Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Frailty trajectory, not blood pressure direction, predicts mortality and cardiovascular disease in adults aged 65 and older: harmonized joint-trajectory analyses of CHARLS and HRS Running title: Frailty trajectory versus blood pressure direction after age 65

Pengpeng Han
Nanyang Central Hospital
Yang Li
Nanyang Central Hospital
Lin Jia
Nanyang Central Hospital
Zhiyu Yuan
yuanzhiyu806@163.com

The First Affiliated Hospital of Henan University of Chinese Medicine

Research Article

Keywords: systolic blood pressure, frailty index, joint trajectories, mortality, cardiovascular disease, older adults

Posted Date: November 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11314734/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

A fall in systolic blood pressure (SBP) after age 65 is ambiguous: it may mark successful treatment or deteriorating health. Whether joint longitudinal phenotypes of SBP and frailty add prognostic meaning beyond frailty itself is unclear.

Methods

Parallel landmark analyses in CHARLS (China) and HRS (USA). Participants were aged 65 years or older at entry with three paired SBP and harmonized 30-item frailty index (FI) measurements (CHARLS n = 1,902; HRS n = 3,839). We independently fitted linear group-based multi-trajectory models, then estimated mortality (attained-age Cox models) and self-reported incident cardiovascular disease (CVD; complementary log-log models) under retention and selection weighting and 10 covariate imputations, decomposing the information contributed by the FI slope, the SBP slope and joint classes.

Results

Four classes emerged per cohort, ordered by frailty severity rather than SBP height. The highest-FI class—ordinary-to-moderate SBP with high, rapidly rising frailty—had mortality hazard ratios (HRs) versus the lowest-FI class of 1.65 (95% CI 1.18–2.31) in CHARLS and 2.21 (1.64–2.97) in HRS, and CVD HRs of 3.21 (1.88–5.49) and 2.51 (1.32–4.77). Rapid FI increase was associated with mortality within every SBP direction (HRs 1.43–2.15); no multiplicative interaction was detected, and the SBP slope itself carried no signal (HR per SD 1.06 and 0.94). Joint classes never outperformed a simpler model of initial status plus the FI slope (change in apparent C-index 0.004–0.010). Only about half of baseline-eligible participants—younger, less frail survivors—completed the three-measurement requirement; weighting left estimates essentially unchanged.

Conclusions

After age 65, the frailty trajectory, not the direction of blood pressure, carries the prognostic signal. A falling SBP warrants concurrent assessment of frailty, but joint trajectory classes are descriptive phenotypes, not a validated prediction tool or a treatment target.

Key Points

• Among adults aged 65 and older with three paired measurements, rapid frailty-index increase was associated with higher mortality within every SBP direction—falling, stable, and rising—in both national cohorts (HRs 1.43–2.15), with no detected SBP-by-frailty interaction.

• Independently fitted joint trajectories were ordered by frailty severity, not blood-pressure height: the highest-risk class combined ordinary-to-moderate SBP with high, rapidly rising frailty (mortality HR 1.65 in CHARLS and 2.21 in HRS; CVD HR 3.21 and 2.51 versus the lowest-frailty class).

• Joint classes added essentially no discrimination beyond initial status plus the frailty slope (change in C-index 0.004–0.010), and only about half of baseline-eligible participants—younger, less frail survivors—entered the complete-trajectory sample.

Background

Hypertension remains a major contributor to cardiovascular disease, yet blood pressure becomes harder to interpret as people age [1]. A lower observed SBP may reflect successful treatment, but it may also accompany weight loss, illness or diminishing physiological reserve. Observational associations between low blood pressure and mortality therefore cannot be read as the effects of lowering blood pressure. Evidence relating blood pressure to mortality differs across frailty levels, reinforcing the need to consider the health state in which a measurement occurs [2, 3].

Frailty summarizes vulnerability across multiple systems. A deficit-accumulation frailty index captures the proportion of assessed health deficits and can be calculated repeatedly [6]. Both frailty level and its longitudinal course are associated with adverse outcomes [7–9]. Blood pressure and frailty may change together, although their association does not establish which process causes the other. A high blood-pressure burden and increasing frailty can coexist, while falling blood pressure may accompany either stable function or worsening health.

Previous studies have examined frailty as a modifier of baseline blood-pressure associations, blood-pressure decline before death, or blood-pressure trajectories preceding frailty [2–5, 10–12]. These approaches establish relatedness but do not directly distinguish joint longitudinal profiles within the same blood-pressure direction. In particular, a fall in SBP is not itself a sufficient description of an older adult's health course. Whether frailty change provides additional prognostic information among people with falling SBP is a clinically relevant question separate from testing a statistical interaction.

We therefore addressed three questions in parallel landmark analyses of CHARLS and HRS, in adults aged at least 65 years at trajectory entry. First, do independently fitted joint SBP–FI models recover broadly corresponding longitudinal profiles in two national cohorts, and how are those profiles ordered—with respect to blood pressure or to frailty? Second, does the prognostic meaning of a given SBP direction depend on concurrent frailty change, or does frailty accumulation carry the same signal in every direction? Third, do joint classes add prognostic information beyond a simpler model of initial status and frailty slope, and how much selection is required to observe three paired assessments? We examined whether frailty accumulation supplies prognostic information alongside SBP change without requiring, or claiming, a synergistic effect.

Methods

Study design and participants

CHARLS and HRS are longitudinal studies of middle-aged and older adults in China and the United States [14, 15]. We analyzed harmonized, participant-level working datasets using an exposure-formation period followed by landmark outcome surveillance. CHARLS trajectories used the 2011, 2013 and 2015 assessments, with landmark in 2015. HRS enhanced face-to-face sequences were processed separately: sequence A used 2006, 2010 and 2014, and sequence B used 2008, 2012 and 2016. Their landmarks were 2014 and 2016. Participants observed in both HRS sequences were assigned only once, retaining sequence A. The available working datasets supported follow-up through 2020 in CHARLS and 2021 for mortality in HRS; HRS CVD assessments extended through 2020.

The primary trajectory sample required age 65 years or older at the first trajectory assessment, survival to landmark, and three paired SBP–FI observations. Mortality analyses included participants with positive post-landmark follow-up. Incident CVD analyses further required no reported heart disease or stroke up to landmark and subsequent CVD assessment or a recorded competing death. Age was checked at trajectory entry, not retrospectively at the landmark. The older entry age in HRS plus its eight-year formation window produced an older landmark population than the four-year CHARLS window. Reporting follows STROBE; the supplementary checklist identifies manuscript locations and unresolved author-level declarations [16].

Blood pressure and harmonized frailty index

SBP was taken from the supplied visit-level systolic blood-pressure variable. The working datasets did not provide a common, documented raw-reading aggregation pipeline, so we did not claim that both cohorts' SBP values were newly recalculated from the second and third readings. Values outside 70–250 mmHg were treated as missing. DBP outside 35–150 mmHg and BMI outside 12–60 kg/m² were treated as missing in corresponding ancillary analyses.

We constructed a common-concept 30-item noncardiovascular FI: five ADL limitations, five IADL limitations, nine mobility limitations, four noncardiovascular chronic conditions, falls, hip fracture, self-rated health, memory, vision, hearing and depressive symptoms. Items were coded from zero to one, with higher values indicating greater deficit. The FI equaled 100 times the mean of available items and required at least 24 of 30 observations. Hypertension, blood pressure, antihypertensive medication, diabetes, heart disease and stroke were excluded from its numerator. The mapping and exact transformations are supplied with the analysis code and supplementary table. This was study-specific common-concept harmonization, not a claim that the questionnaire items were measurement-invariant across countries [6].

Joint trajectory estimation and slope contrasts

We fitted linear Gaussian group-based multi-trajectory models for cohort-standardized SBP and FI using gbmt 0.1.4 [13]. Time was actual years since the first assessment; the three positions were 0, 2 and 4 years in CHARLS and 0, 4 and 8 years in HRS. Standardization used the complete-trajectory fitting sample within each cohort. Two-, three- and four-class candidates were screened. Eligible solutions required convergence, average posterior assignment probability at least 0.70 in every class, odds of correct classification at least 5 and class size at least 5%. We selected the lowest BIC among adequate candidates, reported entropy, and audited the selected solution with two random starts in addition to hierarchical initialization. Classes were ordered independently by mean predicted FI, with C0 the lowest-FI reference. Matching of standardized profiles was descriptive; it was not an external application of a trained classifier.

Individual SBP and FI slopes were estimated against calendar year across the three observations. Falling SBP was defined as slope at or below the within-cohort 25th percentile; rising SBP as at or above the 75th percentile; the middle 50% was the remaining category. Rapid FI increase was defined as slope at or above the cohort-specific 75th percentile. The comparator was nonrapid increase, not necessarily stable or improving FI. Thresholds were calculated without using outcomes. For CHARLS, SBP thresholds were − 3.344 and 3.250 mmHg/year and rapid FI increase was at least 2.900 FI points/year. The corresponding HRS values were − 1.750, 1.750 and 1.563. These relative categories are descriptive and are not clinical thresholds.

Outcomes, covariates and missing data

All-cause mortality used death year and month where available. If only year was recorded, a midyear date was assigned. Participants without a recorded death were censored at their last observed follow-up within the dataset boundary. Incident CVD was the first post-landmark report of physician-diagnosed heart disease or stroke. These broad self-reported outcomes were not adjudicated acute cardiovascular events. CVD onset was known only between assessments; exact onset dates were not manufactured for the primary model. Death before a subsequent CVD report terminated the period history as a competing event.

Model 1 included sex, with attained age supplying the mortality time scale. Model 2 added education, marital status, rural residence, socioeconomic quintile, BMI, smoking, drinking, physical activity, diabetes and antihypertensive use. Model 3 additionally included first-assessment SBP and FI. Covariates other than first SBP/FI were taken from the last available pre-landmark observation, with prior disease status carried across the formation period. The original CVD specification did not include an explicit age or HRS-sequence term; a separately labeled sensitivity analysis added landmark age and HRS sequence for CVD, and prior CVD plus sequence for mortality. This distinction preserves the requested primary specification while assessing its potential residual confounding.

Missing covariates were handled by iterative multivariate imputation with stochastic posterior sampling, including outcome and age/initial-status auxiliary variables. Binary and ordinal covariates were rounded and bounded to their admissible ranges. Estimates and robust within-imputation variances were pooled using Rubin's rules with normal-approximation confidence intervals [17]. Primary, selection-weighted and slope-decomposition analyses used 10 imputations; the remaining sensitivity analyses retained the original five-imputation specification so that they remain numerically comparable with the earlier analysis round. Exposure measurements were not imputed into the complete-trajectory fitting sample.

Selection, retention weighting and association models

We first compared the complete-trajectory sample with all baseline participants aged at least 65 years who had an initial paired SBP–FI observation, and with those not selected. Means, proportions and standardized mean differences quantified selection separately for the HRS sequences and after their combination. Formation-period deaths were reported separately. The post-landmark mortality comparison required observed landmark survival and was not calculated for people who died before the landmark.

Retention weighting used stabilized inverse probabilities of having usable follow-up, estimated from available person-level covariates and initial SBP/FI; endpoint-specific weights were truncated at their 1st and 99th percentiles. To address selection into three paired observations, we fitted separate logistic models for CHARLS and the HRS sequences using baseline age, sex, education, residence, BMI, SBP, FI, smoking, drinking, diabetes, treatment and CVD status. The selection-weight target was baseline-eligible participants documented alive at landmark. Stabilized inverse probability of selection weights (IPSW) were truncated at the 1st and 99th percentiles and multiplied by retention weights. These weights can mitigate observed selection among landmark survivors but cannot recover outcomes of people who died during trajectory formation or remove unmeasured selection.

Mortality associations used delayed-entry attained-age Cox models with ridge penalty 0.01 and robust standard errors. Reported incident CVD used person-period generalized estimating equations with a complementary log-log link, interval-length offset, period indicators and participant-clustered robust covariance. Death was handled by ending the risk history, not by claiming that the primary model estimated a Fine-Gray subdistribution hazard. Model 3 was repeated for rapid versus nonrapid FI increase within each SBP-direction stratum. Continuous, winsorized cohort-standardized SBP and FI slopes and their product assessed multiplicative interaction.

Incremental information, sensitivity analyses and synthesis

The decomposition compared four models on the same endpoint-specific sample: A, Model 3 covariates and initial status; B, A plus FI slope; C, B plus SBP slope; D, A plus joint class. Slope coefficients were expressed per cohort SD after 1st/99th percentile winsorization. We also calculated apparent Harrell C-

indices from auxiliary, weighted time-since-landmark Cox models including landmark age, averaged across 10 imputations. For CVD this ancillary metric used midpoint approximations to report intervals and treated death as censoring; it was not a validated competing-risk discrimination statistic. Differences in these apparent metrics do not establish out-of-sample predictive performance.

Sensitivity analyses delayed mortality follow-up by one or two years among survivors with sufficient follow-up, excluded selected baseline diseases, low BMI or prior CVD, censored before 2019, separated HRS sequences, and multiplied HRS survey and retention weights. Thirty posterior pseudo-class draws assessed classification uncertainty using the original median-covariate sensitivity specification. Diagnostic time-on-study Cox models with age adjustment supplied rank-transformed Schoenfeld tests; mortality associations were also estimated before and after four years. Heart disease and stroke components were examined separately. Descriptive Aalen-Johansen curves used ancillary midpoint CVD times and distinguished reported CVD from death before reported CVD, over a common five-year horizon where supported.

Only the highest-FI versus lowest-FI contrast was combined across cohorts using a two-stage DerSimonian-Laird random-effects model. Intermediate classes were not pooled because their profiles were not assumed identical. With only two cohorts, heterogeneity and pooled uncertainty remain imprecise. All secondary, subgroup and sensitivity comparisons are exploratory; no multiplicity adjustment or causal identification is claimed. Reproducibility files record seeds, software, model diagnostics and aggregate figure source data.

Results

Participants and selection

The complete-trajectory samples comprised 1,902 CHARLS participants and 3,839 HRS participants, including 1,988 in sequence A and 1,851 in sequence B. Mean age at trajectory entry was 70.8 and 72.2 years; mean landmark age was 74.8 and 80.2 years, respectively (Table 1). Mortality models included 1,875 participants and 348 deaths in CHARLS, and 3,726 participants and 1,063 deaths in HRS. The incident-CVD analyses included 1,368 participants with 263 reports and 2,095 participants with 331 reports, respectively.

Table 1
Characteristics of the complete-trajectory samples: CHARLS

Characteristic	Overall	C0	C1	C2	C3
Participants, n	1,902	432	520	471	479
Age at entry, years	70.8 (4.9)	69.9 (4.6)	70.5 (4.7)	71.5 (5.2)	71.4 (5.0)
Age at landmark, years	74.8 (4.9)	73.9 (4.6)	74.5 (4.7)	75.5 (5.2)	75.4 (4.9)
Women, n (%)	902 (47.4)	110 (25.5)	212 (40.8)	276 (58.6)	304 (63.5)
BMI, kg/m²	22.6 (3.8)	22.4 (3.5)	22.0 (3.5)	23.4 (4.0)	22.5 (4.0)
Initial SBP, mmHg	134.8 (22.6)	130.8 (19.2)	120.8 (14.6)	155.2 (19.4)	133.5 (21.5)
Initial FI, points	24.9 (14.2)	11.6 (4.1)	21.9 (7.5)	23.9 (9.4)	41.0 (14.5)
Education level, mean	1.1 (0.3)	1.2 (0.5)	1.1 (0.3)	1.0 (0.2)	1.0 (0.1)
Rural residence, n (%)	1,527 (80.3)	302 (69.9)	423 (81.3)	377 (80.0)	425 (88.7)
Current smoking, n (%)	523 (27.5)	153 (35.4)	166 (31.9)	119 (25.3)	85 (17.7)
Drinking, n (%)	550 (28.9)	154 (35.6)	170 (32.7)	130 (27.6)	96 (20.0)
Diabetes, n (%)	189 (10.0)	19 (4.4)	42 (8.1)	65 (13.8)	63 (13.2)
Antihypertensive use, n (%)	652 (34.4)	101 (23.4)	104 (20.1)	261 (55.4)	186 (39.0)
Prior CVD, n (%)	512 (27.0)	68 (15.8)	117 (22.5)	145 (30.8)	182 (38.1)

Continuous values are mean (SD); categorical percentages use observed denominators. Age at entry and landmark are distinguished. Covariates other than initial SBP/FI refer to the latest available pre-landmark observation. Education is a harmonized ordinal category, not years of schooling. C0–C3 are ordered by mean predicted FI (C0 lowest).

Table 1
(continued). Characteristics of the complete-trajectory samples: HRS

Characteristic	Overall	C0	C1	C2	C3
Participants, n	3,839	777	1,289	1,331	442
Age at entry, years	72.2 (5.4)	70.9 (5.0)	71.6 (4.9)	73.0 (5.6)	73.7 (6.0)
Age at landmark, years	80.2 (5.4)	78.9 (4.9)	79.6 (5.0)	81.0 (5.6)	81.7 (6.0)
Women, n (%)	2,204 (57.4)	384 (49.4)	708 (54.9)	828 (62.2)	284 (64.3)
BMI, kg/m²	28.4 (5.4)	27.0 (4.4)	28.2 (5.1)	29.1 (5.6)	29.6 (6.4)
Initial SBP, mmHg	131.9 (19.3)	133.8 (19.8)	127.1 (15.7)	134.4 (20.8)	134.6 (20.2)
Initial FI, points	19.5 (11.8)	7.6 (3.3)	15.2 (5.3)	24.1 (8.1)	38.9 (12.7)
Education level, mean	2.0 (0.6)	2.2 (0.6)	2.1 (0.6)	1.9 (0.6)	1.8 (0.7)
Rural residence, n (%)	1,117 (29.1)	210 (27.0)	367 (28.5)	399 (30.0)	141 (31.9)
Current smoking, n (%)	205 (5.3)	35 (4.5)	55 (4.3)	77 (5.8)	38 (8.6)
Drinking, n (%)	1,906 (49.6)	478 (61.5)	695 (53.9)	604 (45.4)	129 (29.2)
Diabetes, n (%)	1,021 (26.6)	142 (18.3)	323 (25.1)	388 (29.2)	168 (38.0)
Antihypertensive use, n (%)	2,576 (67.1)	442 (56.9)	822 (63.8)	971 (73.0)	341 (77.1)
Prior CVD, n (%)	1,677 (43.7)	207 (26.6)	500 (38.8)	700 (52.6)	270 (61.1)

Only about half of baseline-eligible participants entered the trajectory sample (CHARLS 1,902 of 3,678, 52%; HRS 3,839 of 8,724, 44%). Complete-trajectory participants were younger and less frail than excluded participants (CHARLS: mean age 70.8 versus 73.0 years, initial FI 24.9 versus 29.5 points, standardized mean differences − 0.39 and − 0.29; HRS: -0.64 and − 0.56). Excluded participants were also more often treated for hypertension (CHARLS 31.2% versus 23.0%) and had higher post-landmark mortality where landmark survival was observable (CHARLS 27.1% versus 18.3%). Deaths during the formation windows numbered 451 in CHARLS and 1,270 and 1,266 in HRS sequences A and B. The selection tables distinguish full eligible pools from documented landmark survivors and are provided in supplementary Tables S_A1a and S_A1b. These differences indicate substantial selection of younger, less frail survivors, rather than representative sampling of all older adults.

Independently estimated joint trajectories

The selected class counts were four in each cohort. Minimum posterior assignment probability was 0.846, minimum odds of correct classification 13.23, and minimum class proportion 11.5%. Entropy was 0.781 in CHARLS and 0.805 in HRS. Candidate-model BIC and random-start results are reported in supplementary Table S_A0. Figure 1 and Table 2 show the fitted values and annual slopes; labels prioritize FI severity rather than implying a uniform blood-pressure pattern.

Table 2
Independently fitted joint trajectory profiles

Cohort class	n (%)	SBP at 3 visits, mmHg	FI at 3 visits, points	SBP slope, mmHg/year	FI slope, points/year	APPA
CHARLS C0	432 (22.7%)	130.5 / 131.5 / 132.4	11.3 / 12.0 / 12.7	0.47	0.34	0.889
CHARLS C1	520 (27.3%)	121.5 / 121.7 / 121.8	20.7 / 22.1 / 23.4	0.06	0.68	0.858
CHARLS C2	471 (24.8%)	155.5 / 154.1 / 152.6	21.9 / 24.2 / 26.5	-0.73	1.13	0.846
CHARLS C3	479 (25.2%)	134.4 / 133.8 / 133.2	36.4 / 41.1 / 45.9	-0.30	2.37	0.920
HRS C0	777 (20.2%)	133.9 / 134.5 / 135.1	7.3 / 8.5 / 9.7	0.15	0.30	0.912
HRS C1	1,289 (33.6%)	127.7 / 127.6 / 127.6	14.3 / 17.0 / 19.6	-0.01	0.67	0.870
HRS C2	1,331 (34.7%)	134.7 / 134.1 / 133.5	22.6 / 27.0 / 31.4	-0.16	1.11	0.882
HRS C3	442 (11.5%)	135.5 / 135.0 / 134.5	36.1 / 43.6 / 51.0	-0.12	1.87	0.919

FI is on the 0–100 scale. Slopes are per calendar year. Class order is ascending mean FI within each cohort. The highest predicted mean SBP occurred in CHARLS C2 and HRS C3, whereas the highest-FI class was C3 in both cohorts; the high-FI label does not imply the highest SBP. APPA, average posterior probability of assignment. Values are fitted linear means, not individual observed measurements.

In CHARLS, the lowest-FI class increased from 11.3 to 12.7 FI points, whereas the highest-FI class increased from 36.4 to 45.9. The latter class had predicted SBP of 134.4, 133.8 and 133.2 mmHg; the highest predicted SBP occurred in C2 (155.5 mmHg at the first assessment). In HRS, the lowest-FI class

increased from 7.3 to 9.7 FI points, whereas the highest-FI class increased from 36.1 to 51.0, with predicted SBP of 135.5, 135.0 and 134.5 mmHg, marginally above C2 (134.7 mmHg). Correspondence between cohorts therefore concerns broad frailty risk architecture, not identical classes, absolute cutpoints or equal exposure durations.

Frailty accumulation within the same SBP direction

Among participants with falling SBP, rapid versus nonrapid FI increase was associated with mortality in CHARLS (HR 1.64, 95% CI 1.03–2.60) and HRS (HR 1.87, 95% CI 1.45–2.43). The corresponding reported incident-CVD estimates were HR 1.71 (95% CI 1.00–2.93) and HR 1.46 (95% CI 0.87–2.45) (Table 4; Fig. 4). The falling-SBP samples included 476 CHARLS participants and 960 HRS participants before endpoint-specific exclusions; the comparator included people with slower FI accumulation, not solely those with unchanged or improving FI.

Table 4
Rapid versus nonrapid FI increase within SBP direction, Model 3

Cohort	SBP direction	n before follow-up	Rapid FI n	Mortality HR (95% CI)	CVD HR (95% CI)
CHARLS	Falling	476	135	1.64 (1.03–2.60)	1.71 (1.00–2.93)
CHARLS	Middle 50%	950	229	2.15 (1.57–2.95)	1.59 (1.09–2.30)
CHARLS	Rising	476	112	1.75 (1.12–2.73)	1.57 (0.86–2.88)
HRS	Falling	960	264	1.87 (1.45–2.43)	1.46 (0.87–2.45)
HRS	Middle 50%	1,919	486	1.43 (1.19–1.73)	1.32 (0.89–1.96)
HRS	Rising	960	210	1.58 (1.17–2.14)	1.46 (0.87–2.47)

Ten imputations and endpoint retention weights. The displayed n is the complete-trajectory direction stratum before endpoint-specific follow-up exclusions; CVD eligibility is narrower. Falling and rising SBP are the lowest and highest slope quartiles; rapid FI increase is the highest FI-slope quartile, and nonrapid includes slower increases. Within-stratum comparisons do not test differences of the FI effect across SBP directions and are not treatment-effect estimates.

The same pattern held in the other SBP directions. Rapid FI increase was associated with mortality in the middle SBP category (HR 2.15, 95% CI 1.57–2.95 in CHARLS; 1.43, 1.19–1.73 in HRS) and among those with rising SBP (HR 1.75, 1.12–2.73; 1.58, 1.17–2.14). For CVD, the association was clearest in the middle category in CHARLS (HR 1.59, 1.09–2.30); the remaining within-direction CVD intervals included 1. Rapid FI increase was thus prognostic for mortality in all six cohort-by-direction cells. These contrasts describe FI-associated prognosis within strata; they do not test whether the FI association differs across SBP directions.

Mortality and incident CVD associations of joint classes

In Model 3, the highest-FI class versus C0 had a mortality HR of 1.65 (95% CI 1.18–2.31) in CHARLS and 2.21 (95% CI 1.64–2.97) in HRS (Table 3; Fig. 2). Incident-CVD estimates were HR 3.21 (95% CI 1.88–5.49) in CHARLS and HR 2.51 (95% CI 1.32–4.77) in HRS. The intermediate-class estimates are reported separately by cohort and were not pooled. The extreme-class random-effects summaries were 1.93 (95% CI 1.46–2.56; I^2 37.1%) for mortality and 2.90 (1.93–4.38; I^2 0%) for CVD; with only two cohorts, these summaries are descriptive. Adjustment for first SBP and FI distinguishes these comparisons from simple baseline frailty associations but does not isolate causal effects. Descriptive competing-risk curves distinguishing reported CVD from death before a subsequent report are shown in Fig. 4, over the supported five-year horizon; the available CHARLS follow-up does not justify a six-year estimate.

Table 3
All-cause mortality, hazard ratios (95% CI)

Contrast	Model 1	Model 2	Model 3	Model 3 P
CHARLS C1 vs C0	1.38 (1.05–1.81)	1.27 (0.96–1.67)	1.25 (0.94–1.66)	0.131
CHARLS C2 vs C0	1.65 (1.24–2.19)	1.52 (1.13–2.05)	1.37 (0.99–1.89)	0.055
CHARLS C3 vs C0	2.14 (1.62–2.82)	1.97 (1.48–2.60)	1.65 (1.18–2.31)	0.003
HRS C1 vs C0	1.12 (0.94–1.33)	1.09 (0.92–1.30)	1.10 (0.93–1.31)	0.266
HRS C2 vs C0	1.78 (1.50–2.10)	1.61 (1.36–1.90)	1.67 (1.37–2.02)	< 0.001
HRS C3 vs C0	2.59 (2.11–3.18)	2.04 (1.64–2.53)	2.21 (1.64–2.97)	< 0.001

Table 3
(continued). Reported incident CVD, hazard ratios (95% CI)

Contrast	Model 1	Model 2	Model 3	Model 3 P
CHARLS C1 vs C0	2.05 (1.39–3.03)	2.35 (1.57–3.52)	2.58 (1.69–3.91)	< 0.001
CHARLS C2 vs C0	2.25 (1.51–3.35)	2.16 (1.40–3.33)	2.17 (1.36–3.47)	0.001
CHARLS C3 vs C0	2.52 (1.68–3.77)	2.67 (1.76–4.06)	3.21 (1.88–5.49)	< 0.001
HRS C1 vs C0	1.80 (1.31–2.47)	1.76 (1.28–2.43)	1.75 (1.24–2.47)	0.002
HRS C2 vs C0	2.25 (1.63–3.12)	2.22 (1.57–3.12)	1.98 (1.28–3.04)	0.002
HRS C3 vs C0	3.12 (2.05–4.76)	3.06 (1.96–4.76)	2.51 (1.32–4.77)	0.005

C0 is the cohort-specific lowest-FI reference. All estimates use the primary specification, endpoint-specific retention weighting and 10 covariate imputations. Mortality uses attained-age Cox models with ridge 0.01 and robust variance; CVD uses interval-length-adjusted complementary log-log GEE. Model 1: sex; Model 2: additional socioeconomic, behavioral, BMI, diabetes and treatment covariates; Model 3: additional first SBP and FI. Explicit age/sequence adjustment for CVD is a separate sensitivity analysis.

Slope decomposition and incremental information

The FI slope carried the prognostic signal; the SBP slope did not. Mutually adjusted, per-SD mortality estimates for the FI slope were 1.35 (95% CI 1.22–1.50) in CHARLS and 1.27 (1.19–1.36) in HRS, versus 1.06 (0.94–1.18) and 0.94 (0.87–1.02) for the SBP slope. No multiplicative SBP-slope-by-FI-slope interaction was detected for mortality or CVD in either cohort (all P values 0.35–0.61); this is absence of detected multiplicative interaction, not proof of an exact zero effect.

Apparent mortality C-indices were 0.707 for initial status (model A), 0.723 after adding the FI slope (B), 0.723 after also adding the SBP slope (C), and 0.711 after adding joint classes instead (D) in CHARLS; the corresponding HRS values were 0.732, 0.749, 0.749 and 0.742. Joint classes therefore never outperformed initial status plus the FI slope for mortality (change in C-index over A: 0.004 and 0.010, versus 0.015 and 0.017 for the FI slope). For CVD, classes added modest apparent discrimination in CHARLS (A 0.619 to D 0.644) but not in HRS (0.619 to 0.628), where the FI slope alone performed comparably (supplementary Table S_A3). These are apparent, not externally validated, metrics.

Robustness and selection weighting

With IPSW multiplied by retention weights, extreme-class associations were 1.57 (95% CI 1.11–2.20) for mortality and 3.02 (1.75–5.23) for reported incident CVD in CHARLS; the corresponding HRS estimates were 2.14 (1.56–2.95) and 2.40 (1.25–4.60). Starting mortality follow-up at year 2 among survivors attenuated the CHARLS estimate (1.15, 0.77–1.72) but not the HRS estimate (2.16, 1.51–3.09); thirty posterior class draws gave 1.82 (1.24–2.67) and 2.21 (1.62–3.02) (Fig. 3; supplementary tables). Combined endpoint weights had 99th percentiles of at most 1.82 and effective sample size fractions of 96.1–96.8%. These estimates, including their attenuation and uncertainty, are reported without requiring that every sensitivity analysis remain statistically significant. Additional adjustment for age and HRS sequence in CVD, and prior CVD and sequence in mortality, is shown separately from the primary specifications; time-stratified estimates and proportional-hazards diagnostics are provided so that a single HR is not assumed constant across follow-up.

Discussion

Principal findings

Three findings emerge, each closing one question posed at the outset. First, joint trajectories were recoverable in both cohorts, but they were ordered by frailty, not by blood pressure. The highest-risk class combined ordinary-to-moderate SBP (134.4 mmHg in CHARLS, 135.5 in HRS) with the highest and most rapidly rising frailty index (36.4 to 45.9 points over four years in CHARLS; 36.1 to 51.0 over eight years in HRS), whereas the class with the highest SBP (CHARLS C2, 155.5 mmHg) carried only intermediate frailty. The intuitive archetype of a “high blood pressure, high frailty” phenotype did not emerge in either cohort.

Second, blood pressure direction carried no independent prognostic signal. Rapid frailty increase was associated with mortality within every SBP direction—falling, stable and rising—in both cohorts (HRs 1.43–2.15 across all six cohort-by-direction cells), the continuous SBP-slope-by-FI-slope interaction was null, and the SBP slope itself was unassociated with mortality (HR per SD 1.06 in CHARLS and 0.94 in HRS). Falling blood pressure is therefore not a distinct risk state; it is one of several settings in which the same frailty signal can be missed. Its clinical importance is not that it is special, but that it is the setting in which misreading is most likely and most costly: a falling SBP is the reading most often filed as success.

Third, the joint classification did not improve on a simpler description. Adding classes to initial SBP and FI changed the apparent mortality C-index by 0.004 (CHARLS) and 0.010 (HRS), and the four-class model did not outperform a model with initial status plus the FI slope alone (CHARLS C 0.711 versus 0.723); for CVD the classes added modest discrimination in CHARLS but not in HRS. The value of the joint classes is descriptive and clinically interpretive—locating an individual within a longitudinal profile—not predictive.

Finally, the price of observing three paired measurements was substantial and is now quantified: only 52% of CHARLS and 44% of HRS baseline-eligible participants entered the trajectory sample, and they were younger, less frail and less often treated than those excluded, with 451 and 2,536 deaths during formation in CHARLS and HRS respectively. Stabilized selection weighting left the extreme-class associations essentially unchanged, indicating robustness among landmark survivors, but no weighting scheme can speak for participants who died before the exposure window closed. These phenotypes describe survivors of the trajectory period, not all adults aged 65 and older.

Comparison with existing evidence

These observations extend earlier work on frailty-stratified blood-pressure associations by considering both longitudinal measurements before outcome surveillance [2, 3]. Ravindrarajah and colleagues described declining SBP near the end of life in adults over 80 years, illustrating why low or falling SBP can reflect reverse causation [4]. Satish and colleagues likewise examined the clinical significance of falling blood pressure in older adults [5]. Chinese studies have related SBP trajectories or blood-pressure change to frailty and mortality, while multi-state analyses have studied blood pressure preceding frailty transitions [10–12]. Our design does not overturn that literature; it adds within-direction frailty comparisons, explicit slope decomposition and quantified selection across two cohorts.

The null multiplicative interaction does not negate the clinical phenotypes: classes encode combinations of level and slope that a product term cannot represent, but the data do not support a claim of biological synergy. Equally, the within-direction homogeneity of the FI association argues against reading any blood-pressure direction as intrinsically benign or malignant; the prognostic content lies in the frailty course measured alongside it.

Differences between the cohorts remain informative rather than inconvenient. HRS participants had a longer exposure-formation period and were older at landmark; health care, questionnaire wording and disease recognition also differ. Absolute slope thresholds and intermediate classes therefore need not match. Only the extreme-FI contrast was synthesized, and the two-cohort heterogeneity estimate should not be read as evidence that the common entry-age restriction has resolved cross-country differences.

Clinical and research implications

The practical residue is narrow but real: when an older adult's blood pressure falls, the frailty course should be read alongside the number—weight, function, mood, comorbidity burden—because a falling SBP accompanied by rapidly accumulating deficits marked a mortality risk (HR 1.64 and 1.87 in the two cohorts) that the falling number alone did not resolve. This is a prompt for broader assessment, not a demonstrated mechanism. These observational findings do not justify relaxing blood-pressure targets, stopping antihypertensive drugs, or interpreting a rise in SBP as protective.

For research, joint trajectories provide a clinically interpretable longitudinal description, but they are not yet a stand-alone risk calculator: apparent discrimination is not externally validated, cohort-specific thresholds are relative, and three sparse assessments cannot separate treatment response from disease-related change. Future studies should use denser measurements, documented treatment changes, adjudicated events and designs that distinguish within-person health decline from treatment effects, and should test transportability by applying a fitted classification rule to an external cohort rather than by independent model fitting.

Strengths and limitations

Selection and survivor bias are the foremost limitations. Completing three assessments required survival and continued participation for four years in CHARLS and eight years in HRS. The selected participants were younger and less frail than excluded baseline-eligible participants, with substantial formation-period mortality. IPSW addressed measured selection among documented landmark survivors and produced stable weights, but it cannot reconstruct outcomes of formation-period decedents, correct unobserved health trajectories or establish generalizability to all adults aged 65 years and older. National sampling frames do not make this complete-measurement analysis nationally representative.

This was an exploratory secondary analysis, and the entry-age restriction and additional contrasts were introduced during manuscript revision after an earlier broader-age analysis. They were not part of a prospectively registered protocol. The revised estimates should therefore be treated as hypothesis-generating, with future preregistered replication needed.

Second, the cohorts differed in measurement intervals and landmark age despite a common entry-age restriction. Blood-pressure aggregation in the supplied working variables could not be harmonized anew from raw readings. The FI used common concepts but some questions and depressive-symptom scales differed; formal measurement invariance was not tested. Gaussian latent-class models approximate a

bounded FI and continuous heterogeneity, and selected classes depend on candidate numbers and initialization. Posterior-draw sensitivity does not replace a complete bootstrap of model selection.

Third, heart disease and stroke were self-reported, and their dates were interval censored. Undiagnosed events before death can be missed, and the primary CVD model is not a subdistribution model. Midpoint curves and C-indices are explicitly ancillary approximations. Death-year imputation and differing follow-up periods add timing uncertainty. Fourth, residual confounding, treatment indication, reverse causation and time-varying illness remain possible. The original CVD adjustment omitted an explicit age term, which we addressed only in a separately labeled sensitivity analysis. Averaged Cox HRs may conceal time-varying associations; delayed-start and time-stratified results were reported rather than assuming proportionality.

The main strengths are the landmark ordering of exposure and outcomes, the common-concept noncardiovascular FI, independent cohort-specific model screening, comparisons within the same SBP direction, explicit separation of selection weighting, adjusted association, slope decomposition and apparent discrimination, and the quantified selection analysis. These features improve transparency but do not convert an observational analysis into evidence about optimal treatment targets.

Conclusions

In adults aged 65 and older who survived and completed three paired assessments, the frailty trajectory carried the prognostic signal for mortality and reported cardiovascular disease within every direction of blood-pressure change. Independently fitted joint classes described these patterns parsimoniously, but they did not improve on a simpler model of initial status plus frailty slope, and the three-measurement requirement selected a younger, less frail survivor population whose experience these phenotypes describe. When blood pressure falls in an older adult, the course of health deficits should be read alongside the number. These longitudinal phenotypes inform interpretation and hypothesis generation; they do not define treatment targets or a validated prediction instrument.

Abbreviations

ADL, activities of daily living; BIC, Bayesian information criterion; CHARLS, China Health and Retirement Longitudinal Study; CVD, cardiovascular disease; FI, frailty index; HR, hazard ratio; HRS, Health and Retirement Study; IADL, instrumental activities of daily living; IPCW, inverse probability of censoring or retention weighting; IPSW, inverse probability of selection weighting; SBP, systolic blood pressure; SD, standard deviation; SMD, standardized mean difference.

Declarations

Ethics approval and consent to participate

This study is a secondary analysis of existing CHARLS and HRS working datasets. The CHARLS and HRS study protocols were approved by the Peking University ethics review committee (IRB00001052-11015) and the University of Michigan institutional review board, respectively, with written informed consent obtained from participants under the source-study protocols. The present secondary analysis used de-identified public-use data and was exempted from ethics review by the authors' institutional ethics committee.

Consent for publication

Not applicable. The manuscript presents aggregate results and no identifiable participant material.

Clinical trial number

Not applicable.

Availability of data and materials

Participant-level CHARLS and HRS data are available to registered researchers from the respective study websites under their data-use terms. Analysis code, variable mappings, aggregate result tables and figure source data are assembled in a reproducibility package prepared for public repository deposit upon acceptance; no repository accession or DOI is represented as existing.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Authors' contributions

P.H. conceptualised the study, conducted the formal analysis, developed the methodology and wrote the original draft. Y.L. and L.J. curated data and validated results. Z.Y. supervised the project and reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the CHARLS and HRS participants and study teams. HRS is sponsored by the National Institute on Aging (U01 AG009740) and conducted by the University of Michigan. During the preparation of this work the authors used AI-assisted tools for language editing, code drafting and output organisation. All numerical results, code, references and interpretations were independently reviewed and verified by the authors, who take full responsibility for the integrity of the work.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957–80. 10.1016/S0140-6736(21)01330-1.
2. Todd OM, Wilkinson C, Hale M, Wong NL, Hall M, Sheppard JP, et al. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. Age Ageing. 2019;48:627–35. 10.1093/ageing/afz072.
3. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med. 2012;172:1162–8. 10.1001/archinternmed.2012.2555.
4. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality over 80 years of age: cohort study using electronic health records. Circulation. 2017;135:2357–68. 10.1161/CIRCULATIONAHA.116.026687.
5. Satish S, Zhang DD, Goodwin JS. Clinical significance of falling blood pressure among older adults. J Clin Epidemiol. 2001;54:961–7. 10.1016/S0895-4356(01)00360-2.
6. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24. 10.1186/1471-2318-8-24.
7. Fan J, Yu C, Guo Y, Bian Z, Sun Z, Yang L, et al. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. Lancet Public Health. 2020;5:e650–60. 10.1016/S2468-2667(20)30113-4.
8. Li X, Schottker B, Holleczek B, Brenner H. Association of longitudinal repeated measurements of frailty index with mortality: cohort study among community-dwelling older adults. EClinicalMedicine. 2022;53:101630. 10.1016/j.eclinm.2022.101630.
9. Chamberlain AM, Finney Rutten LJ, Manemann SM, Yawn BP, Jacobson DJ, Fan C, et al. Frailty trajectories in an elderly population-based cohort. J Am Geriatr Soc. 2016;64:285–92. 10.1111/jgs.13944.
10. Yu BY, Hu XM, Matala R, Mo YH, Liu JL, Jin JG, et al. Association between trajectories of systolic blood pressure and frailty outcome in middle-aged and older adults. J Nutr Health Aging. 2024;28:100202. 10.1016/j.jnha.2024.100202.

11. Chen Y, Wang Y, Xu Y, Shi S, Tian Z, Jiang K, et al. Relationship between changes in late-life blood pressure and the risk of frailty and mortality among older population in China: a cohort study based on CLHLS. Hypertens Res. 2024;47:1881–91. 10.1038/s41440-024-01674-y.
12. Anker D, Carmeli C, Zwahlen M, Rodondi N, Santschi V, Henchoz Y, et al. How blood pressure predicts frailty transitions in older adults in a population-based cohort study: a multi-state transition model. Int J Epidemiol. 2022;51:1167–77. 10.1093/ije/dyab210.
13. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. Stat Methods Med Res. 2018;27:2015–23. 10.1177/0962280216673085.
14. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43:61–8. 10.1093/ije/dys203.
15. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort profile: the Health and Retirement Study (HRS). Int J Epidemiol. 2014;43:576–85. 10.1093/ije/dyu067.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7. 10.7326/0003-4819-147-8-200710160-00010.
17. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393. 10.1136/bmj.b2393.

Figures

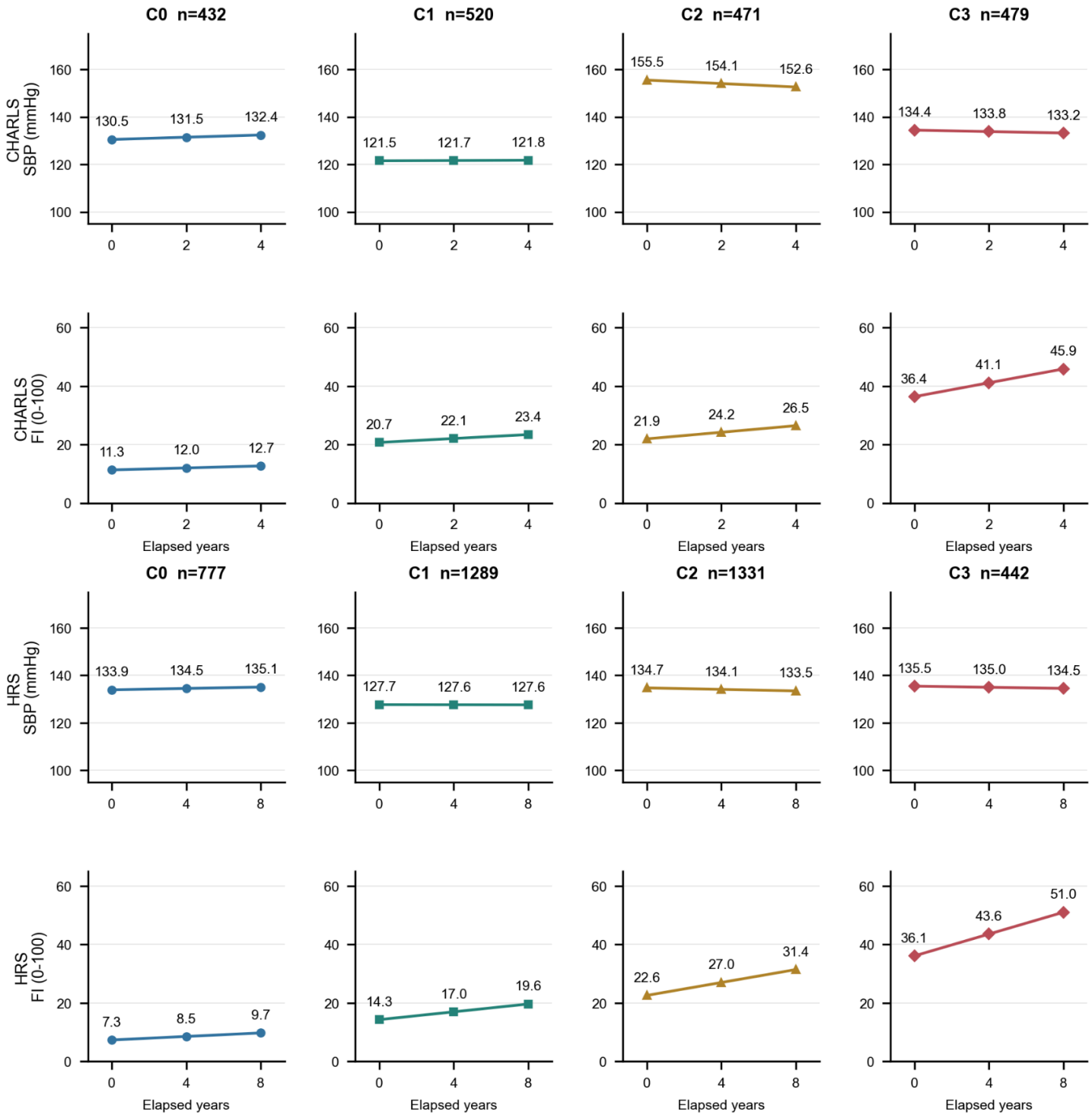


Figure 1

Independently estimated joint SBP–frailty profiles in CHARLS and HRS. Each column is a within-cohort class ordered by mean FI. Fitted SBP and FI values at all three visits are annotated. Time is actual elapsed years (CHARLS 0, 2, 4; HRS 0, 4, 8). Class n counts participants with three paired measurements. The highest mean SBP occurred in CHARLS C2 and HRS C3, which need not coincide with the highest-FI class. Lines are fitted means, not causal trajectories.

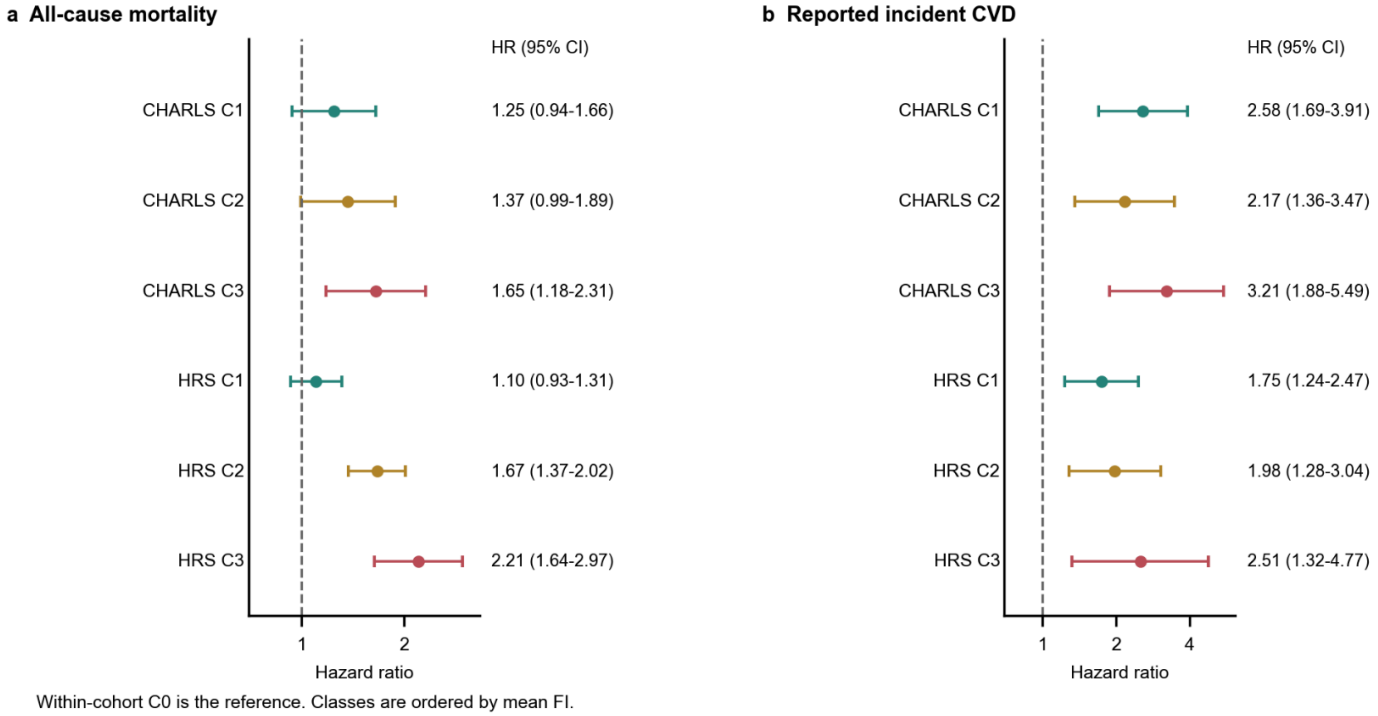


Figure 2

Model 3 adjusted associations of joint class with mortality and reported incident CVD. Cohort-specific classes are compared with the lowest-FI C0 reference. Points show HRs; bars show robust 95% CIs pooled across 10 imputations. The mortality time scale is attained age. CVD uses person-period complementary log-log GEE. Intermediate classes are not pooled or presumed identical across countries.

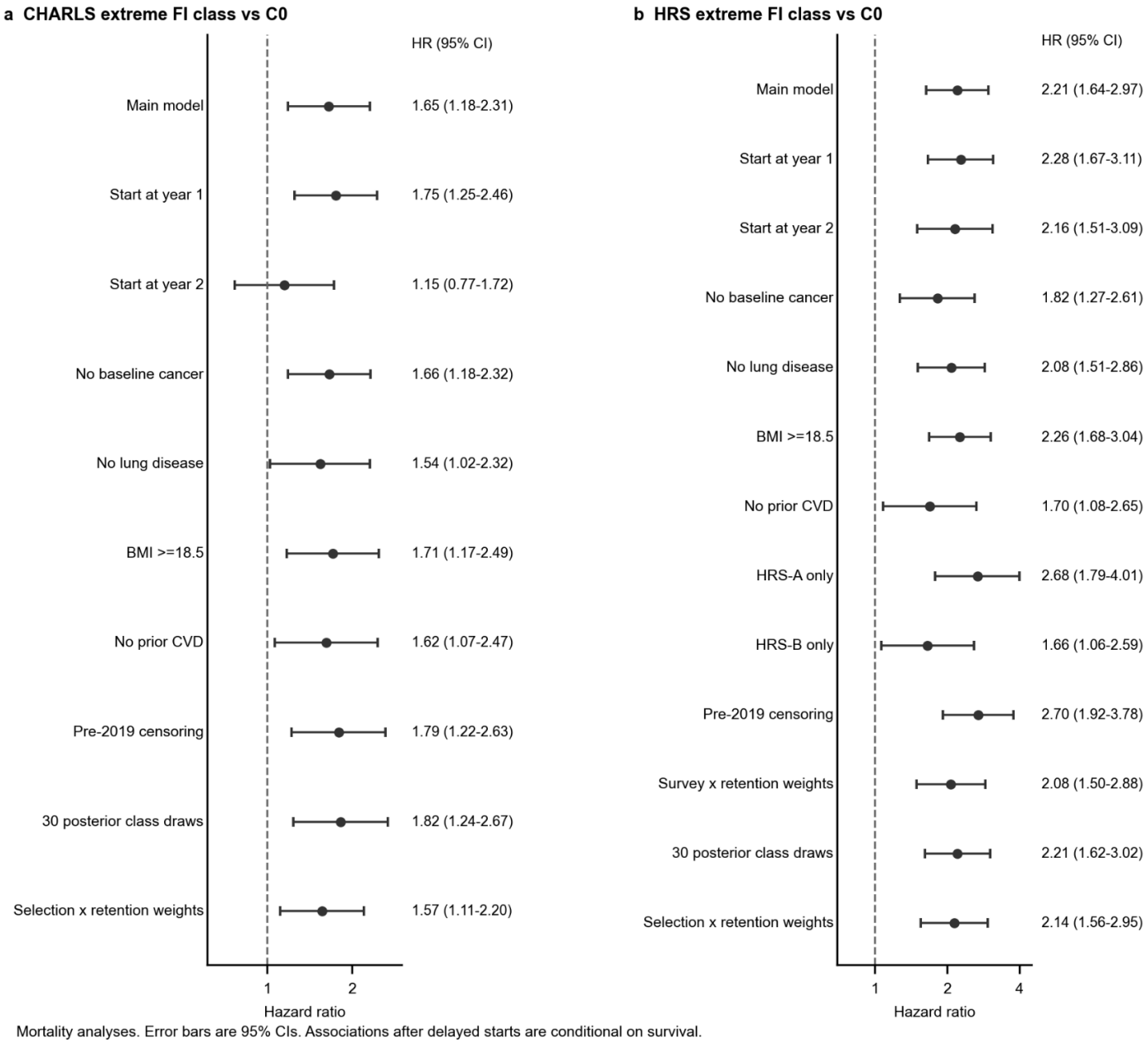


Figure 3

Mortality robustness analyses for the highest-FI versus lowest-FI class. The main and IPSW-by-retention-weighted analyses use 10 imputations; most remaining sensitivity analyses retain the original five-imputation specification for comparability with the earlier analysis round. Year 1/2 analyses begin follow-up later among documented survivors, using delayed entry. Posterior sensitivity uses 30 draws and the original median-covariate specification. Error bars are 95% CIs. Weight stability does not establish absence of unmeasured selection.

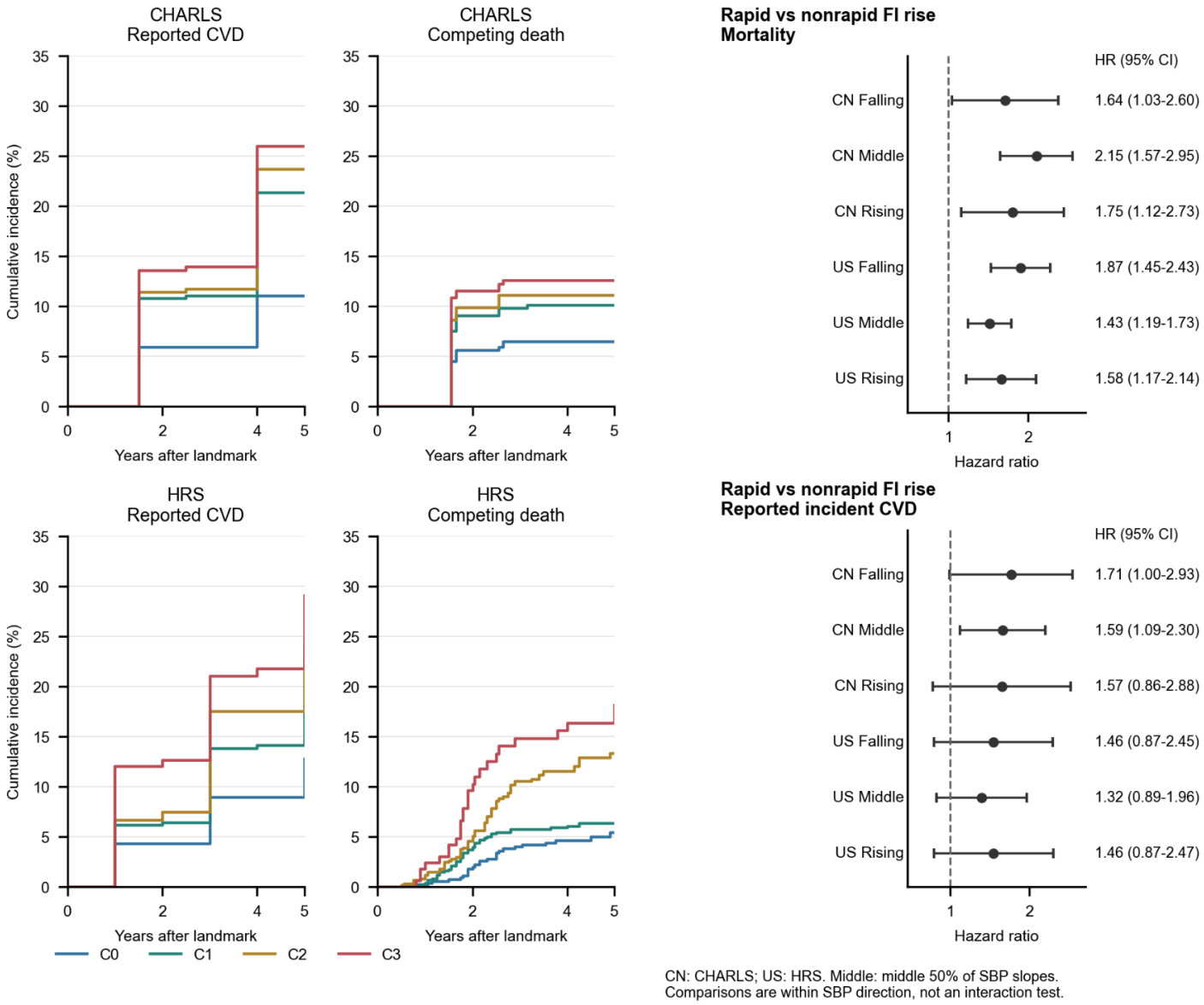


Figure 4

Cumulative incidence and within-direction comparisons. Left: unadjusted Aalen-Johansen estimates for reported CVD and death before reported CVD over the supported common five-year range. Ancillary CVD times use interval midpoints; no six-year CHARLS risk is extrapolated. Right: Model 3 rapid versus nonrapid FI increase contrasts within falling, middle-quartile and rising SBP groups; points and bars show HRs and 95% CIs with 10 imputations and retention weights. CN denotes CHARLS; US denotes HRS. These contrasts are not interaction or causal treatment tests.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables.docx