.24 as having mild frailty; >0.24–0.36 as moderate frailty and >0.36 as severe frailty. Estimates of prevalence for these categories were 50, 35, 12 and 3%, respectively.

#### Internal validation cohort

Prevalence estimates for older people defined as fit, mild frailty, moderate frailty, and severe frailty were consistent with the development cohort at 50, 35, 12 and 3%.

Risk of mortality, unplanned hospitalisation and nursing home admission increased for those with mild, moderate and severe frailty at 1, 3 and 5 years, compared with fit older people (Table 2). Mortality data are also presented in a Kaplan–Meier survival curve (Figure 1). At any age, those with increasing frailty had lower mean life expectancy (Figure 2).

Absolute numbers and percentages of the population experiencing outcomes of mortality, unplanned hospitalisation and nursing home admission for older people characterised as fit, mild, moderate and severe frailty are presented in Supplementary data, Table S2, available in *Age and Ageing* online.

The eFI demonstrated good discrimination for the outcomes of mortality and nursing home admission, and moderate discrimination for the outcome of hospitalisation (Table 3). *c* Statistic estimates for these outcomes at 12 months were 0.72, 0.74 and 0.66, respectively. Pseudo- $R^2$  estimates of calibration were low for all outcomes (Table 3).

#### **External validation cohort**

The CTV3 codes were mapped to 36 deficits containing 1,574 corresponding Read 2 codes (Box 1). The prevalence

 Table 2. Unadjusted and adjusted 1, 3 and 5 year hazard ratios for outcomes of mortality, unplanned hospitalisation and nursing home admission for older people with mild, moderate and severe frailty

Outcome	Internal validation c	cohort		External validation cohort			
	Mild frailty	Moderate frailty	Severe frailty	Mild frailty	Moderate frailty	Severe frailty	
	•••••		• • • • • • • • • • • • • • •		• • • • • • • • • • • • •		
1 Year mortality H	IR (95% CI)						
Unadjusted	2.71 (2.56–2.88)	5.87 (5.51–6.24)	10.28 (9.50–11.12)	2.55 (2.44–2.66)	5.30 (5.07–5.54)	9.36 (8.88–9.87)	
Adjusted	1.92 (1.81–2.04)	3.10 (2.91–3.31)	4.52 (4.16–4.91)	1.86 (1.78–1.95)	3.02 (2.88–3.16)	4.50 (4.26–4.76)	
3 Year mortality H	IR (95% CI)						
Unadjusted	2.49 (2.41–2.57)	5.20 (5.02-5.39)	9.01 (8.60–9.45)	2.34 (2.29–2.40)	4.69 (4.58–4.82)	8.35 (8.09-8.61)	
Adjusted	1.77 (1.71–1.83)	2.78 (2.68-2.89)	3.99 (3.79-4.20)	1.73 (1.68–1.77)	2.70 (2.63-2.77)	4.06 (3.93-4.19)	
5 Year mortality H	IR (95% CI)						
Unadjusted	2.40 (2.34-2.46)	4.88 (4.75-5.02)	8.57 (8.25-8.91)	2.23 (2.19-2.27)	4.36 (4.28-4.45)	7.75 (7.55–7.94)	
Adjusted	1.72 (1.68-1.77)	2.64 (2.57-2.72)	3.83 (3.68-3.99)	1.66 (1.63-1.69)	2.54 (2.49-2.60)	3.84 (3.74-3.94)	
1 Year unplanned	hospitalisation HR (95%	o CI)					
Unadjusted	2.08 (2.00-2.16)	3.50 (3.35-3.66)	5.73 (5.38-6.10)	2.35 (2.28-2.43)	4.65 (4.49-4.81)	8.10 (7.77-8.45)	
Adjusted	1.93 (1.86-2.01)	3.04 (2.90-3.19)	4.73 (4.43-5.06)	2.03 (1.96-2.10)	3.50 (3.38-3.63)	5.58 (5.34-5.84)	
3 Year unplanned	hospitalisation HR (95%	6 CI)		· · · ·			
Unadjusted	1.94 (1.90-1.98)	3.10 (3.01-3.18)	4.69 (4.50-4.90)	2.20 (2.16-2.25)	4.07 (3.98-4.16)	6.89 (6.69-7.10)	
Adjusted	1.78 (1.74-1.82)	2.63 (2.55-2.71)	3.76 (3.60-3.94)	1.89 (1.85-1.93)	3.03 (2.96-3.11)	4.66 (4.51-4.80)	
5 Year unplanned	hospitalisation HR (95%	6 CI)		· · · ·	· · · ·		
Unadjusted	1.87 (1.84–1.90)	2.98 (2.91-3.04)	4.36 (4.20-4.53)				
Adjusted	1.71 (1.68–1.74)	2.50 (2.44-2.56)	3.43 (3.31-3.58)				
1 Year nursing ho	me admission HR (95%	CI)	· · · · ·				
Unadjusted	3.11 (2.69-3.59)	7.85 (6.76-9.12)	15.43 (12.84-18.56)				
Adjusted	1.89 (1.63-2.15)	3.19 (2.73-3.73)	4.76 (3.92–5.77)				
3 Year nursing hor	me admission HR (95%	CI)					
Unadjusted	2.75 (2.56-2.95)	6.39 (5.92-6.90)	11.62 (10.48-12.89)				
Adjusted	1.67 (1.56-1.80)	2.60 (2.40-2.82)	3.55 (3.19-3.96)				
5 Year nursing hor	me admission HR (95%	CI)	. ,				
Unadjusted	2.54 (2.42-2.67)	5.44 (5.16-5.75)	9.79 (9.06-10.58)				
Adjusted	1.59 (1.51–1.67)	2.30 (2.18–2.44)	3.12 (2.88–3.38)				

For all outcomes the comparator is fit older people. All data adjusted for age and sex.

HR, hazard ratio; CI, confidence interval.

NB: Hospitalisation outcome for external validation cohort includes only those practices (n = 158) with HES linked data.

of individual deficits is presented in Supplementary data, Table S2, available in *Age and Ageing* online. The mean eFI score was 0.15 (SD 0.10). The 99th centile eFI score was



**Figure 1.** Five-year Kaplan–Meier survival curve for the outcome of mortality for categories of fit, mild frailty, moderate frailty and severe frailty (internal validation cohort).



**Figure 2.** Relationship between age, electronic frailty index score and mortality (internal validation cohort).

0.42. Prevalence estimates for fit, mild, moderate and severe using the cut-points determined in the development cohort were 43, 37, 16 and 4%, respectively.

Risk of mortality and hospitalisation increased for those with mild, moderate and severe frailty (Table 2). Emergency admission rates per 1,000 person-years at risk increased from 90.1 (95% CI 90.0–91.1) for those identified as fit; 211.3 (95% CI 209.5–213.1) for those with mild frailty; 407.3 (95% CI 403.3–411.4) for those with moderate frailty; and 706.7 (95% CI 696.1–717.3) for those with severe frailty. The mean number of bed-days per emergency admission increased from 9.0 (SD 19.1) for those identified as fit; 9.6 (SD 17.4) for those with mild frailty; 10.3 (SD 16.5) for those with moderate frailty; and 71.1 (SD 18.5) for those with severe frailty (Supplementary data, Table S3, available in *Age and Ageing* online).

c Statistic estimates for 12-month mortality and hospitalisation were 0.76 and 0.71, respectively (Table 3). Pseudo- $R^2$ estimates of calibration were low for all outcomes (Table 3).

#### Discussion

We have developed, internally validated and externally validated the eFI using routinely collected EHR data from over 900,000 older people in the UK using GP records contained in two large, independent, representative primary care databases. We have applied a well-established theoretical framework of frailty and followed international guidelines to develop and validate our model.

The primary aim of the eFI is to identify categories of frailty, so the assessment of utility should be based primarily on the predictive validity of frailty categories for adverse outcomes. We constructed categories of fit, mild, moderate and severe frailty, and these categories identify older people at increased risk of mortality, hospitalisation and nursing home admission at 1, 3 and 5 years. Estimates of predictive validity obtained from the internal validation cohort were broadly similar to those obtained following external validation in an independent dataset.

Implementation of the eFI into routine primary care practice could represent a major advance in the care of older people with frailty, through provision of more appropriate, goal-orientated care, referral for evidence-based interventions and signposting to local authority and voluntary services. Following implementation into the SystmOne EHR, we have established a frailty collaborative to develop and evaluate new models of primary care for older people with

Table 3.  $\iota$  Statistic and pseudo- $R^2$  estimates for the outcomes of mortality, unplanned hospitalisation, and nursing home admission

Outcome	Internal validation cohort					External validation cohort						
	1 Year		3 Year		5 Year		1 Year		3 Year		5 Year	
	С	$R^2$	С	$R^2$	С	$R^2$	С	$R^2$	С	$R^2$	С	$R^2$
Mortality	0.72	0.04	0.70	0.06	0.69	0.09	0.76	0.02	0.75	0.02	0.75	0.02
Emergency hospitalisation	0.66	0.03	0.64	0.05	0.63	0.06	0.71	0.02	0.69	0.02		
Nursing home admission	0.74	0.04	0.72	0.04	0.70	0.04						

Box	I. List o	of 36 def	f <mark>icits co</mark> n	tained in th	e
eFI.					

Activity limitation	Memory and cognitive problems
Appendia and baematinic deficiency	Mobility and transfer problems
A sub-sitis	Orteonomic and transfer problems
Arthritis	Osteoporosis
Atrial fibrillation	Parkinsonism and tremor
Cerebrovascular disease	Peptic ulcer
Chronic kidney disease	Peripheral vascular disease
Diabetes	Polypharmacy
Dizziness	Requirement for care
Dyspnoea	Respiratory disease
Falls	Skin ulcer
Foot problems	Sleep disturbance
Fragility fracture	Social vulnerability
Hearing impairment	Thyroid disease
Heart failure	Urinary incontinence
Heart valve disease	Urinary system disease
Housebound	Visual impairment
Hypertension	Weight loss and anorexia
Hypotension/syncope	
Ischaemic heart disease	

frailty as part of the Yorkshire and Humber Academic Health Science Network Improvement Academy [23].

Routine identification of frailty in primary care using the eFI could also result in improvements in secondary care and specialist services, for example cancer services [24]. Further investigation of the utility of the eFI in these different settings will help guide improvements in care.

#### Strengths of the study

We followed published standard rules for the development and validation of a cumulative deficit FI based on primary care EHR data. Two independent researchers hand searched all potential Read codes for inclusion to reduce the risk of missing potentially relevant codes. The study made use of routine coded clinical data, which means that the index can be readily incorporated into clinical computer systems, automatically populated, and made available for use in clinical practice with no additional clinical resource required.

The eFI has robust predictive validity and good discrimination for nursing home admission, hospitalisation and mortality. These outcomes are of particular importance for older people and health and social care systems internationally, and the predictive validity and discrimination characteristics of the eFI across all three outcomes adds considerable weight to the clinical utility of the tool in terms of individual and population health planning.

A key strength of the research is that the eFI codes were translated from CTV3 to Read 2 for the external validation. These codes can be mapped to primary care coding schemes that are used in other countries, which means that the eFI has potential for future international implementation. The successful mapping process, closely aligned baseline characteristics and similar estimates for adverse outcomes obtained in the ResearchOne and THIN cohorts, provides confidence that the eFI may have potential for international implementation following further validation.

#### Limitations of the study

There are a number of important limitations. There was evidence of good discrimination for the outcomes of mortality, nursing home admission and hospitalisation using linked HES data, but calibration scores were low, indicating that the eFI did not explain variability in these outcomes. However, the primary aim was to apply an internationally established model to develop a FI using routine primary care data and to establish frailty categories with predictive validity for adverse outcomes. Our a priori methodological approach that assigned equal weighting to each variable is consistent with the recognition that, in frailty, the absolute predicted risk is of primary clinical interest [25]. A methodological approach inconsistent with the cumulative deficit model of frailty would have been required if the primary aim had been to develop a model that prioritised discrimination and calibration. Even in light of these considerations, estimates for discrimination for outcomes of mortality and nursing home admission were similar to estimates reported from large epidemiological studies using research standard cumulative deficit models [18].

THIN has routine HES linkage available for a proportion of practices, which is considered the most reliable method of identifying unplanned hospitalisation. ResearchOne does not have routine HES linkage, so we used coded evidence of unplanned hospitalisation, which has been used in previous studies [26]. The differences in estimates for hospitalisation for those with mild, moderate and severe frailty in the ResearchOne and THIN cohorts may be a result of the methods used for identifying hospitalisation in the two cohorts.

We defined cut-points for estimation of frailty categories using population quartiles. Establishing construct validity of the eFI by comparison to a research standard FI would enable calibration of frailty categories but would require data linkage to large epidemiological studies and was beyond the scope of this study.

#### Conclusion

We have developed and externally validated an eFI using data from over 900,000 UK primary care patients. The eFI can be automatically populated with routinely collected primary care EHR data. Although the eFI has been developed and validated using UK data, it has potential for mapping to international standard coding systems. The eFI enables identification of older people who are fit, and those with mild, moderate and severe frailty. Using the eFI, increasing severity of frailty identifies older people who are at increased risk of future nursing home admission, hospitalisation, longer length of hospital stay, and mortality.

These outcomes are of key importance for older people, their families and health and social care systems internationally. Implementation of the eFI in routine primary care could

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enable better targeting of evidence-based interventions, improve planning of health services utilisation and facilitate the development of more appropriate, proactive, goal-orientated care for older people with frailty.

## **Key points**

- International guidelines recommend routine identification of frailty.
- Currently available tools require additional resource and may be inaccurate.
- We have developed and externally validated an eFI using routine primary care data.
- The eFI has robust predictive validity for outcomes of nursing home admission, hospitalisation and mortality.
- Routine implementation of the eFI could enable delivery of evidence-based interventions to modify frailty trajectories.

## Supplementary data

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

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## **Conflicts of interest**

C.B. and J.P. are employees of TPP, who own and license SystmOne primary care electronic health record software, which has implemented the eFI. A.C. and E.A.T. have received travel and accommodation expenses from TPP to speak at meetings regarding this work. All other authors declare no conflicts of interest.

## Intellectual property

Copyright and database rights for the eFI are held by the University of Leeds. The eFI is licensed under terms stating that it is freely available to providers of electronic health record systems on the basis that the licensor will not charge any additional premium to its end users that is attributable to the inclusion of the eFI.

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## **Ethics committee approval**

This study was approved by the ResearchOne project committee under the terms of the favourable approval by the National Research Ethics Service Research Ethics Committee North East (REC reference number 11/NE/0184) and by the THIN scientific review committee.

## References

- 1. Clegg A, Young J, Iliffe S, Olde-Rikkert M, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752–62.
- **2.** Fried LP, Tangen CM, Walston J *et al.* Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–56.
- **3.** Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc 2006; 54: 975–9.
- 4. Rodriguez-Manas L, Fried LP. Frailty in the clinical scenario. Lancet 2014; 385: e7–9.
- **5.** Turner G, Clegg A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age Ageing 2014; 43: 744–7.
- 6. Morley JE, Vellas B, van Kan GA *et al.* Frailty consensus: a call to action. J Am Med Dir Assoc 2013; 14: 392–7.
- Clegg A, Rogers L, Young J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. Age Ageing 2015; 44: 148–52.
- Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001; 1: 323–36.
- **9.** Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc 2010; 58: 681–7.
- **10.** Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008; 8: 24.
- **11.** Health and Social Care Information Centre. http://systems. hscic.gov.uk/data/uktc/readcodes (23 November 2014, date last accessed).
- **12.** de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. Fam Pract 2006; 23: 253–63.
- **13.** ResearchOne Health and Care Database. Available from http://www.researchone.org (1 June 2014, date last accessed).
- 14. The Health Information Network Database. Available from http://www.thin-uk.com (1 June 2014, date last accessed).
- **15.** SystmOne Electronic Health Record System. Available from http://www.tpp-uk.com/products/systmone (1 June 2014, date last accessed).

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- INPS Vision IT Solution. Available from http://www.inps.co. uk/vision (1 June 2014, date last accessed).
- Dawes R. The robust beauty of improper linear modelling in decision making. Am Psychol 1979; 34: 571–82.
- Rockwood K, Song X, MacKnight C et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173: 489–95.
- Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiol Drug Saf 2009; 18: 76–83.
- 20. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2013. ISBN 3-900051-07-0. http:// www.R-project.org/ (1 June 2014, date last accessed).
- Health and Social Care Information Centre Technology Reference data Update Distribution site. Available from https:// isd.hscic.gov.uk/trud3/user/guest/group/0/home.

- 22. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP, 2011.
- **23.** Yorkshire and Humber Academic Health Science Network Improvement Academy. Available from http://www. improvementacademy.org/improving-quality/healthy-ageing. html (1st December 2016, date last accessed).
- **24.** Handforth C, Clegg A, Young C *et al.* The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015; 26: 1091–101.
- **25.** Rockwood K, Theou O, Mitnitski A. What are frailty instruments for? Age Ageing 2015; 44: 545–7.
- **26.** Hippisley-Cox J, Coupland C. Predicting risk of emergency admission to hospital using primary care data: derivation and validation of QAdmissions score. BMJ Open 2013; 3: e003482.

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# Association of CRP gene polymorphisms with CRP levels, frailty and co-morbidity in an elderly Chinese population: results from RuLAS

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## Abstract

**Objectives:** to examine the associations of two common CRP gene polymorphisms with CRP levels, frailty and co-morbidity in an elderly Chinese population.

Design: a population-based cohort study.

Setting and participants: we obtained data on 1,723 elderly participants aged 70-84 from the ageing arm of the Rugao Longevity and Ageing study (RuLAS), a population-based observational cohort study conducted in Rugao, Jiangsu province, China.

**Measurements:** the genotyping of two common CRP gene polymorphisms (rs1205 and rs3093059) was performed. Items concerning the frailty index and co-morbidity were collected.

**Results:** the mean age of the study population was  $75.3 \pm 3.9$  years, and 53.5% (n = 922) were women. The minor allele frequencies of rs1205 and rs3093059 were 42.4% (C allele) and 16.9% (C allele), respectively. The polymorphisms rs1205 and rs3093059 were

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