Association of longitudinal repeated measurements of frailty index with mortality: Cohort study among community-dwelling older adults

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Summary

Background Frailty indices (FIs), defined by accumulation of health deficits, have been shown to be strongly related to mortality in older adults. However, previous studies mostly relied on FI measurement at a single point of time. We aimed to investigate the association of frailty with mortality according to longitudinal repeated measurements of FI in a large population-based cohort study in Germany.

Methods Among 9912 men and women aged 50–75 years living in Saarland, Germany and recruited in the ESTHER study in 2000–2002, a FI based on 30 deficits was determined at baseline, 2-, 5-, 8-, and 11-year follow-up. Hazard ratios (HRs) were calculated to assess the associations of FI with all-cause mortality and cause-specific mortality during 14 years of follow-up using Cox proportional hazards models that included FI as a time-varying covariate.

Findings During the 14-year follow-up, a total of 2483 deaths were observed, of which 859 and 863 were due to cancer and cardiovascular diseases (CVD), respectively. The time-varying FI showed consistently strong associations with mortality throughout 14 years of follow-up, with HRs (95% confidence intervals) for frail (FI≥ 0·35) versus non-frail (FI≤ 0·11) participants of 4·72 (4.05–5.51), 2·55 (1·95–3·34) and 7·52 (5·69–9·94) for all-cause, cancer, and CVD mortality, respectively. Gradually decreasing associations with increasing length of follow-up would have been obtained by using baseline FI only.

Interpretation Longitudinal repeated measures of FI show strong, consistent associations with mortality, especially CVD mortality, throughout extended periods of follow-up among community-dwelling older adults.

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Introduction

Frailty is a complex age-related clinical condition characterized by a decreased physiological capacity across several organ systems.[1] Studies have shown that frail individuals are predisposed to various negative health

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Research in context

Evidence before this study

Frailty is an established risk factors for negative health outcomes, including mortality. Using the search terms "frailty" AND "mortality", we searched PubMed and Embase for epidemiological studies from inception to May 30, 2022 without language restriction. A large number of studies, systematic reviews and meta-analyses have investigated the associations of frailty with mortality risk and quite consistently reported a modestly increased risk in frail individuals. However, frailty was typically defined at a single point of time only.

Added value of this study

In this study, we measured frailty using a 30-items frailty index (FI) and regularly updated the FI during long-term follow up. We then assessed the associations of FI with all-cause mortality and cause-specific mortality during up to 14 years of follow-up by including these longitudinal repeated measurements of FI as a time-varying covariate.

The time-varying FI more showed consistently strong associations with all-cause, cancer and CVD mortality throughout 14 years of follow-up. Gradually decreasing associations with increasing length of follow-up were seen by using baseline FI only.

Implications of all the available evidence

Our results suggest that frailty may account for a much larger share of mortality than previously thought. The longitudinal repeated measurements of FI may be highly informative with respect to all-cause and cause-specific mortality risk.

outcomes, such as falls, fractures, hospitalization, disability, dementia, and mortality.[2,3] In the past decades, the rapid expansion of the ageing population has brought a concomitant rise in frail individuals and led to frailty being one of the most serious global public health challenges.[1]

A number of tools to measure frailty have been developed, including two widely accepted instruments, the performance and questionnaire based approach suggested by Fried et.al.,[4] the frailty phenotype, and the questionnaire based approach suggested by Rockwood et.al.,[5] the frailty index (FI). FI defines frailty by a deficit accumulation approach and represents the proportion of deficits present across a range of symptoms, signs, diagnoses or limitations in activities of daily living. FI has been reported to be strongly associated with mortality independent of chronological age in a dose-response manner.[6,7] The vast majority of epidemiological studies have assessed the associations according to exclusive baseline FI only.[7,8] However, frailty has been reported to be a dynamic and reversible process throughout the lifespan[9–11] and FI generally increases with age on the population level.[12] Longitudinal repeated measurements of FI therefore may capture a more complete and precise picture of the association of FI with mortality than FI that was determined at a single point of time only.

In this large cohort study of initially 50–75 years old adults from Germany, FI was regularly updated during long-term follow up to assess frailty trajectories and associations with mortality.

Methods

Study population and data collection

Our analysis is based on baseline and follow-up data from the ESTHER study, which is an ongoing prospective population-based cohort study conducted in Saarland, Germany. Details of the study design and participants of this ongoing cohort study have been reported previously.[13,14] Briefly, 9940 older adults (age 50–75 years) were recruited by their general practitioners (GPs) during routine health checkups between 2000 and 2002 and have been followed up every two to three years since then. At baseline and each follow-up, a standardized questionnaire was used to collect information on sociodemographic, medical, and lifestyle factors. Questionnaires were designed to ensure maximum possible consistency between questions across consecutive follow-ups. The follow-up questionnaires were sent by regular mail with reminders. Participants who did not return the full questionnaire were subsequently mailed a short version of the questionnaire. Comprehensive medical data, including history of major diseases and drug prescriptions, were collected from the GPs' records. Body mass index was calculated based on self-reported weight and height values, and categorized as proposed by the World Health Organization (underweight<18.5; normal range 18.5–<25.0; overweight 25.0–<30.0; obese≥30.00). It is worth noting that information on self-reported smoking at baseline was found to be highly consistent with the results assessed using serum cotinine measurements in a subgroup of 1500 study participants.[15]

Ethics statement

The study was approved by the ethics committees of the medical faculty of Heidelberg University and of the medical board of the state of Saarland. Written informed consent was obtained from each participant.

Frailty assessment

Frailty was assessed using a FI, which was proposed according to Rockwood Frailty score[5] and defined as the proportion of present deficits of all deficits included in the frailty assessment. Deficits selection and FI

construction were conducted following a standard procedure.[16] Potential variables for FI construction were selected from the baseline questionnaire and were included if they met the following criteria: have associations with a wide range of health problems and disabilities, are not nearly universal in middle-age, the prevalence generally increases with age, have 1 % or more prevalence, and have less than 5 % missing values. Ultimately, 30 variables comprising history of diseases (6 items), history of major disease events (4 items), daily medication (11 items), difficulties in activities of daily living (6 items), general health (1 item), and life-style related factors (2 items) were identified for the construction of the FI. The lists of deficits used to define FI and prevalences of these deficits at baseline and each follow-up are shown in Table 1. Each variable was recorded as 1 or 0 to indicate presence or absence of the deficit. Additional intermediate values were employed for variables with more than two categories.

Among 9940 participants of the ESTHER study, 28 participants were excluded due to lack information on vital status. Ultimately, 9912 participants were included in this analysis. Updated values of the FI were determined based on information collected at the 2-, 5-, 8-, and 11- year follow-ups. As described previously,[17,18] modified Fried frailty was measured in a subgroup of 3112 study participants of the ESTHER cohort at 8-year follow-up, which defined frailty according to 5 criteria: weight loss, weak grip strength, slow gait speed, self-reported exhaustion and low physical activity.[4] Participants were considered as frail if they fulfilled three or more of the five criteria, pre-frail if they fulfilled one or two criteria. With reference to the modified Fried frailty criteria, we further categorized FI into three levels of frailty: non-frail ($0 \leq FI \leq 0{\cdot}110$), pre-frail ($0{\cdot}110 < FI < 0{\cdot}350$), and frail ($FI \geq 0{\cdot}350$)[18]

Mortality ascertainment

The vital status of each participant was collected through record linkage with population registries at each follow-up until December 31, 2015. The completeness of follow-up for all-cause mortality was 99·9%. Death certificates for 97·7% of deceased participants were obtained from local health authorities and were used to define mortality from specific causes, including cancers (ICD-10 codes C00–C97 and D37–D48) and cardiovascular diseases (CVDs, ICD-10 codes I00–I99).

Statistical analysis

For all variables with missing values (Supplementary Table 1), a multiple imputation procedure by the procedure PROC MI was utilized to impute the missing values. Details of the multiple imputation procedure have been described previously.[18] Briefly, the Markov Chain Monte Carlo method of the SAS procedure PROC MI was employed to impute 5 data sets in a step-wise approach of 4 multiple imputations beginning with baseline variables (age, sex, and all 30 variables), followed by the addition of variables of the 2-, 5-, and 8-year follow-up while keeping variables of previous follow-up rounds (variables at previous follow-ups, follow-up years, and mortality) in the imputation model. The further analyses were performed in the five imputed data sets and combined by the SAS procedure PROC MIANALYZE.

Socio-demographic characteristics of the study population are presented by standard methods and stratified by sex and age (50–64 and 65–75 years). With inclusion of all participants successfully followed-up at each follow-up, eleven-year frailty trajectories were plotted by sex and age according to means of baseline and up to 11-year follow-up FIs. Prevalence of frailty status (non-frail, pre-frail, and frail) at baseline and various follow-ups were comprehensively assessed and compared. Eleven years of longitudinal changes of frailty status between two adjacent follow-ups were presented by Sankey plot using the R programming package "ggalluvial".

Using Cox proportional hazard models, we first investigated the associations between baseline FI and mortality risk according to length of follow-up (2-year, 5-year, 8-year, 11-year, and 14-year), adjusting for age, sex, alcohol consumption (grams per day), and smoking status (never smoker, former smoker, and current smoker).

For assessing associations of longitudinal repeated measurements of FI with mortality risk, we included the baseline and follow-up FIs into the Cox proportional hazard models as time-varying variable,[19,20] using the same model-based adjustments as described above. The associations of baseline and time-varying FI with mortality risk over various lengths of follow-up were assessed separately. Hazard ratios (HRs) per 0·1 percent units increment of baseline and time-varying FI of all-cause and cause-specific mortality (cancer-specific and CVD-specific mortality) were calculated. The proportional hazards assumption was checked by scaled Schoenfeld residuals plots.[21]

In addition to regression models including FIs as continuous variables, we also run regression models including baseline and follow-up FIs as categorical variables (non-frail, pre-frail, and frail) with the participants who were non-frail serving as reference group. Furthermore, we conducted subgroup analyses for the association of frailty with mortality by sex and age (50–64 years / 65–75 years), and we tested for statistical significance of interactions by age and sex including pertinent product terms in the models using FI as continuous predictor.

Statistical analyses were carried out in SAS 9·4 (SAS Institute, Cary, NC). Statistical significance was defined by P-value < 0·05 in two-sided testing.

Variable name	Coding	Baseline (*N*=9912)	2-year follow-up (*N*=9341)	5-year follow-up (*N*=8181)	8-year follow-up (*N*=6807)	11-year follow-up (*N*=4863)
History of diseases (7 items)						
Coronary artery disease	Yes	15·1	16·5	18·5	25·4	27·1
Heart failure	Yes	11·3	12·6	13·2	16·8	17·8
Diabetes	Yes	14·4	6·7	20·1	25·0	27·9
Cancer	Yes	7·8	9·8	12·4	15·6	17·9
Glaucoma	Yes	4·1	5·4	6·7	8·5	9·8
Cataract	Yes	10·5	5·6	21·4	28·0	33·5
Parkinson	Yes	0·6	1·2	1·9	2·9	3·6
History of major disease events (4 items)						
Myocardial infarction	Yes	5·6	5·7	6·3	7·0	7·4
Stroke	Yes	3·5	4·4	5·6	7·9	9·0
Joint replacement	Yes	0·8	1·0	1·3	1·9	2·2
Femoral neck fracture	Yes	2·9	4·5	7·0	11·0	13·1
Drugs (10 items)						
Anti-hypertensives	Yes	43·9	52·2	59·8	67·8	75·8
Lipid lowering drugs	Yes	11·3	17·0	22·6	32·8	38·5
Vasodilatators	Yes	6·0	6·3	6·0	6·2	6·2
Heart glycosides	Yes	2·5	2·7	2·4	2·1	2·1
Prescribed aspirin	Yes	1·6	18·7	21·9	30·3	40·5
Anti-osteoporotic drugs	Yes	1·0	1·9	3·6	6·3	7·6
Anxiolytics	Yes	2·1	1·9	2·1	3·2	3·2
Sedatives	Yes	1·6	1·9	1·6	3·3	3·3
Anti-dementive drugs	Yes	1·0	1·8	1·8	3·1	3·5
Drugs against prostatic hyperplasia and incontinence	Yes	3·3	5·7	6·3	8·8	10·3
Difficulties in activities of daily living (6 items)						
Difficulties in moderate activities	Yes	8·5	8·4	10·1	10·7	11·5
	Limited	35·5	31·9	36·3	37·3	37·7
	No	55·7	59·6	52·4	49·1	47·5
Difficulties in climbing several flights of stairs	Yes	13·4	12·6	12·7	13·3	12·9
	Limited	40·9	37·4	38·7	38·7	37·6
	No	45·2	49·8	47·6	45·0	46·2
Limits in normal work or activities due to pain	Extremely limited	5·3	5·7	4·5	5·0	4·6
	Quite a lot	17·3	15·6	14·5	16·5	15·1
	Moderate	21·7	20·3	20·3	20·8	20·1
	A bit	28·5	27·5	26·6	28·9	28·0
	Not at all	26·8	30·9	33·2	25·7	28·9
Limits in certain work or activities	Yes	34·7	33·6	32·4	35·7	34·6
Limits in contact with others	Always	1·1	1·3	1·1	1·5	1·5
	Mostly	5·8	5·3	5·1	5·7	5·4
	Sometimes	21·0	18·9	17·4	19·5	17·7
	Rare	23·4	19·5	20·3	23·9	22·3
	Never	48·3	55·0	55·0	46·6	49·9
Limits in activities due to mental health	Yes	28·5	25·6	21·7	26·1	22·7
General health (1 items)						
General self-rated health	Poor	2·4	2·6	2·5	2·4	3·6
	Less good	29·3	26·7	25·7	24·0	26·0
	Good	60·1	61·7	61·6	61·4	60·1
	Very good	6·8	7·5	8·9	8·6	8·3
	Excellent	1·4	1·5	1·3	3·7	2·0
Life-style related factors (2 items)						
Underweight or overweight	35·0≤BMI	5·8	5·0	4·8	5·8	4·2
	30·0≤BMI<35·0	19·7	18·4	16·7	16·3	11·8
	25·0≤BMI<30·0 or BMI<18·5	47·5	50·5	55·9	61·7	71·6
Lack of vigorous physical activity	0 hour/week	29·9	31·6	40·1	40·2	45·3

***Table 1*: Deficits included in the frailty index calculation and proportions of status of each deficit (%) at each follow-up.**
Abbreviation: BMI, body mass index.

Role of funding source
No funder had any role in study design, data collection, data analyses, interpretation of the data, writing of the report, or decision to publish the study. All authors had full access to dataset used in this study and took the decision to submit for publication.

Results

Baseline characteristics of the participants stratified by sex and age are presented in Table 2. The mean (standard deviation, SD) age of the participants was 62·1 (6·6) years. A slight majority of participants were females (54·9%) or aged between 50 and 64 years (61·4%). Around three quarters of the participants were overweight or obese. Female participants had lower levels of school education, reported less alcohol consumption, and were less often overweight, engaging in medium or high physical activity, and current and former smokers than males. Sixty-five- to 75-year-old participants reported less physical activity and included lower proportions of current smokers than 50–64 years old participants.

Figure 1 and Supplementary Figure 1 show mean FI values and prevalences of frailty status by sex and age across various follow-ups. Both mean FI and prevalence of frailty increased with age. Mean FI of all participants increased from 0·145 (SD = 0·960) at baseline to 0·205 (SD = 0·120) at 11-year follow-up. The prevalence of frail participants in all subjects increased from 0·149 (baseline) to 0·344 (11-year follow-up). Compared with females, males had slightly higher FIs and proportions of frail subjects at each follow-up. Furthermore, the means of FIs and proportions of frail subjects were substantially higher in participants aged between 65–75 years than 50–64-year-old participants.

Supplementary Figure 2 presents the flows of frailty status alteration between two adjacent follow-ups. For each follow-up, nearly one quarter (from baseline to 2-year follow-up) to half (from 5-year to 8-year follow-up) of non-frail participants in each preceding follow-up progressed from non-frail to pre-frail. At each follow-up, about half of the frail participants were progressed from individuals who were pre-frail in each preceding follow-up. In contrast, few pre-frail subjects converted to non-frail and even fewer frail subjects converted to pre-frail.

During 14 years of follow-up, a total 2483 deaths were observed, of which approximately half occurred before the 11-year follow-up, and the other half between 11- and 14-year follow-up (Supplementary Table 2). Of the deceased, 859 died due to cancers and 863 due to CVD.

	Overall (*N*=9912)	Females (*N*=5446)	Males (*N*=4466)	Aged 50-64 years (*N*=6087)	Aged 65-75 years (*N*=3825)
Deceased (N/%)	3035 (30·6)	1323 (24·3)	1712 (38·3)	1196 (19·7)	1839 (48·1)
Age (means ± SD, years)	62·1±6·6	62·1±6·7	62·2±6·5	57·9±4·4	68·9±2·9
Male sex (%)	4466 (45·1)	NA	NA	2734 (44·9)	1732 (45·3)
Educational levels (N/%)[a]					
Low (≤9 years)	7215 (74·7)	4133 (77·9)	3082 (70·7)	4385 (73·2)	2830 (77·1)
Intermediate (10-11 years)	1369 (14·2)	819 (15·4)	550 (12·6)	898 (15·0)	471 (12·8)
High (≥12 years)	1076 (11·1)	351 (6·6)	725 (16·6)	706 (11·8)	370 (10·1)
Body mass index (N/%)[b]					
Underweight (<18·5 kg/m^2)	48 (0·5)	34 (0·6)	14 (0·3)	27 (0·4)	21 (0·6)
Normal weight (18·5-<25·0 kg/m^2)	2665 (26·9)	1697 (31·2)	968 (21·7)	1710 (28·1)	955 (25·0)
Overweight (25·0-<30·0 kg/m^2)	4667 (47·2)	2286 (42·1)	2381 (53·4)	2763 (45·5)	1904 (49·8)
Obesity (≥30·0 kg/m^2)	2517 (25·4)	1420 (26·1)	1097 (24·6)	1576 (25·9)	941 (24·6)
Physical activity (N/%)[c]					
Inactive (< 1 hour of physical activity/week)	2114 (21·4)	1421 (26·2)	693 (15·6)	1064 (17·5)	1050 (27·6)
Low (1-2 hours of physical activity/week)	4512 (45·7)	2545 (46·9)	1967 (44·2)	2739 (45·1)	1773 (46·6)
Medium or high (>= 2 hours of light and vigorous physical activity/week)	3256 (33·0)	1466 (27·0)	1790 (40·2)	2274 (37·4)	982 (25·8)
Smoking status (N/%)					
Never smoker	4958 (50·0)	3602 (66·1)	1356 (30·4)	2842 (46·7)	2116 (55·3)
Former smoker	3286 (33·2)	2545 (46·9)	1967 (44·2)	1992 (32·7)	1294 (33·8)
Current smoker	1668 (16·8)	1466 (27·0)	1790 (40·2)	1253 (20·6)	415 (10·9)
Alcohol consumption (grams per day, means ± SD)	9·7±14·0	5·6±9·6	14·7±16·6	10±14·6	9·2±12·9

***Table 2*: Characteristics of study population by sex and age from ESTHER study.**
Abbreviation: SD, standard deviation; NA, not available.
[a] Data missing for 252 participants.
[b] Data missing for 15 participants.
[c] Data missing for 30 participants.

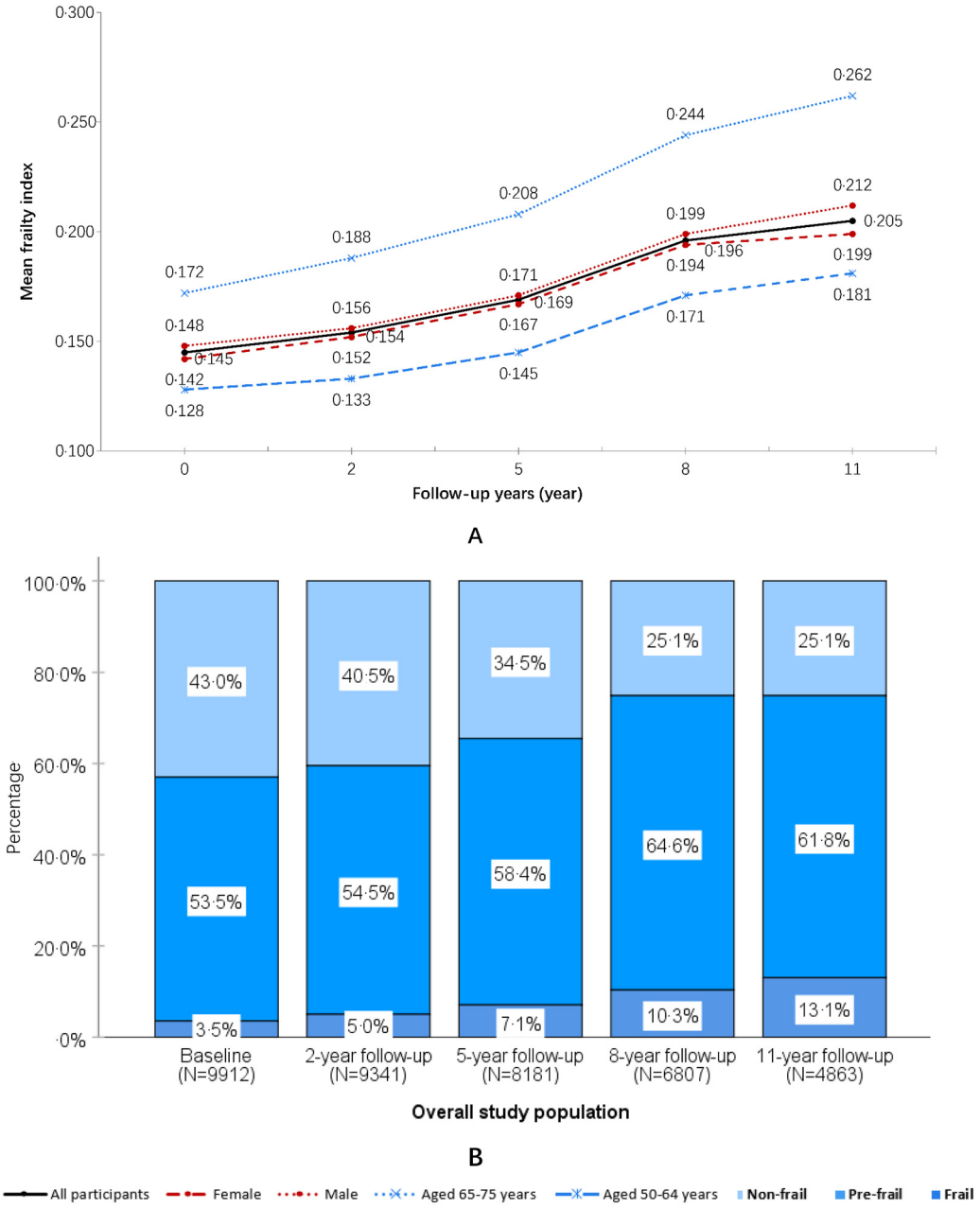

Figure 1. Eleven-year trajectories of frailty by age and sex and proportions of frailty status at each follow-up. A, Eleven-year frailty index trajectories by age and sex. B, Proportions of frailty status in overall study population at each follow-up.

Figure 2 shows the association of FI with all-cause mortality according to length of follow-up and modelling the FI as a time-varying variable or using baseline FI only. The associations of baseline FI with all-cause mortality were gradually attenuated by the length of follow-up. The multivariable adjusted HRs [95% confidence intervals (95% CIs)] for all-cause mortality risk per 0·1 increase of baseline FI were highest at the 2-year follow-up with 1·68 (95% CI 1·52–1·86) and reached a minimum of 1·48 (95% CI 1·43–1·54) at 14-year follow-up. For each 10 percent unit increase of time-varying FI, the corresponding multivariable adjusted HRs (95% CI) for risk of all-cause mortality were highly consistent between the 5-year follow-up (1·59 (1·49–1·70)) and 14-year follow-up (1·59 (1·53–1·66)), which was substantially higher than the corresponding HRs for baseline FI only.

With all follow-up lengths, a clear dose-response relationship with baseline FI was seen. However,

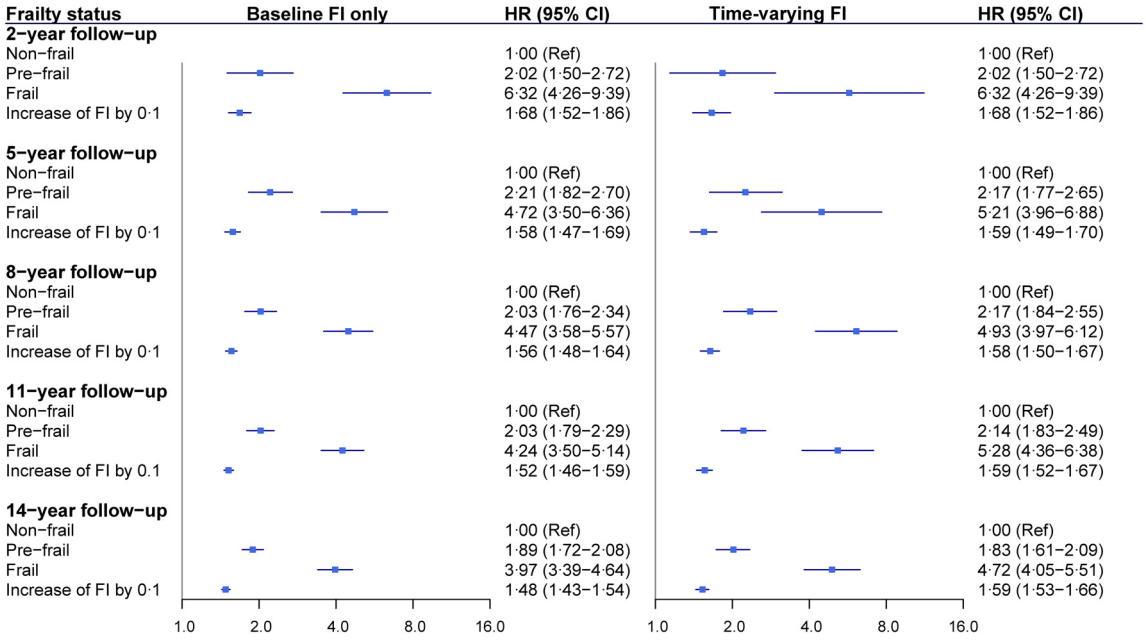

Figure 2. Association of FI with all-cause mortality according to length of follow-up and whether FI was modelled as a time-varying variable or only with baseline FI. Models were adjusted for age, sex, alcohol consumption (grams per day), and smoking status (never smoker, former smoker, and current smoker).

Abbreviations: FI, frailty index; HR, hazard ratio; CI, confidence interval.

multivariable adjusted hazard ratios (95% CIs) for pre-frail and frail compared to non-frail participants were attenuated from 2·21 (1·82−2·70) and 4·72 (3·50−6·36) to 1·89 (1·72−2·08) and 3·97 (3·39−4·64) after 14 years of follow-up. By contrast, hazard ratios remained stable when frailty status was modelled as a time-varying variable and were 1·83 (1·61−2·09) and 4·72 (4·05−5·51) after 14 years of follow-up for pre-frailty and frailty, respectively.

Figures 3 and 4 illustrate the associations of baseline and time-varying FI with up to 14-year follow-up for cancer-specific mortality and CVD-specific mortality, respectively. The associations of baseline FI with cancer-specific mortality and CVD-specific mortality were likewise slightly attenuated by the length of follow-up. In contrast, stronger and constant associations were observed for time-varying FI with each follow-up length. Overall, frailty was much stronger associated with CVD mortality than with cancer mortality, with adjusted hazard ratios (95% CIs) for pre-frail and frail compared to non-frail individuals of 2·43 (1·89−3·12) and 7·52 (5·69 −9·94), respectively, for CVD mortality and 1·57 (1·30 −1·89) and 2·55 (1·95−3·34), respectively, for cancer mortality during 14 years of follow-up in analyses using the time-varying FI.

Similarly strong associations between time-varying FI and mortality were seen among women and men, and participants 50−64 years and 65−75 years (Supplementary Table 3−5). None of the tests for interactions between time-varying FI and these covariates reached statistical significance ($P > 0.05$).

Discussion

In this long-term population-based prospective cohort comprising 9912 participants, we evaluated the risk of mortality according to longitudinal repeated measurements of FI. Both levels of FI and the proportions of frail participants gradually increased with age and there was significant variability in the progression of frailty. We observed clear dose-response relationships between FI values and all-cause, cancer and CVD mortality, with associations being substantially stronger and consistent across various lengths of follow-up when FI was considered as a time-varying predictor variable rather than being based on a single measurement at baseline.

The increase in prevalence of frailty with age is well established in both cross-sectional and longitudinal studies in aging research. For example, in a cross-sectional study among 993 adults aged 70+ conducted in Spain,[22] prevalence of frailty (measured by Fried frailty[4]) was reported to be 7·1%, 14·5%, 29·7%, 31·8%, and 43·2%, in participants aged 70−74, 75−79, 80−84, 85−89 and over 90 years, respectively. In a cohort study conducted in 350 older adults (≥65 years) residing in long-term care facilities in Korea, the prevalence of frailty (measured by Fried frailty[4]) increased from 25.8% to 35.2% during three years of follow-up.[12] The

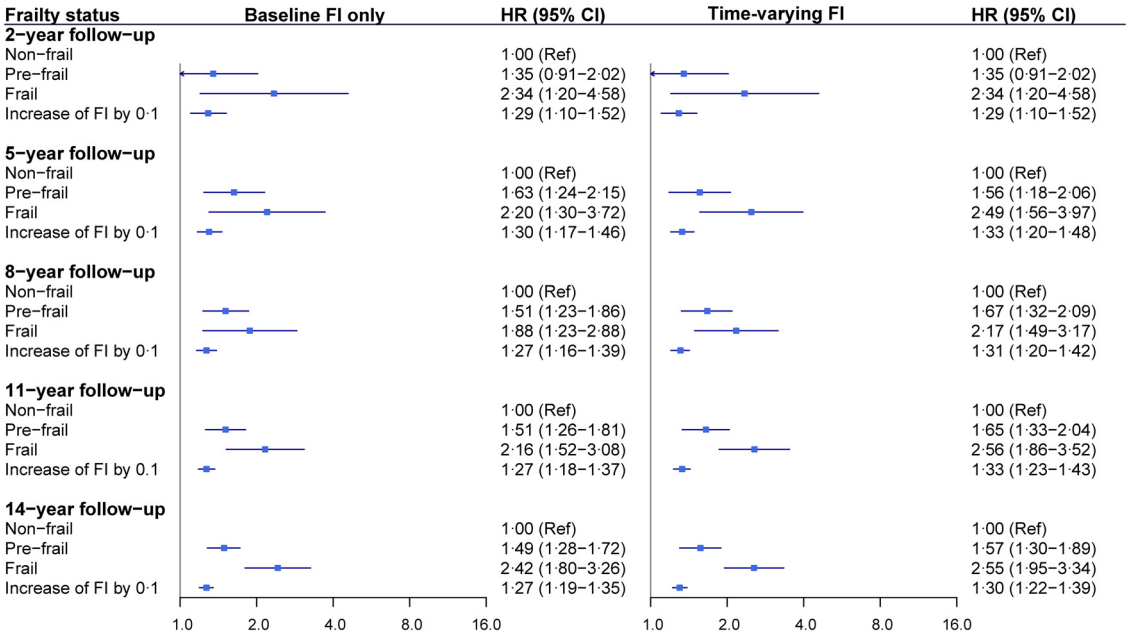

Figure 3. Association of FI with cancer-specific mortality according to length of follow-up and whether FI was modelled as a time-varying variable or only with baseline FI. Models were adjusted for age, sex, alcohol consumption (grams per day), and smoking status (never smoker, former smoker, and current smoker).

Abbreviations: FI, frailty index; HR, hazard ratio; CI, confidence interval.

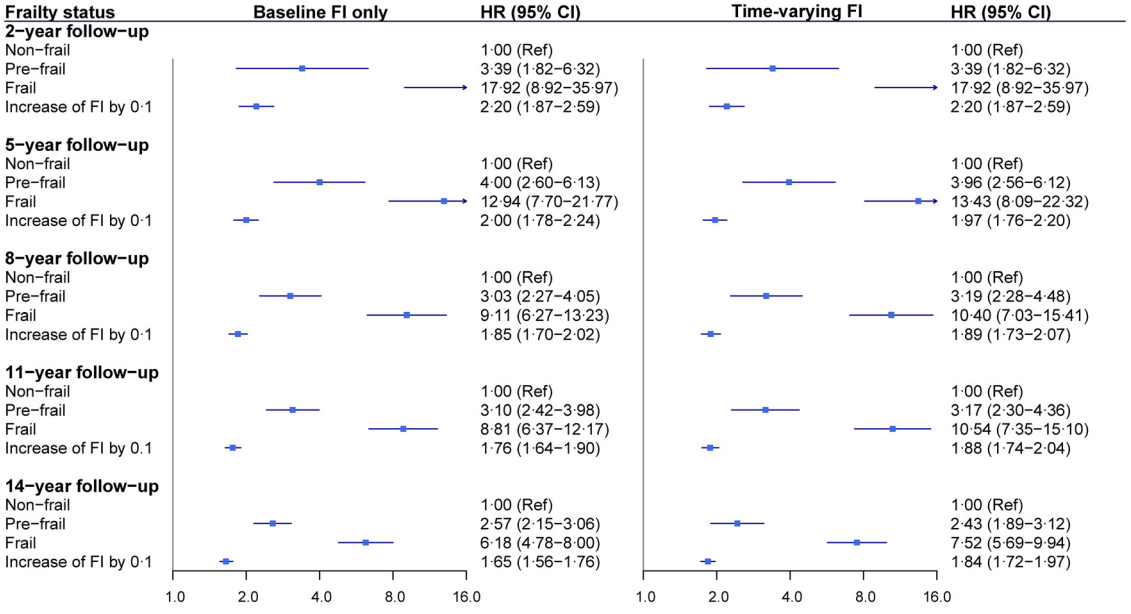

Figure 4. Association of FI with CVD-specific mortality according to length of follow-up and whether FI was modelled as a time-varying variable or only with baseline FI. Models were adjusted for age, sex, alcohol consumption (grams per day), and smoking status (never smoker, former smoker, and current smoker).

Abbreviations: CVD, cardiovascular disease; FI, frailty index; HR, hazard ratio; CI, confidence interval.

increase in frailty prevalence with age is in line with the expected consequence of the cumulative decline in multiple physiological systems occurring at older age.

Nevertheless, in agreement with results from other recent studies,[11,23,24] our study demonstrates that there is substantial inter-individual variability in development and progression of frailty with increasing age, including the possibility of regression of frailty. A variety of factors contributes to the development of frailty and frailty transitions, including nutritional status,[25] environmental factors,[26] diseases,[24] and psychological factors.[24] Therefore, these changeable characteristics make frailty a comprehensive and reversible health condition.[27] The observed correlation of FI and age and the dynamic and reversible characteristic of frailty therefore support the hypothesis that single-point estimates of FI might be not sufficient to disclose its full effects. Our study also suggests men accumulate more deficits than women. Previous studies have also assessed sex differences in frailty and shown consistently higher frailty prevalence rates and FI among women than among men.[28,29] A vast majority of these published studies have assessed the FI in population aged older than 65 years.[28,29] In our study, approximately 60% of the participants aged between 50 and 64 years. The sex difference observed in our study might be caused by the higher incidence and prevalence of CVD and smoking and their adverse consequences among men in this age group.

Few recent studies have investigated the associations of frailty with mortality using repeated assessment of FI, especially in younger population.[30–32] Verghese et.al.[33] assessed the association using multiple assessments of FI and reported similar associations with mortality as in our study. However, with only 1196 older adults (mean age >74 years) and 139 deceased, this study did not assess cause-specific mortality. Stolz et. al.[31] conducted an analysis based on 4 longitudinal studies of aging of older adults (mean age >73 years) and reported that FI changes predicted mortality independently of baseline FI differences. Another previous analysis based on the Longitudinal Aging Study Amsterdam (total n=995, mean age=76·5 years) used two measurements of FI taken three years apart and found the later measurement to be more effective than the change between both measurements in improving mortality predictions.[32] We assessed the association in a very large sample including a large number of participants between 50 and 64 years of age and expanded the existing evidence to much younger population. In both our and previous studies, the associations of the FI with mortality persisted after adjustment for multiple sociodemographic and lifestyle factors, which indicate that FI captures information beyond self-reported adverse environmental and lifestyle factors that affect frailty over the life course.

There are several potential explanations for the association of frailty with mortality. Frailty is strongly associated with reduced physical and cognitive function,[34] both of which may contribute to poor vital prognosis. Another widely accepted explanation is that frailty and mortality risk share common underlying causes such as chronic inflammation, poor nutritional status, or environmental factors, which may be prodromal indicators of the underlying frailty processes.[35,36] To what extent these factors contribute to the association between frailty and mortality should be addressed in detail in future research.

The much stronger associations with mortality seen for repeated measurements of FI than for single measurements of FI at baseline seen in our study may suggest that similar patterns might also be expected for other health outcomes that are related to mortality, such as the incidence of various age-related diseases or health impairments. While our study was focused on the association between frailty and mortality, we suggest use of repeated measurements of FI for potential prediction models for assessing the impact of frailty on other aging related health outcomes in future research. Moreover, the findings of our study that there is high interindividual variability of frailty trajectories including reversibility of frailty underline the concept that frailty is not an irreversible fate, and that efforts to prevent progression or even reversal of frailty are as important as efforts to prevent frailty in the first place.

There are several strengths of our study including the large sample size, comprehensive long-term follow-up with multiple repeat ascertainments of FI, and a relatively wide age range of the study population, including both "younger" (50–64 years) and older (65–75 years) "old adults". However, our study also has some limitations. First, our frailty index was based on self-reported characteristics. Several items, such as limitations or difficulties in daily activities, might be affected by imperfect reporting. Second, although the majority of variables to define our FI are easy-to-collect and readily available in routine medical charts, longitudinal repeated assessment at multiple points of time may be difficult to achieve in routine clinical practice. Third, although the selection of items included in the FI was based on pre-defined criteria, it was limited by the kind of information collected in our study. For example, the FI included several items on medications and major diseases, which are not fully independent, and results are not fully comparable to those obtained in other studies with different items included in FI construction. Fourth, as with all long-term longitudinal studies in older populations, the increasing attrition of less healthy subjects most likely has led underestimation of the increase in FI values and frailty prevalence over time.

In conclusion, this 14-year longitudinal study among community-dwelling older adults in Germany suggests that frailty may be more strongly related to mortality than previously disclosed by studies in which frailty was mostly determined at a single point of time.

Longitudinal repeated measurements of FI may be highly informative with respect to all-cause and cause-specific mortality risk. Further research should address in more detail the determinants and prognostic role of deterioration of frailty at old age and possibilities to prevent or even reverse such deterioration.

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Data sharing statement

Restrictions due to informed consent apply to the availability of these data.

Declaration of interests

No potential conflicts of interest were disclosed.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101630.

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