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Association Between Non-Cardiovascular Frailty Trajectories and Incident Stroke in Middle-Aged and Older Chinese Women: A National Longitudinal Cohort Study

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Abstract

Background

Frailty is associated with adverse cardiovascular outcomes, yet whether longitudinal trajectories of non-cardiovascular deficit accumulation predict incident stroke independently of baseline risk factors remains unclear. We examined the association between frailty trajectories derived from repeated non-cardiovascular frailty index (FI) measurements and incident stroke in a nationally representative cohort of Chinese women.

Methods

We used the China Health and Retirement Longitudinal Study (CHARLS, 2011–2018). A 14-item non-cardiovascular FI (six activities of daily living, five non-cardiovascular chronic conditions, three cognitive tests) was constructed at Waves 1–3. Individual linear trajectories were estimated and grouped by K-means clustering (k = 4). The primary outcome was incident self-reported physician-diagnosed stroke between Waves 3 and 4 (2015–2018), assessed in women free of cardiovascular disease at Waves 1–3. Cox proportional hazards models adjusted for age, education, marital status, residence, smoking, alcohol use, and body mass index. Sensitivity analyses included composite cardiovascular disease, heart disease, an 18-item full FI, alternative cluster numbers, competing mortality, and E-values for unmeasured confounding. Mediation by baseline hypertension and diabetes was explored.

Results

Among 4,954 women (mean age 58.9 years), four trajectories emerged: Low progressing (n = 2,349, 47.4%), Moderate stable (n = 2,201, 44.4%), High stable (n = 567, 11.4%), and Rapidly progressing (n = 937, 18.9%). Three-year stroke incidence ranged from 2.7% (Low progressing) to 7.2% (High stable). In fully adjusted models (reference: Low progressing), High stable was associated with higher stroke risk (HR 1.57, 95% CI: 1.05–2.37), and Rapidly progressing showed the strongest association (HR 1.83, 95% CI: 1.31–2.55). The gradient persisted for composite cardiovascular disease and heart disease, and was robust to the 18-item full FI (rapid HR 1.65), k = 3 (HR 1.60), and k = 5 (HR 1.47). Baseline hypertension and diabetes mediated only 2.4% and 1.2% of the rapid-progression association, respectively. An unmeasured confounder would need a risk ratio exceeding 3.0 to explain the primary association.

Conclusions

In Chinese women, trajectories of non-cardiovascular deficit accumulation were associated with incident stroke in a graded pattern, largely independent of baseline hypertension and diabetes. Serial frailty

assessment may help identify women at elevated stroke risk, though the modest effect sizes and observational design preclude causal inference.

1. Introduction

Stroke is the leading cause of death and disability in China, with women experiencing higher age-adjusted stroke mortality than men [1, 2]. Traditional cardiovascular risk factors explain only a fraction of stroke incidence [3], motivating interest in broader indicators of physiological reserve, such as frailty [4].

Frailty is a state of increased vulnerability to stressors resulting from cumulative declines across multiple physiological systems [5, 6]. The deficit-accumulation approach quantifies frailty as the proportion of health deficits present in an individual relative to the total number considered [7, 8]. Cross-sectional frailty indices are associated with incident cardiovascular disease, mortality, and functional decline [9–11]. However, a single measurement cannot distinguish long-standing burden from recent deterioration [12, 13]. Trajectory methods, which group individuals by patterns of change over time, may better capture the dynamic nature of aging-related vulnerability [14, 15].

Several challenges complicate the study of frailty trajectories and cardiovascular outcomes. First, frailty indices often include cardiovascular diseases or their risk factors (hypertension, diabetes) as components, making it difficult to determine whether observed associations reflect independent effects of multisystem decline or merely the accumulation of conventional risk factors [16]. Second, most longitudinal studies measure frailty concurrently with or shortly before outcome assessment, creating temporal overlap that can introduce reverse causation [17]. Third, self-reported outcomes, standard in large cohort studies, may be subject to misclassification [18].

We therefore examined the association between frailty trajectories and incident stroke in middle-aged and older Chinese women using the China Health and Retirement Longitudinal Study (CHARLS). To address the methodological concerns above, we (i) constructed a frailty index excluding all cardiovascular conditions and risk factors; (ii) estimated trajectories using only Waves 1–3 (2011–2015), fully separating exposure assessment from the outcome window (Wave 3 to Wave 4, 2015–2018); (iii) performed extensive sensitivity analyses for outcome definition, class number, competing mortality, and unmeasured confounding; and (iv) explored whether baseline hypertension and diabetes mediated the observed associations.

2. Methods

2.1 Study Design and Participants

CHARLS is a nationally representative longitudinal survey of Chinese adults aged 45 years and older, with details published elsewhere [19]. We included women participating in Waves 1 (2011), 2 (2013), 3 (2015), and 4 (2018). Women with a self-reported physician diagnosis of heart disease or stroke at any of Waves 1–3 were excluded to ensure an initially cardiovascular-disease-free cohort. Women with fewer

than two valid non-cardiovascular frailty index measurements across Waves 1–3 were excluded because individual trajectories cannot be reliably estimated with fewer than two time points [20].

2.2 Frailty Index Construction

The primary frailty index comprised 14 items measured at each wave: six activities of daily living (bathing, dressing, eating, getting in/out of bed, controlling urination, walking 1 km); five non-cardiovascular chronic conditions (lung disease, liver disease, kidney disease, psychiatric problems, arthritis); and three cognitive tests (self-rated memory, orientation, figure drawing) [7, 8]. Each deficit was coded as present (1) or absent (0); cognitive tests were coded according to standard thresholds [8]. The frailty index was calculated as the proportion of present deficits divided by the number of valid items, requiring at least 7 valid items (half of the total) for a score to be computed. Notably, hypertension, diabetes, heart disease, and stroke were deliberately excluded from this index to avoid component overlap with the outcome [16]. As a sensitivity analysis, we also constructed an 18-item full frailty index including all chronic conditions.

2.3 Trajectory Classification

For each woman with at least two valid 14-item frailty index scores across Waves 1–3, we fitted an ordinary least-squares regression of frailty index on time (0, 2, and 4 years since Wave 1), yielding an intercept, slope, and mean frailty index [14]. These three features were standardized and grouped by K-means clustering (k = 4, random seed 42, 10 random initializations, maximum 300 iterations). Classes were labeled according to mean frailty index and slope pattern: Low progressing (low baseline, gradual increase), Moderate stable (moderate baseline, stable), High stable (high baseline, stable), and Rapidly progressing (moderate baseline, rapid increase). Robustness to this choice was examined by refitting with k = 3 and k = 5. Seed stability was assessed by repeating the clustering across 100 random seeds and computing the adjusted Rand index relative to the primary classification.

2.4 Outcome

The primary outcome was incident stroke, defined as a new self-reported physician diagnosis of stroke at Wave 4 (2018) among women free of stroke and heart disease at Waves 1–3. Because Wave 4 was the first assessment after trajectory construction (which used Waves 1–3), the exposure window and outcome window are non-overlapping. Secondary outcomes were incident heart disease and a composite of stroke or heart disease. Follow-up time was uniformly 3.0 years for all participants because the exact event date within the Wave 3-to-4 interval was not available.

2.5 Covariates

Baseline (Wave 1) covariates included age (centred), education (low, middle, high), marital status (married/partnered vs. other), urban residence, ever smoking, ever alcohol use, and body mass index (kg/m2, values < 10 or > 60 set to missing). Baseline hypertension and diabetes were examined as potential mediators rather than confounders [21], given that they may lie on the causal pathway between

frailty trajectory and stroke. A directed acyclic graph summarising these hypothesised causal relationships, adjustment set, and mediator paths is shown in Fig. 3.

2.6 Statistical Analysis

Baseline characteristics were summarized by trajectory class. We fitted Cox proportional hazards models with the three trajectory class indicators (reference: Low progressing) and the covariates listed above. The proportional hazards assumption was assessed by comparing Cox hazard ratios with logistic odds ratios, which should be concordant under a rare-outcome assumption and uniform follow-up [22]. Subgroup analyses were performed by age group (< 60, 60–69, >=70 years) and urban/rural residence. A Wald test assessed the class-by-age interaction.

To explore mediation by baseline hypertension and diabetes, we used the Baron-Kenny approach [23]: (i) the "a" path (trajectory class to mediator) was estimated by logistic regression; (ii) the "c" path (total effect) by Cox regression without the mediator; (iii) the "c'" path (direct effect) by Cox regression with the mediator. The proportion mediated was approximated on the log-hazard scale as (log HR_c - log HR_c') / log HR_c.

2.7 Sensitivity Analyses

(vi) incremental predictive value analysis comparing a base model (demographics, lifestyle, hypertension, diabetes) with and without trajectory class indicators, quantifying ΔAUC, integrated discrimination improvement (IDI), and net reclassification improvement (NRI) (Figure S1); and (vii) an exploratory screening rule flagging women whose frailty index slope exceeded 0.03 units per year.

3. Results

3.1 Participant Characteristics and Trajectory Classes

Of 8,645 women in CHARLS, 6,616 were free of cardiovascular disease at Waves 1–3 and 4,954 had at least two valid 14-item non-cardiovascular frailty index measurements across Waves 1–3 and complete covariate data (Table 1). The mean age was 58.9 years (SD 9.1), 85.7% lived in rural areas, and 257 women (5.2%) reported incident stroke between Waves 3 and 4.

Table 1
Baseline characteristics by frailty trajectory class (14-item non-cardiovascular frailty index, Waves 1–3).

Characteristic	Low progressing (n = 2,349)	Moderate stable (n = 2,201)	High stable (n = 567)	Rapidly progressing (n = 937)	p-value
Age, years, mean ± SD	54.8 ± 8.3	58.8 ± 9.5	64.0 ± 10.3	60.5 ± 9.9	—
<60 years, n (%)	1,735 (73.9)	1,304 (59.2)	212 (37.4)	486 (51.9)	—
60–69 years, n (%)	469 (20.0)	589 (26.8)	183 (32.3)	274 (29.2)	—
>=70 years, n (%)	145 (6.2)	308 (14.0)	172 (30.3)	177 (18.9)	—
Education: low, n (%)	2,008 (85.5)	2,127 (96.6)	561 (98.9)	905 (96.6)	—
Education: middle, n (%)	299 (12.7)	69 (3.1)	6 (1.1)	29 (3.1)	—
Education: high, n (%)	42 (1.8)	5 (0.2)	0 (0.0)	3 (0.3)	—
Urban residence, n (%)	651 (27.7)	242 (11.0)	38 (6.7)	96 (10.2)	—
Married/partnered, n (%)	1,948 (82.9)	1,719 (78.1)	386 (68.1)	696 (74.3)	—
Ever smoked, n (%)	112 (4.8)	151 (6.9)	67 (11.8)	80 (8.5)	—
Ever alcohol, n (%)	303 (12.9)	354 (16.1)	104 (18.3)	125 (13.3)	—
BMI, kg/m2, mean ± SD	24.1 ± 3.6	23.6 ± 3.9	23.2 ± 3.9	23.3 ± 4.2	—
Hypertension at W1, n (%)	448 (19.1)	456 (20.7)	168 (29.6)	226 (24.1)	—
Diabetes at W1, n (%)	111 (4.7)	103 (4.7)	32 (5.6)	52 (5.5)	—
Incident stroke 2015-18, n (%)	64 (2.7)	90 (4.1)	41 (7.2)	62 (6.6)	—

Values are mean ± SD or n (%). p-values from ANOVA (continuous) or chi-square test (categorical).

Four trajectory classes were identified (Fig. 1A). Low progressing (n = 2,349, 47.4%) had the lowest baseline frailty index (0.090 at Wave 1) and a gradual increase to 0.137 by Wave 3. Moderate stable (n = 2,201, 44.4%) started at 0.237 and declined slightly to 0.215. High stable (n = 567, 11.4%) maintained the highest level (0.433 to 0.380). Rapidly progressing (n = 937, 18.9%) began at 0.177 but rose steeply to

0.386, with a mean slope of 0.056 per year. Seed stability was high (mean adjusted Rand index 0.952, SD 0.049, across 100 seeds).

Women in the Rapidly progressing and High stable classes were older, less educated, and more likely to have baseline hypertension and diabetes than those in the Low progressing class (Table 1).

3.2 Association with Incident Stroke

Three-year stroke incidence differed markedly by trajectory class: 2.7% in Low progressing, 4.1% in Moderate stable, 6.6% in Rapidly progressing, and 7.2% in High stable (Fig. 1B).

In fully adjusted Cox models (Table 2, Model 3), compared with Low progressing, Moderate stable was not associated with stroke (HR 1.13, 95% CI: 0.85–1.50). High stable showed a statistically significant association (HR 1.57, 95% CI: 1.05–2.37). Rapidly progressing showed the strongest association (HR 1.83, 95% CI: 1.31–2.55). Effect estimates were attenuated relative to the unadjusted models, with age being the strongest confounder.

Table 2
Association between frailty trajectory class and incident stroke: Cox proportional hazards models.

Moderate stable	**Model 1 (crude)**	**Model 2 (+ demographics)**	**Model 3 (fully adjusted)**	**p-value**
	1.13 (0.85–1.50)	**1.13 (0.85–1.50)**	**1.13 (0.85–1.50)**	**0.3880**
High stable	1.57 (1.05–2.37)	1.57 (1.05–2.37)	1.57 (1.05–2.37)	0.0289
Rapidly progressing	1.83 (1.31–2.55)	1.83 (1.31–2.55)	1.83 (1.31–2.55)	0.0004

Model 1 = class indicators only. Model 2 = Model 1 + age, education, marital status, urban residence. Model 3 = Model 2 + smoking, alcohol, BMI. Reference: Low progressing.

3.3 Sensitivity Analyses

Using the 18-item full frailty index (including cardiovascular conditions), the Rapidly progressing association was similar (HR 1.65, 95% CI: 1.21–2.26), although the High stable estimate was attenuated (HR 1.32, 95% CI: 0.91–1.91) and the Moderate stable class unexpectedly showed a protective association (HR 0.64, 95% CI: 0.48–0.87) (Table 2). This counterintuitive finding likely reflects class redefinition when cardiovascular conditions are included as deficits: the 18-item 'Low progressing' class captured women with hypertension and diabetes (prevalence 25.3% and 5.7%, respectively) who would otherwise be classified as higher burden, whereas the 'Moderate stable' class excluded many of these women (hypertension 8.4%, diabetes 1.5%). Because hypertension and diabetes are strong stroke predictors, their redistribution across classes creates an artificial protective effect for Moderate stable.

For the composite cardiovascular disease outcome, both High stable (HR 1.86, 95% CI: 1.44–2.41) and Rapidly progressing (HR 1.69, 95% CI: 1.36–2.11) were associated with higher risk. For heart disease specifically, the pattern was similar but effect sizes were smaller (rapid HR 1.48, 95% CI: 1.15–1.92) (Fig. 2).

Adding trajectory class to a base model comprising age, education, marital status, residence, smoking, alcohol, body mass index, hypertension, and diabetes improved the AUC only modestly (from 0.655 to 0.665; ΔAUC = 0.010, 95% CI: -0.008 to 0.030), with an integrated discrimination improvement of 0.005 (95% CI: 0.002–0.008) and a continuous net reclassification improvement of 0.232 (95% CI: 0.107–0.376). The categorical NRI at 5% and 10% risk thresholds was 0.069 and 0.066, respectively. With k = 3 clusters, the rapid-progression class (22.4% of women) showed HR 1.60 (95% CI: 1.23–2.08); with k = 5, the corresponding class (14.7%) showed HR 1.47 (95% CI: 1.08–2.01), confirming that the high-risk phenotype and its approximately 1.5-to-1.8-fold hazard are robust to the number of classes.

Competing mortality was low (3.0% died between Waves 3 and 4 without a stroke event). Outcome distributions are shown in Figure S2. Stroke risk ratios were minimally affected by whether deaths were censored or excluded (Rapidly progressing: 6.62% vs 6.97%; High stable: 7.23% vs 7.92%).

E-values, defined as the minimum risk ratio with which an unmeasured confounder must be associated with both the exposure and the outcome to fully explain an observed association [24], indicated that an unmeasured confounder would need to be associated with both trajectory membership and incident stroke by a risk ratio of at least 3.06 to explain away the Rapidly progressing association, and 2.53 for the High stable association. The lower confidence limit E-values were 1.95 and 1.27, respectively.

3.4 Subgroup Analyses

Subgroup results are shown in Figure S3. The association between Rapidly progressing and stroke was strongest in the 60–69 age group (HR 2.42, 95% CI: 1.38–4.23) and weakest in women under 60 (HR 1.38, 95% CI: 0.84–2.27), though the class-by-age interaction was not statistically significant (Wald chi-square = 1.91, 3 df, p = 0.59) (Table 3). Among rural women, both High stable (HR 1.71, 95% CI: 1.12–2.61) and Rapidly progressing (HR 1.75, 95% CI: 1.22–2.51) were associated with stroke. Urban estimates were imprecise due to small numbers (urban Rapidly progressing HR 2.75, 95% CI: 1.18–6.41, n = 709, events = 31).

Table 3
Subgroup analyses and sensitivity analyses for the association between frailty trajectory class and incident stroke.

Analysis	Moderate stable HR (95% CI)	High stable HR (95% CI)	Rapidly progressing HR (95% CI)	n (events)
Primary (14-item non-CVD FI)	1.13 (0.85–1.50)	1.57 (1.05–2.37)	1.83 (1.31–2.55)	4,954 (219)
Sensitivity: 18-item full FI	0.64 (0.48–0.87)	1.32 (0.91–1.91)	1.65 (1.21–2.26)	4,957 (219)
Sensitivity: Composite CVD	1.21 (1.00-1.45)	1.86 (1.44–2.41)	1.69 (1.36–2.11)	4,954 (639)
Sensitivity: Heart disease	1.20 (0.97–1.48)	1.74 (1.29–2.34)	1.48 (1.15–1.92)	4,954 (458)
Age < 60 years	0.96 (0.65–1.42)	1.98 (1.07–3.67)	1.38 (0.84–2.27)	3,044 (100)
Age 60–69 years	1.46 (0.89–2.41)	1.50 (0.75–2.99)	2.42 (1.38–4.23)	1,278 (86)
Age > = 70 years	1.00 (0.44–2.27)	1.27 (0.50–3.22)	1.83 (0.77–4.33)	632 (33)
Urban residence	0.96 (0.45–2.07)	0.24 (0.02–3.27)	2.75 (1.18–6.41)	709 (31)
Rural residence	1.17 (0.86–1.59)	1.71 (1.12–2.61)	1.75 (1.22–2.51)	4,245 (188)
k = 3 sensitivity	—	—	1.60 (1.23–2.08)	—
k = 5 sensitivity	—	—	1.47 (1.08–2.01)	—
E-value (point estimate)	—	2.53	3.06	—

All models fully adjusted (Model 3 covariates) unless otherwise specified. Reference: Low progressing. E-value = minimum risk ratio for an unmeasured confounder to fully explain the association.

3.5 Mediation Analyses

The mediation paths are illustrated in Figure S4. Baseline hypertension and diabetes explained only a small fraction of the Rapidly progressing association. The odds of hypertension were 13% higher (OR 1.13, p = 0.22) and diabetes 26% higher (OR 1.26, p = 0.19) in the Rapidly progressing versus Low progressing class, but neither association was statistically significant. Controlling for hypertension reduced the rapid-progression hazard ratio from 1.83 to 1.61 (approximately 2.4% mediated); controlling for diabetes reduced it to 1.62 (approximately 1.2% mediated). These findings suggest that the association between frailty trajectory and stroke is largely independent of these traditional cardiovascular risk factors, at least as measured at baseline.

3.6 Exploratory Screening Threshold

As an exploratory step toward clinical translation, the individual frailty index slope alone discriminated incident stroke poorly (AUC 0.55). A rule flagging women whose slope exceeded 0.03 per year identified 23.4% of the cohort with 77.0% specificity but only 31.1% sensitivity; flagged women had a 5.7% three-year stroke incidence versus 3.8% among unflagged women. Given the low positive predictive value (5.7%), this rule is best viewed as a population-level risk stratification tool rather than a clinical screening test.

4. Discussion

In this nationally representative cohort of Chinese women, trajectories of non-cardiovascular deficit accumulation were associated with incident stroke in a graded pattern. Women with rapidly progressing frailty had approximately 1.8 times the stroke risk of those with low, slowly progressing frailty, even after adjustment for age, socioeconomic factors, and lifestyle behaviours. Notably, baseline hypertension and diabetes mediated only a small fraction of this association, suggesting that the predictive information captured by frailty trajectories extends beyond conventional cardiovascular risk factors.

4.1 Principal Findings in Context

Our findings align with prior studies linking frailty to cardiovascular outcomes [9–11], but extend them in three ways. First, by excluding cardiovascular conditions and risk factors from the frailty index, we demonstrate that multisystem deficit accumulation predicts stroke even when it is operationalised without cardiovascular components. This addresses a longstanding concern that frailty-cardiovascular associations may be tautological [16]. Second, by constructing trajectories from Waves 1–3 and assessing outcomes in the subsequent non-overlapping interval, we reduce the risk that pre-clinical stroke influenced frailty measurement. Third, the mediation analysis suggests that the pathway from frailty trajectory to stroke is largely direct, not mediated through hypertension or diabetes as measured at baseline.

The stronger association for stroke than for heart disease is noteworthy. Stroke is closely linked to cerebrovascular aging, endothelial dysfunction, and chronic inflammation [25]—processes that parallel the multisystem decline captured by the frailty index. By contrast, heart disease encompasses diverse phenotypes (ischaemic, valvular, arrhythmic) with varying relationships to global physiological reserve.

4.2 Methodological Considerations

Several strengths deserve emphasis. We used a nationally representative sample with a strict temporal separation between exposure (Waves 1–3) and outcome (Wave 3 to 4) assessment. The non-cardiovascular frailty index avoids component overlap with the outcome. Extensive sensitivity analyses examined alternative FI definitions, outcome specifications, class numbers, competing mortality, and

unmeasured confounding. The high seed stability (mean adjusted Rand index 0.952) supports the reproducibility of the classification.

Several limitations also merit emphasis. First, stroke was ascertained by self-reported physician diagnosis, which may cause outcome misclassification. Non-differential misclassification would bias associations toward the null, but differential misclassification (e.g., frailer women more likely to seek care and receive diagnoses) could inflate estimates. The coherent gradient across classes and the non-cardiovascular FI definition argue against purely random reporting noise, but we cannot exclude systematic bias. Second, the uniform 3-year follow-up interval precludes formal tests of proportional hazards, exact event dating, and Fine-Gray competing-risk modelling [26]. We mitigated this by confirming concordance between Cox and logistic estimates and by showing minimal impact of competing mortality. Third, despite the zero-overlap design, residual confounding by unmeasured factors (diet, physical activity, medication use, inflammatory biomarkers) cannot be excluded. The E-value of 3.06 for the primary association indicates that only a confounder of moderate-to-strong strength could fully explain the result; while such confounders are plausible, the combination of the non-cardiovascular FI, temporal separation, and mediation analysis strengthens confidence that the association is not entirely artefactual. Fourth, results in this female, predominantly rural Chinese cohort may not generalise to men or other populations.

4.3 Clinical and Research Implications

The feasibility of embedding frailty assessment into routine primary care records, as demonstrated by the development and validation of the electronic frailty index [27], suggests that trajectory-based risk stratification could be operationalised in real-world settings if its predictive value improves in larger or biomarker-enriched cohorts.

The modest effect sizes (HR 1.6–1.8), the small incremental predictive value (ΔAUC 0.010, 95% CI crossing the null), and the low discriminative ability of the frailty slope (AUC 0.55) suggest that frailty trajectories are unlikely to serve as effective screening tools for individual stroke prediction. Their primary value may lie in highlighting the dynamic nature of aging-related vulnerability at the population level and in generating mechanistic hypotheses about multisystem decline and cerebrovascular risk, rather than in direct clinical translation to individual risk stratification. The high specificity (77%) but low sensitivity (31%) of the slope-based rule implies that most strokes occur in women not flagged as rapidly progressing—consistent with the multifactorial aetiology of stroke. Future research should examine whether incorporating frailty trajectory into existing cardiovascular risk scores (e.g., China-PAR) improves risk stratification [28].

From a research perspective, our findings highlight the importance of separating cardiovascular components from frailty indices when studying cardiovascular outcomes. They also underscore the value of temporal separation between exposure and outcome assessment in observational studies of frailty and incident disease. Future studies with biomarker data (e.g., inflammatory markers, grip

strength, gait speed) could clarify the biological pathways linking multisystem decline to cerebrovascular events [29].

Our findings are consistent with evidence that frailty is a distinct clinical syndrome with important implications for clinical practice and public health [30] and with the recognised dynamic natural history of the frailty syndrome [31]. Sex differences in frailty prevalence and consequences [32], together with the substantial burden of frailty among community-dwelling older people in China [33], underscore the value of sex-specific, population-based evidence. Meta-analytic data confirm that frailty predicts mortality and other adverse outcomes [34], and comparisons of frailty indices in older women [35], as well as studies demonstrating that frailty states transition dynamically over time rather than following a fixed course [36, 37], support the trajectory-based perspective adopted in this study. Incorporating frailty assessment into the cardiovascular care of older adults [38], applying appropriate methods for survival analysis with competing risks [39], and using refined metrics to quantify incremental predictive value beyond the AUC [40] should inform the design of future studies with longer follow-up.

5. Conclusion

In Chinese women, trajectories of non-cardiovascular deficit accumulation were associated with incident stroke in a graded pattern, largely independent of baseline hypertension and diabetes and robust to alternative outcome definitions and class numbers. While the observational design and self-reported outcome preclude causal inference, these findings suggest that trajectories of non-cardiovascular deficit accumulation capture aging-related vulnerability associated with stroke risk, largely independent of conventional risk factors. The modest incremental predictive value, however, indicates that frailty trajectories are unlikely to improve individual risk prediction meaningfully beyond standard cardiovascular risk assessment.

Declarations

Ethics approval and consent to participate

The CHARLS project was approved by the Ethical Review Committee of Peking University (IRB identification number: IRB00001052-11015). All original CHARLS participants provided written informed consent before data collection. The present secondary data analysis was conducted in full accordance with the principles outlined in the Declaration of Helsinki. This study uses publicly released fully de-identified CHARLS datasets without access to personal identifiable information, so additional institutional ethical review and separate participant informed consent were waived. All analytical procedures strictly followed ethical standards for human observational research.

Clinical trial number: not applicable.

This is a cross-sectional secondary analysis of population cohort survey data, not an interventional clinical trial, so no trial registration exists.

Consent for publication

Not applicable. This manuscript only reports aggregated population-level statistical results and does not contain any identifiable individual information, clinical images, or personal case records.

Availability of data and materials

The original CHARLS datasets used in this study are publicly accessible after official registration and application via the CHARLS official website (http://charls.pku.edu.cn/). Researchers can apply for data access following the platform's standard application procedures. The analytical code generated during the current study is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Lu Jiaping performed data cleaning, descriptive statistics, primary regression analysis, and drafted the original manuscript. Xu Qiulian assisted in participant screening according to inclusion and exclusion criteria, sorted baseline characteristic data, and revised the results section. Xu Heng proposed the research hypothesis, designed the overall analytical framework, supervised all statistical procedures, repeatedly revised the full manuscript, and served as the corresponding author. All authors have read and approved the final version to be submitted.

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Figures

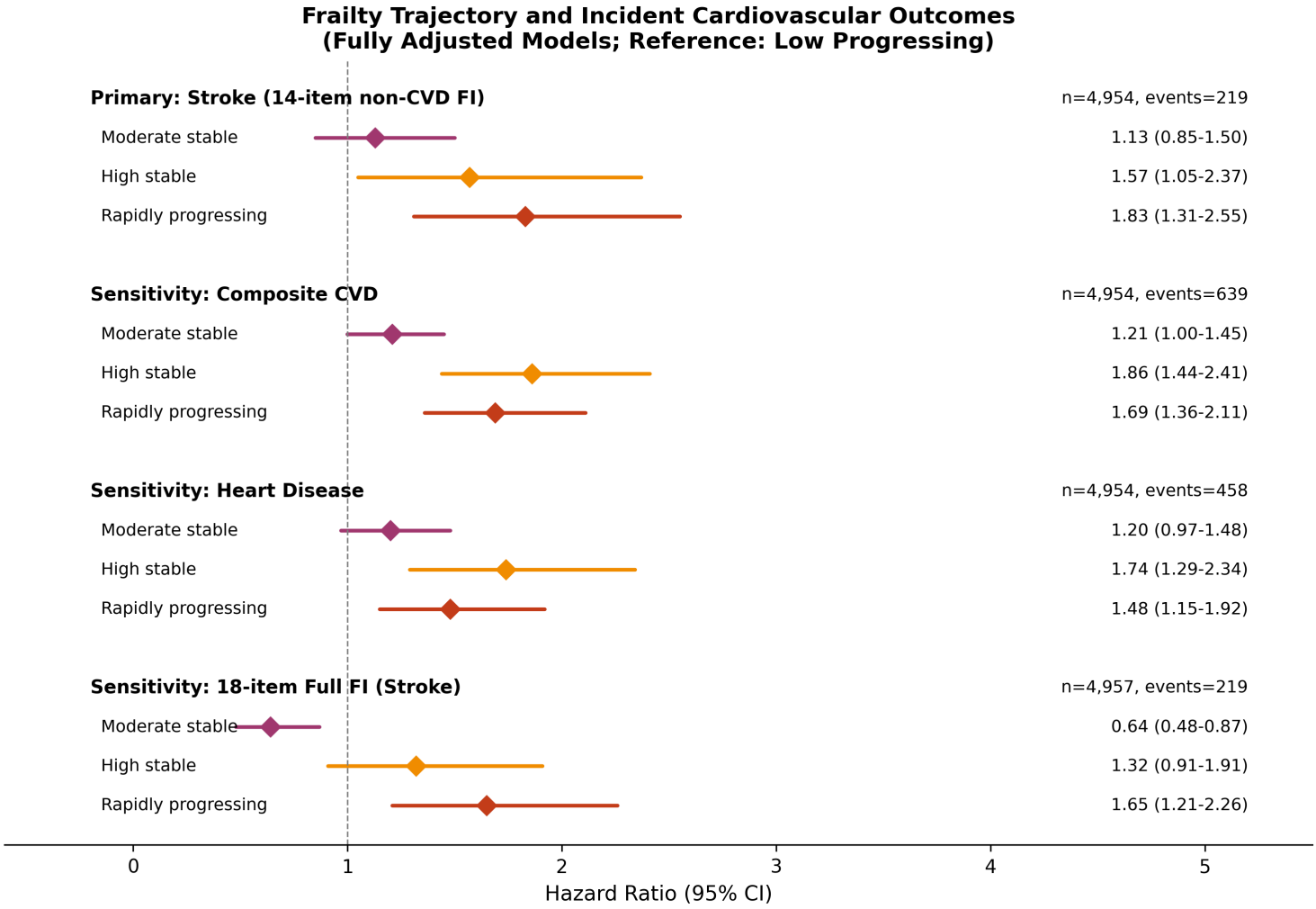


Figure 2

Association between frailty trajectory class and cardiovascular outcomes. Forest plot showing hazard ratios (reference: Low progressing) for incident stroke (primary outcome), composite cardiovascular disease, and heart disease. Squares represent point estimates and horizontal lines represent 95% confidence intervals. Models are fully adjusted for age, education, marital status, residence, smoking, alcohol, body mass index, hypertension, and diabetes.

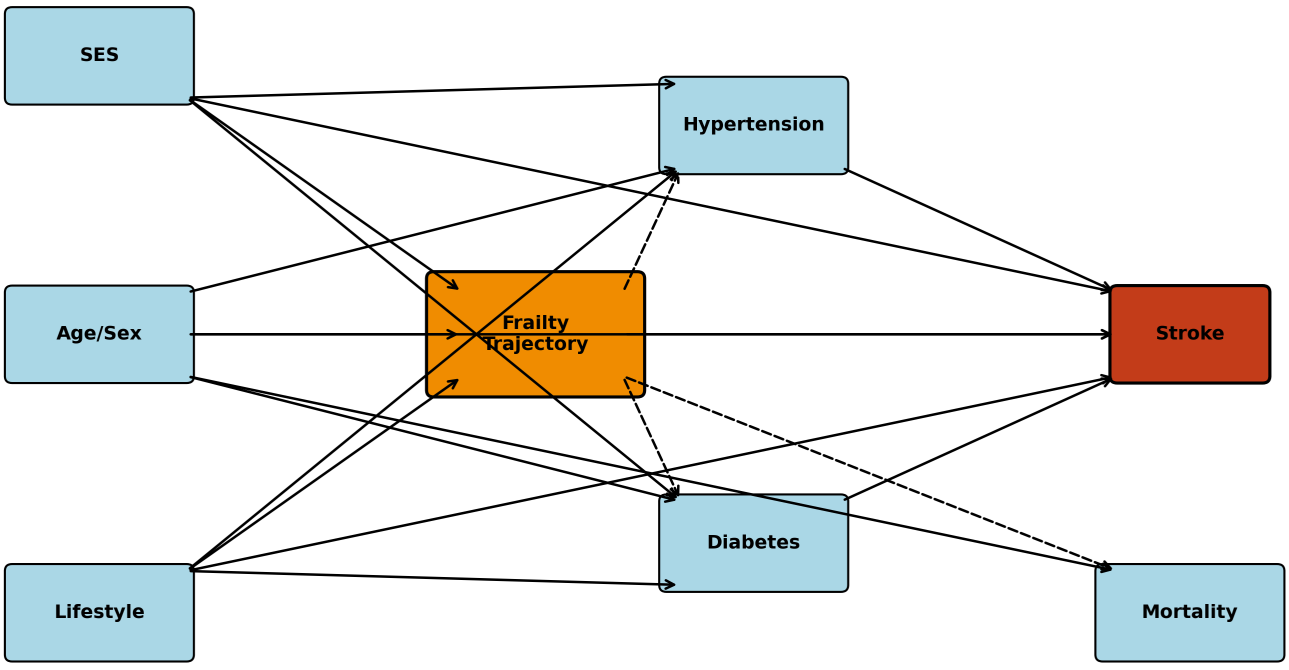


Figure 3

Directed acyclic graph depicting hypothesised relationships between frailty trajectory class and incident stroke. Age, education, marital status, residence, smoking, alcohol, and body mass index are treated as confounders and adjusted for in all models. Baseline hypertension, diabetes, heart disease, and stroke are excluded from the frailty index (non-cardiovascular FI) to reduce collider bias. The DAG was drawn using DAGitty.

Supplementary Files

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