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Frailty index changes before and after incident cardiovascular disease

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ABSTRACT

Background Cardiovascular disease (CVD) and frailty are interrelated conditions prevalent in aging populations, yet their dynamic temporal relationship remains underexplored. This study investigates longitudinal changes in frailty trajectories before and after incident CVD across diverse cohorts.

Methods Utilizing data from four longitudinal, multinational cohorts (ELSA, HRS, CHARLS, SHARE; n = 66,537), we constructed the frailty index (FI) based on age-related health deficits, using 40, 40, 42, and 44 items from ELSA, HRS, CHARLS and SHARE, respectively. Linear mixed models assessed FI changes pre- and post-CVD, adjusting for demographics, lifestyle, and baseline FI. Sensitivity analyses excluded hypertension, diabetes, and arthritis to mitigate confounding.

Results Frailty increased steadily before CVD onset (pre-CVD slope: ELSA β = 0.005, HRS β = 0.005, CHARLS β = 0.012, SHARE β = 0.007; all P < 0.001), with an acute FI spike at diagnosis (post-CVD acute change: ELSA β = 0.024, HRS β = 0.031, CHARLS β = 0.046, SHARE β = 0.038; all P < 0.001). Post-CVD, frailty progression further accelerated (ELSA β = 0.008, HRS β = 0.005, CHARLS β = 0.017, SHARE β = 0.010; all P < 0.001). Sensitivity analyses confirmed robustness across age strata and FI definitions.

Conclusions This first multinational study demonstrates bidirectional acceleration of frailty around CVD onset, highlighting their close temporal interplay. These findings suggest that incorporating frailty assessment into CVD management may help identify high-risk individuals and support timely, multidimensional care in aging populations.

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, particularly among older adults.[1,2] With age being the strongest risk factor, the incidence and prevalence of CVD are expected to rise as global populations age. This trend is likely to place significant strain on healthcare resources and increase societal costs.[2,3] Aging is associated with the increased likelihood of frailty, which is a condition characterized by greater vulnerability to stressors due to dysregulation across multiple physiological systems.[4] Recent studies have demonstrated that frailty is not only highly prevalent in individuals with CVD,[5,6] but also serves as a powerful prognostic indicator for poor cardiovascular outcomes.[7,8] As a result, the relationship between frailty and CVD has garnered considerable attention in both clinical and research settings.

While previous studies have shown that frailty and pre-frailty increase the risk of incident CVD, they have largely focused on baseline frailty status, without adequately addressing how changes in frailty over time may influence CVD risk.[9–11] He, *et al.*[12] recently highlighted that frailty progression is associated with an elevated risk of incident CVD. However, their study primarily categorized frailty into discrete states (e.g., robust, pre-frail, frail), which may not fully capture the dynamic and continuous nature of frailty and its evolving relationship with CVD events.[13]

Importantly, frailty is dynamic in nature. Understanding frailty as a dynamic process, especially its evolution around CVD events, has critical implications for clinical practice. Identifying how frailty changes in the pre- and post-CVD periods may help healthcare providers to identify individuals at higher risk for accelerated frailty progression, allowing for earlier intervention strategies aimed at mitigating frailty. Early detection and

intervention, such as tailored rehabilitation programs or lifestyle modifications, could potentially alter the trajectory of frailty progression, reducing the adverse outcomes associated with both CVD and frailty. Furthermore, this approach could shift the focus of care from reactive to preventive, by addressing frailty during a window where intervention may be most effective.

The present study leverages longitudinal data from four large and nationally representative cohort studies: the English Longitudinal Study of Ageing (ELSA), the Health and Retirement Study (HRS), the China Health and Retirement Longitudinal Study (CHARLS) and Survey of Health, Ageing and Retirement in Europe (SHARE). We aim to elucidate the dynamic interplay between CVD and frailty. Specifically, we assess the longitudinal changes in frailty index (FI) before CVD diagnosis, as well as the acute and long-term impact of CVD events on frailty progression. This research could contribute to better clinical management of frailty in aging populations, reducing the societal burden associated with both CVD and frailty and improving quality of life for affected individuals.

METHODS

Study Design and Population

The ELSA, HRS, CHARLS and SHARE were all prospective and nationally representative cohorts conducted in UK, the USA, the China and in the Europe, respectively,[14–17] with participants followed up approximately biennially. In this study, wave 2 (2004) of ELSA, and wave 4 (1998) of HRS, wave 1 (2011) of CHARLS and wave 4 (2010) of SHARE served as the baseline. Subsequent follow-up surveys were employed to track the outcome until the final follow-up survey, which was wave 9 (2018–2019) of ELSA, and wave 15 (2020) of HRS, wave 4 (2018) of CHARLS and wave 9 (2021) of SHARE. The ELSA, HRS, CHARLS and SHARE were approved by London Multi-Centre Research, the University of Michigan, the Ethics Review Committees of Peking University and the Ethics Council of Max Planck Society respectively. Informed consent was obtained from each participant in these four cohorts (see the supplementary materials chapter Ⅰ).

Assessment of Frailty

Frailty was evaluated by the FI, which was calculated by the accumulation of multiple age-related health deficits. In the current study, we constructed the FI following standard procedures described previously.[18,19] Deficits associated with health status were included in the FI if they met the following criteria: the deficit involves multiple body systems and a range of physiological areas; the prevalence of the deficit generally increases with age; the deficit is not nearly universal in middle-aged. After screening baseline self-reported or measured data, we selected 40, 40, 42, and 44 variables from ELSA, HRS, CHARLS and SHARE, respectively, to construct the FI, involving disease (excluding heart disease and stroke), symptoms, disability, physical function, depression, and cognition (see Supplement Table1). Each deficit was dichotomised or mapped into the 0·00–1·00 interval, with 0·00 indicating the absence of a deficit (the healthiest state) and 1·00 indicating the maximal expression of the deficit (the unhealthiest state). For each participant, when the number of missing items did not exceed 20%, the FI was calculated by dividing the number of existing deficits by the total number of available items. Participants with more than 20% missing items among frailty components were excluded from FI calculation. Therefore, the FI is a continuous variable ranging from 0 to 1, with a higher FI indicating a greater degree of frailty. We validated the FI we constructed in each cohort, and the results are shown in the Supplement Table2 and Supplement Table3. The FI is positively correlated with age, the frequency distribution is right-skewed, the average score for females is higher than that for males, and 99% of the sample scores are less than 0.7. This result is consistent with the characteristics that the FI mentioned by Rockwood, *et al*. should possess,[19] indicating that the FI we constructed is robust. Rate of change in FI refers to the annualized change in the frailty index, calculated from linear mixed models as the slope of FI over time. In fact, a higher rate indicates faster frailty progression.

Assessment of Incident CVD

In the ELSA, HRS, CHARLS and SHARE, CVD was ascertained based on self-reported physician-diagnosed heart disease (including angina, heart attack, congestive heart failure, and other heart problems) or stroke (the methodology for the ascertainment of CVD is outlined in the Supplementary material chapter Ⅲ). In brief, participants were inquired whether they were diagnosed with heart disease or stroke by doctors. Those who reported being diagnosed with heart disease or stroke

were considered to have CVD. We recorded the CVD diagnosis date as the midpoint between the date of the last interview and the date of the interview reporting CVD.

Covariates

We characterized the sample demographics by examining covariates including age, gender, education level, marital status, smoking status, drinking status, physical activity, and body mass index (BMI). For consistency among the ELSA, HRS, CHARLS and SHARE, marital status was divided into two categories: married or partnered and other marital status (separated, divorced, unmarried, or widowed). Education was classified into three levels: below high school, high school, and college or above. Smoking status was categorized as never smokers and smokers. Drinking status was categorized into frequent drinking (more than once a month) and infrequent drinking (once or less a month) based on drinking frequency in the past year. Similarly, physical activity levels were classified based on whether one engages in vigorous activities each week. BMI was determined by weight divided by height squared (kg/m^2).

Statistical Analyses

The baseline demographic characteristics of the study population were described in relation to the occurrence of CVD. Continuous variables are expressed as mean ± SD or median [interquartile range (IQR)], and categorical variables are expressed as *n* (%).

We employed linear mixed models to analyze repeated measures and longitudinal data (see the supplementary materials chapter Ⅳ). To examine differences in pre-CVD FI changes between participants who developed CVD and those who did not, we fitted the first model that included incident CVD (yes or no), time (years since baseline to incident CVD or the end of follow-up), and the interaction of CVD with time ("CVD × time"). This interaction term reflects the difference in pre-CVD FI change rates between the CVD group and the non-CVD group. We developed a second model using the data of participants to evaluate the acute FI changes after an incident CVD. A time-varying variable was used to evaluate the effect of incident CVD on FI changes (the value of this variable changed from 0 to 1 at the time of CVD onset). In the third model, we incorporated time after CVD onset. The post-CVD time variable assessed the longer-term effect of CVD on FI increase during the follow-up period, indicating the change in the annual rate of FI increase after CVD onset compared to the pre-CVD period.

To test the reliability of the primary findings, we performed the following sensitivity analyses: (1) because hypertension, diabetes, and arthritis were cardiovascular risk factors in their own right, we re-constructed the FI after excluding these three items from the original FI and subsequent analyses; (2) stratified analyses were performed by age (middle-aged: < 65 years; older: ≥ 65 years); and (3) we have re-established the FI, excluding participants with missing FI items from the calculation of the FI and subsequent analyses.

All statistical analyses were performed using R software (version 4.4.0). Statistical tests were two-sided, and differences were deemed statistically significant at $P < 0.05$.

RESULTS

Figure 1 illustrates the selection process of the study population. Among 94065 participants from the ELSA, HRS, CHARLS and SHARE, we first excluded 710 participants at baseline who were unable to have an FI calculated due to more than 20% missing items. In addition, 20,107 participants with CVD at baseline and 6711 participants who were lost to follow-up were excluded. The remaining 66,537 participants were included in the final analyses.

Table 1 presents the baseline characteristics of the participants, grouped by the presence or absence of CVD during follow-up (total follow-up 184,647.8 person-years in ELSA; total follow-up 864,984.8 person-years in HRS; total follow-up 74,867.25 person-years in CHARLS; total follow-up 494,939.4 person-years in SHARE). A total of 7231 participants from ELSA (female: 56.58%, mean age: 65.03 years), 15,357 from HRS (female: 59.05%, mean age: 65.42 years), 10964 participants from CHARLS (female: 49.16%, mean age: 61.81 years) and 32,985 participants from SHARE (female: 58.10%, mean age: 64.16 years) were included in the main analyses. During the follow-up period, 15890 participants developed CVD, including 1480 from ELSA, 5931 from HRS, 2084 from CHARLS and 6395 from SHARE. Compared with participants without CVD, individuals with CVD were older, were more likely to be smokers, had a higher BMI and FI, more likely to be male in the ELSA, HRS, and SHARE, had lower physical activity intensity in the ELSA,

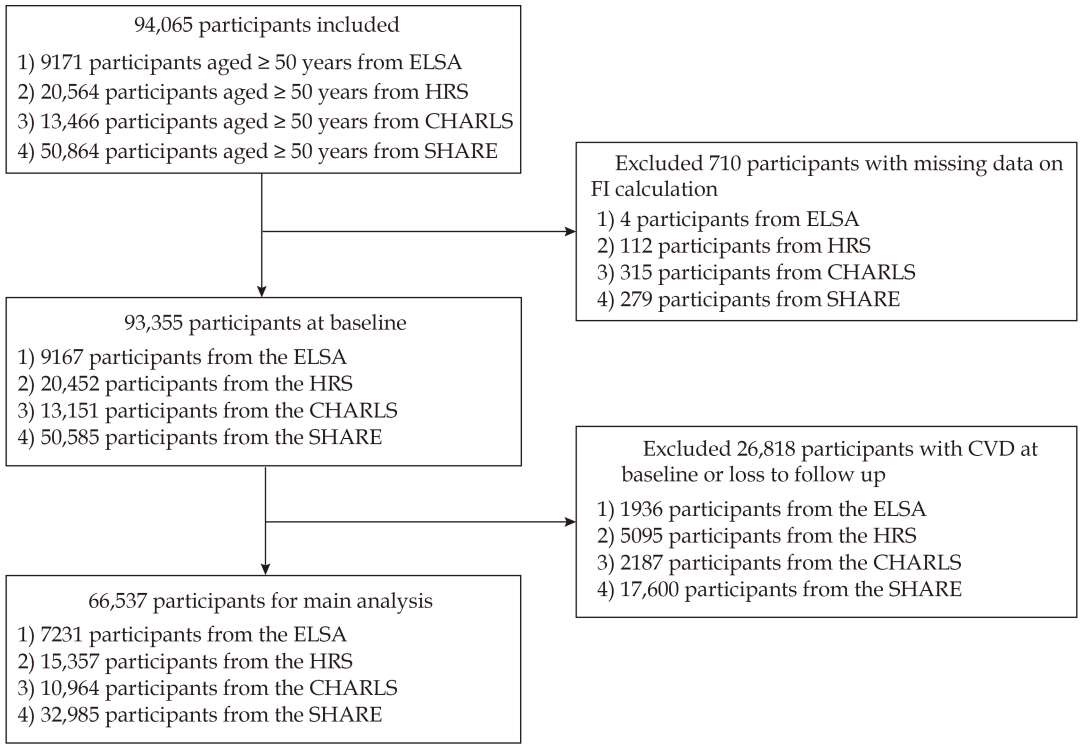

Figure 1 Chart of participant selection for the present study population.

CHARLS and SHARE, and were less likely to be married or have a partner in the ELSA and SHARE.

As illustrated in Table 2, in the ELSA, participants who eventually developed CVD exhibited an average annual increase in the FI of 0.006 (95% CI: 0.005–0.006) prior to the event, compared to those who did not develop CVD. Similar patterns were observed in the HRS (β = 0.005/y; 95% CI: 0.005–0.006), CHARLS (β = 0.013/y; 95% CI: 0.012–0.016), and SHARE cohorts (β = 0.009/y; 95% CI: 0.009–0.010). After adjusting for baseline covariates including age, sex, education, marital status, smoking and drinking habits, and baseline FI, the rate of FI increase remained significantly higher among participants who developed CVD during follow-up (ELSA: β = 0.005/y, 95% CI: 0.004–0.005; HRS: β = 0.005/y, 95% CI: 0.004–0.005; CHARLS: β = 0.012/y, 95% CI: 0.010–0.013; SHARE: β = 0.007/y, 95% CI: 0.007–0.008).

Table 3 shows that the population experienced an acute FI change after adjustment for calendar time and acute increase in CVD. When comparing changes in FI before and after the onset of CVD, the results showed that participants with CVD experienced an acute increase in FI during diagnosis of CVD (ELSA, β = 0.030, 95% CI: 0.026–0.034; HRS, β = 0.031, 95% CI: 0.028–0.033; CHARLS, β = 0.045, 95% CI: 0.040–0.050; SHARE, β = 0.048, 95% CI: 0.046–0.051). After adjusting for baseline variables, the results still demonstrated a significant acute increase in FI during the event (ELSA, β = 0.024, 95% CI: 0.019–0.028; HRS, β = 0.031, 95% CI: 0.028–0.033; CHARLS, β = 0.046, 95% CI: 0.041–0.050; SHARE, β = 0.038, 95% CI: 0.035–0.040).

Additionally, the FI increased at a significantly faster rate after the onset of CVD compared to before. The results are shown in Table 4, indicating that the rate of FI increase accelerated in the population with CVD in all four cohorts (ELSA, β = 0.008/y, 95% CI: 0.008–0.009; HRS, β = 0.006/y, 95% CI: 0.005–0.006; CHARLS, β = 0.021/y, 95% CI: 0.018–0.024; SHARE, β = 0.013/y, 95% CI: 0.013–0.014). After adjusting the baseline variables, the results remained statistically significant (ELSA, β = 0.008/y, 95% CI: 0.007–0.008; HRS, β = 0.005/y, 95% CI: 0.005–0.006; CHARLS, β = 0.017/y, 95% CI: 0.014–0.020; SHARE, β = 0.010/y, 95% CI: 0.009–0.010).

Figure 2 illustrates changes in the FI scores before and after the CVD event. In individuals without CVD, FI scores gradually increased. However, in those with CVD, FI scores rose sharply after the event, indicating a rapid progression of frailty. Post-CVD, frailty levels remained high and continued to increase. This consistent trend across four cohorts underscores the significant im-

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Table 1 Baseline characteristics of the study participants according to incident CVD during follow-up.

Variables		ELSA				HRS				CHARLS				SHARE			
	Overall sample (*n* = 7231)	No incident CVD (*n* = 5751)	Incident CVD (*n* = 1480)	*P*-overall	Overall sample (*n* = 15357)	No incident CVD (*n* = 9426)	Incident CVD (*n* = 5931)	*P*-overall	Overall sample (*n* = 10964)	No incident CVD (*n* = 8880)	Incident CVD (*n* = 2084)	*P*-overall	Overall sample (*n* = 32985)	No incident CVD (*n* = 26590)	Incident CVD (*n* = 6395)	*P*-overall
Sex				0.010				0.003				< 0.001				< 0.001
Male	3140 (43.42)	2453 (42.65)	687 (46.42%)		6288 (40.95)	3770 (40.00)	2518 (42.45)		5574 (50.84)	4654 (52.41)	920 (44.15)		13820 (41.90)	10849 (40.80)	2971 (46.46)	
Female	4091 (56.58)	3298 (57.35)	793 (53.58%)		9069 (59.05)	5656 (60.00)	3413 (57.55)		5390 (49.16)	4226 (47.59)	1164 (55.85)		19165 (58.10)	15741 (59.20)	3424 (53.54)	
Age, yrs	65.03 ± 9.54	64.55 ± 9.60	66.88 ± 9.09	< 0.001	65.42 ± 10.08	65.10 ± 10.37	65.93 ± 9.58	< 0.001	61.81 ± 8.46	61.65 ± 8.59	62.48 ± 7.85	< 0.001	64.16 ± 9.25	63.32 ± 9.06	67.68 ± 9.20	< 0.001
Education				0.759				0.003				0.013				< 0.001
Below high school	2661 (40.13)	2109 (40.00)	552 (40.62)		4056 (26.42)	2531 (26.86)	1525 (25.71)		9770 (89.12)	7920 (89.20)	1850 (88.77)		12789 (38.77)	10011 (37.65)	2778 (43.44)	
High school	3024 (45.60)	2416 (45.83)	608 (44.74)		8490 (55.30)	5112 (54.26)	3378 (56.95)		759 (6.92)	629 (7.08)	130 (6.24)		13082 (39.66)	10683 (40.18)	2399 (37.51)	
Collage or above	946 (14.27)	747 (14.17)	199 (14.64)		2807 (18.28)	1779 (18.88)	1028 (17.33)		434 (3.96)	330 (3.72)	104 (4.99)		7114 (21.57)	5896 (22.17)	1218 (19.05)	
Vigorous activity ≥ 1 times per week				0.443				0.127				< 0.001				< 0.001
Yes	2132 (29.78)	1707 (30.00)	425 (28.93)		7048 (45.91)	4279 (46.42)	2769 (46.69)		1525 (35.01)	1278 (36.31)	247 (29.55)		16984 (51.73)	14120 (53.34)	2864 (45.02)	
No	5027 (70.22)	3983 (70.00)	1044 (71.07)		8303 (54.09)	5142 (54.58)	3161 (53.31)		2831 (64.99)	2242 (63.69)	589 (70.45)		15848 (48.27)	12351 (46.66)	3497 (54.98)	
Smoking status				0.199				0.017				0.001				0.046
Smokers	4490 (62.10)	3549 (61.72)	941 (63.58)		8765 (57.62)	5304 (56.85)	3461 (58.83)		8173 (80.25)	6549 (79.61)	1624 (82.90)		17412 (53.60)	13964 (53.32)	3448 (54.73)	
Never smokers	2740 (37.90)	2201 (38.28)	539 (36.42)		6447 (42.38)	4025 (43.15)	2422 (41.17)		2012 (19.75)	1677 (20.39)	335 (17.10)		15076 (46.40)	12224 (46.68)	2852 (45.27)	

Continued

Variables	ELSA				HRS				CHARLS				SHARE			
	Overall sample (*n* = 7231)	No incident CVD (*n* = 5751)	Incident CVD (*n* = 1480)	*P*-overall	Overall sample (*n* = 15357)	No incident CVD (*n* = 9426)	Incident CVD (*n* = 5931)	*P*-overall	Overall sample (*n* = 10964)	No incident CVD (*n* = 8880)	Incident CVD (*n* = 2084)	*P*-overall	Overall sample (*n* = 32985)	No incident CVD (*n* = 26590)	Incident CVD (*n* = 6395)	*P*-overall
Drinking ≥ 1 times per month				0.066				0.347				< 0.001				0.361
Yes	5756 (90.56)	4574 (90.92)	1182 (89.21)		7681 (50.02)	4686 (49.71)	2995 (50.51)		7240 (68.39)	5762 (67.38)	1478 (72.59)		15826 (79.50)	12998 (79.63)	2828 (78.93)	
No	600 (9.44)	457 (9.08)	143 (10.79)		7675 (49.98)	4740 (50.29)	2935 (49.49)		3347 (31.61)	2789 (32.62)	558 (27.41)		4081 (20.50)	3326 (20.37)	755 (21.07)	
Marital status				0.112				0.093				0.464				< 0.001
Married or partnered	5121 (70.83)	4098 (71.27)	1023 (69.12)		10448 (68.11)	6365 (67.60)	4083 (68.91)		10862 (99.07)	8794 (99.03)	2068 (99.23)		24821 (75.32)	20239 (76.18)	4582 (71.76)	
Other marital status	2109 (29.17)	1652 (28.73)	457 (30.88)		4893 (31.89)	3051 (32.40)	1842 (31.09)		102 (0.93)	86 (0.97)	16 (0.77)		8131 (24.68)	6328 (23.82)	1803 (28.24)	
BMI, mean (SD), kg/m2	27.92 (4.88)	27.77 (4.84)	28.46 (4.99)	< 0.001	26.82 (5.10)	26.44 (4.95)	27.43 (5.28)	< 0.001	23.54 (4.01)	23.39 (3.93)	24.20 (4.29)	< 0.001	26.81 (4.67)	26.63 (4.58)	27.60 (4.95)	< 0.001
Frailty index, mean (SD)	0.13 (0.13)	0.12 (0.12)	0.16 (0.14)	< 0.001	0.14 (0.13)	0.14 (0.14)	0.15 (0.13)	< 0.001	0.15 (0.14)	0.14 (0.14)	0.18 (0.15)	< 0.001	0.11 (0.11)	0.11 (0.11)	0.15 (0.13)	< 0.001

CVD: cardiovascular disease; CHARLS: China Health and Retirement Longitudinal Study; *ELSA: English Longitudinal Study of Ageing; HRS: Health and Retirement Study; SHARE: the Survey of Health: Ageing and Retirement in Europe; BMI: body mass index

Table 2 Pre-CVD-diagnosis mean difference in rate of change in frailty index scores between participants who did and did not have an incident CVD.

	ELSA		HRS		CHARLS		SHARE	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Unadjusted	0.006 (0.005–0.006)	<0.001	0.005 (0.005–0.006)	<0.001	0.013 (0.012–0.016)	<0.001	0.009 (0.009–0.010)	<0.001
Adjusted	0.005 (0.004–0.005)	<0.001	0.005 (0.004–0.005)	<0.001	0.012 (0.010–0.013)	<0.001	0.007 (0.007–0.008)	<0.001

*Results reported adjusted for baseline age, sex, education, marital status, smoking status, alcohol consumption, baseline frailty index. CVD: cardiovascular disease.

Table 3 Acute change in frailty index after an incident CVD vs before CVD among participants with an incident CVD.

	ELSA		HRS		CHARLS		SHARE	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Unadjusted	0.030 (0.026–0.034)	<0.001	0.031 (0.028–0.033)	<0.001	0.045 (0.040–0.050)	<0.001	0.048 (0.046–0.051)	<0.001
Adjusted	0.024 (0.019–0.028)	<0.001	0.031 (0.028–0.033)	<0.001	0.046 (0.041–0.050)	<0.001	0.038 (0.035–0.040)	<0.001

*Results reported adjusted for baseline age, sex, education, marital status, smoking status, alcohol consumption, baseline frailty index. CVD: cardiovascular disease.

Table 4 Rate of change in Frailty Index after an incident CVD among participants with an incident CVD.

	ELSA		HRS		CHARLS		SHARE	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Unadjusted	0.008 (0.008–0.009)	<0.001	0.006 (0.005–0.006)	<0.001	0.021 (0.018–0.024)	<0.001	0.013 (0.013–0.014)	<0.001
Adjusted	0.008 (0.007–0.008)	<0.001	0.005 (0.005–0.006)	<0.001	0.017 (0.014–0.020)	<0.001	0.010 (0.009–0.010)	<0.001

*Results reported adjusted for baseline age, sex, education, marital status, smoking status, alcohol consumption, baseline frailty index. CVD: cardiovascular disease.

pact of CVD on frailty and underscores the necessity for timely interventions to slow frailty progression and improve long-term health outcomes.

Sensitivity Analyses

When using the adjusting FI items after excluding three items of hypertension, diabetes, and arthritis, the results were consistent with the main analyses in ELSA, HRS, CHARLS and SHARE (Supplement Table 4–6). After adjusting for baseline covariates, participants who developed CVD experienced a faster increase in FI before diagnosis compared with those who had no CVD throughout the follow-up period (SupplementTable 4). When comparing changes in FI before and after the onset of CVD, the findings revealed that participants with CVD experienced an acute change in FI after the onset of CVD. After adjusting for baseline covariates, the results remained statistically significant (Supplement Table 5). Furthermore, the FI increased significantly faster after the onset of CVD compared to before (Supplement Table 6). The sensitivity analysis results for age are consistent with our main analysis results; after adjusting for baseline variables, the findings remained similar (Supplement Table 7–12). The results of the sensitivity analysis for the FI align with those of our primary analysis; upon controlling for baseline variables, the outcomes remained consistent (Supplementary Table 13–15).

Nonresponse Analyses

We categorized the frailty of the baseline population into Robust, Pre-frail, and Frail based on previous research,[12] and provided a description of their baseline

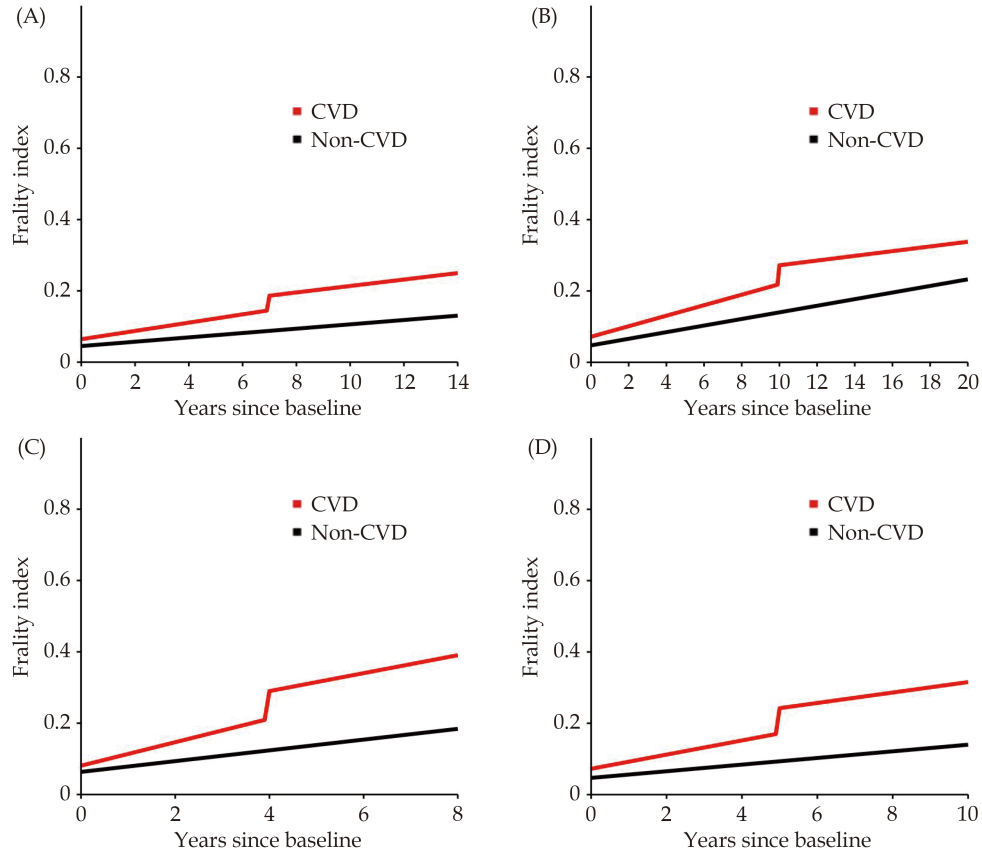

Figure 2 Predicted mean change in FI scores before and after an incident CVD. (A): English Longitudinal Study of Ageing; (B): Health and Retirement Study; (C): China Health and Retirement Longitudinal Study; (D): Survey of Health, Ageing and Retirement in Europe. Predicted values of FI Scores were calculated for a 70-year-old woman with a body mass index of 28 kg/m^2, alcohol consumption of = 1 drink per month. Black lines represent the trajectory for CVD-free participants; red lines represent the trajectory for participants with incident CVD. Natural slopes of FI decline in CVD-free participants and the pre-CVD FI decline slopes in those who developed CVD were estimated from the fully adjusted models in Table 2. Acute changes in FI Scores and post-CVD slopes were estimated from the models in Table 4.

characteristics (Supplement Table 16–19). In the four cohorts, frail participants were older, more likely to be female, less likely to be married or partnered, and had lower education than robust participants. We excluded 710 participants from this study due to incomplete data necessary for the calculation of the FI. These participants (0.75%) may be older, have lower education levels, had a lower BMI (Supplement Table 20–23). Concurrently, of the 93,355 participants with complete data at the baseline, 26,818 (28.73%) were excluded from this study because they either had CVD at the baseline or were lost to follow-up. These participants had a higher FI and BMI compared to those included in the study. The excluded participants also had higher percentages of covariates such as being male in the ELSA, HRS and SHARE, having an education level below high school, a higher frequency of drinking in the HRS and CHARLS, being smokers, and engaging in vigorous activity less than one times per week (Supplement Table24–27).

DISCUSSION

This study reveals the dynamic trajectory of FI changes before and after the onset of CVD. We found that frailty progresses more rapidly prior to the occurrence of CVD, with a sharp increase in the FI at the time of the event, followed by further acceleration of frailty progression afterward. To our knowledge, this is the first multinational study to capture systematically the bidirectional acceleration of frailty around CVD onset, offering novel insights into the interplay between CVD and frailty. Frailty is a common syndrome in older adults, characterized by declines in physical, mental, and functional domains, which increases susceptibility to dis-

eases and the risk of mortality. Our study shows that CVD is a significant trigger altering the slope of the frailty trajectories. This finding enhances our understanding of frailty, particularly considering its strong links to cognitive function, quality of life, and even mortality.

The acceleration of the FI before the onset of CVD may be associated with shared risk factors, including chronic inflammation, metabolic dysregulation, and reduced physical activity,[20–22] which can simultaneously affect both frailty and cardiovascular health. Prior research has highlighted that frailty is a significant risk factor for CVD,[23] with studies showing that frailty progression before CVD onset is associated with increased cardiovascular risk.[12] However, these studies have typically analyzed changes in frailty without fully capturing the dynamic nature of frailty acceleration in the period before CVD events. In contrast, our study emphasizes this dynamic acceleration of frailty, identifying individuals with rapid frailty progression prior to CVD development. By recognizing frailty acceleration early, interventions could be implemented to slow its progression and reduce CVD risk, offering a new preventive strategy in cardiovascular care.

At the time of CVD onset, we observed a sharp increase in the FI, indicating a significant, immediate worsening of frailty. This acute exacerbation is likely related to the physiological stress induced by the CVD event itself, including factors such as inflammation, ischemia, and hemodynamic instability.[24,25] Our findings support the view that CVD events act as major stressors, leading to an immediate and substantial increase in frailty. This underscores the importance of intensive management and monitoring during the event period to mitigate the impact of these stressors on frailty and overall health. Furthermore, our study also shows that after the onset of CVD, frailty continues to progress in the long term. This long-term acceleration of frailty may be related to the cumulative effects of CVD on multiple physiological systems,[5,26,27] including the cardiovascular system, musculoskeletal system, and cognitive functions. Chronic inflammation, ongoing cardiovascular damage, and reduced physical activity[28,29] due to CVD-related symptoms may contribute to the sustained deterioration of frailty. While it is possible that the ascertainment of CVD might lead to the identification of other conditions that could influence the FI—such as memory diseases, mental illness, or other comorbidities—our study design and sensitivity analyses effectively addressed this potential bias. By excluding conditions such as hypertension, diabetes, and arthritis, which are established CVD risk factors and could directly influence frailty, we ensured that the observed frailty acceleration was not simply a result of diagnostic increases associated with the CVD event. The continued increase in frailty after CVD further emphasizes the need for long-term interventions to address the broad impacts of CVD on aging and frailty. Managing frailty post-CVD is crucial for improving long-term patient outcomes and preventing the exacerbation of other chronic diseases.

This study has several strengths. It provides novel insights into the dynamic relationship between frailty and CVD, highlighting how frailty accelerates both before and after CVD onset. The use of data from large, diverse cohorts enhances the generalizability of the findings across different populations and regions. Additionally, rigorous sensitivity analyses were conducted to exclude the impact of well-established CVD risk factors such as hypertension, diabetes, and arthritis, ensuring that the observed frailty acceleration was not simply a result of diagnostic bias associated with the CVD event.

However, there are several limitations to the study. First, CVD was ascertained via self-reported diagnoses. Although prior studies have demonstrated reasonable validity of self-reported heart disease and stroke, this approach may introduce misclassification or reporting bias, which could affect the accuracy of CVD onset timing and potentially influence frailty trajectory estimates. Secondly, while the FI is a well-established tool, it may not capture all dimensions of frailty, such as cognitive function, in all cohorts, potentially limiting the accuracy of frailty assessment. Thirdly, the FI was constructed using slightly different numbers of items across cohorts due to data availability. Although sensitivity analyses using alternative FI definitions and stratified analyses by cohort showed consistent temporal patterns, potential differences in item selection and cultural or regional context may affect the cross-cohort comparisons. Fourthly, although the study controlled for a wide range of potential confounders, residual confounding from unmeasured factors, such as genetics, lifestyle, or environmental influences, may still exist, which could affect both frailty progression and CVD risk. Although the study identifies associations between frailty and CVD, the observational

nature of the research prevents the establishment of causal relationships. Therefore, our findings should be interpreted as reflecting temporal associations rather than causal relationships. More research is needed in the future, especially randomized assignments of interventions targeting frailty or cardiovascular risk factors, or determining causal relationships through more frequent assessments of frailty. Meanwhile, treating death as loss to follow-up may introduce selection bias, as participants with higher frailty levels are more likely to die or drop out, which could lead to estimation bias in the overall level and progression of frailty. Lastly, in our study, the FI ranges from 0 to 1. The estimated increases in FI associated with incident CVD across the four cohorts were typically in the range of 0.005 to 0.048. While these effects are statistically significant, they are relatively small. However, even small changes in frailty can have significant long-term impacts on individuals, leading to increased healthcare needs and potential loss of independence, particularly in an aging population. Given the growing burden of chronic diseases like CVD, even modest increases in frailty can place considerable strain on healthcare systems.

This study reveals the dynamic trajectory of frailty acceleration before and after the onset of CVD, highlighting the temporal relationship between frailty and CVD. Our findings support early identification of high-risk individuals and targeted interventions. Frailty screening in patients with incident CVD enables timely interventions, while integrating frailty assessment into community chronic disease programs may prevent functional decline and reduce healthcare burden.

DISCLOSURE

Fundings

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Conflict of interests

None.

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Data Availability Statement

Data from all cohorts used in this study are publicly available to qualified researchers. The ELSA data can be obtained from the UK Data Service after registration and acceptance of the End User Licence (https://www.elsa-project.ac.uk). The HRS data are accessible upon registration at the official website (https://hrs.isr.umich.edu); restricted data require an additional application. The CHARLS data are available upon online application and approval at (https://charls.pku.edu.cn). The SHARE data can be freely accessed for scientific use after registration at (https://share-eric.eu). Detailed access procedures are provided on each cohort's website.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The research protocol was approved by including ELSA (approved by National Research and Ethics Service Committee South Central-Berkshire), HRS (approved by National Institute on Aging and the Social Security Administration, NIA U01AG009740), CHARLS (approved by the Ethical Review Committee of Perking University, IRB00001052–11015), SHARE (approved by the Ethics Council of Max Planck Society), So the detailed ethical approval could be found on respective origin surveys. Meanwhile, written informed consent was also obtained from any participant.

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