

Physical Multimorbidity Phenotypes and Elevated Depressive Symptoms Among Chinese Adults With a History of Stroke: Derivation and Temporal Validation in CHARLS

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Abstract

Background

Latent multimorbidity phenotypes may be more clinically interpretable than disease counts, but phenotype studies are often vulnerable to unstable class solutions, classification error, and absence of validation. We derived physical multimorbidity phenotypes among adults with a history of stroke and tested their reproducibility and association with elevated depressive symptoms in non-overlapping participants.

Methods

The derivation sample comprised 486 participants reporting physician-diagnosed stroke in the 2011 baseline wave of the Harmonized China Health and Retirement Longitudinal Study (CHARLS). Bernoulli latent class models used 11 physical conditions. Stability was evaluated in 200 bootstrap samples, and outcome inference was repeated across 300 posterior pseudo-class draws. The 2011 class prevalences and conditional probabilities were then frozen and applied, without refitting, to 918 different participants whose earlier stroke reports were absent and whose first study report of stroke occurred in 2013, 2015, or 2018. Elevated depressive symptoms were defined as a 10-item Center for Epidemiologic Studies Depression Scale score ≥ 10 . Adjusted logistic models included sociodemographic, behavioural, functional, and validation-wave covariates.

Results

The selected solution contained high-complexity, cardiometabolic, and low-comorbidity classes. Across bootstrap samples, median correlations with the original condition profiles were 0.966, 0.982, and 0.985, respectively. In the derivation complete-case model ($n = 409$), the high-complexity class was associated with elevated depressive symptoms versus the low-comorbidity class (adjusted odds ratio [aOR] 2.59, 95% CI 1.30–5.16); posterior pseudo-class inference gave aOR 2.35 (1.09–5.03). The association replicated in the temporal validation sample ($n = 782$; aOR 1.74, 1.17–2.60) and in a response-weighted analysis (1.93, 1.22–3.06). Cardiometabolic-class estimates were null. In a common complete-case subset, a simple disease-count model had marginally better fit and discrimination than the class model.

Conclusions

A high-complexity physical multimorbidity phenotype showed a reproducible association with elevated depressive symptoms in non-overlapping later-wave CHARLS participants. The classes add clinical interpretability but did not outperform disease count for statistical fit. Because validation remained

within CHARLS and exposures and symptoms were measured concurrently within each wave, external prospective validation is still required.

1. Introduction

Stroke remains a major cause of death and disability worldwide. Recent Global Burden of Disease estimates and the World Stroke Organization describe a growing absolute burden and emphasize surveillance, prevention, coordinated secondary care, and rehabilitation [1–5]. Depression is among the most frequent neuropsychiatric problems after stroke. Contemporary syntheses report substantial, time-varying depressive morbidity across regions and clinically important subgroups, including people with aphasia [6–9]. Screening instruments can identify elevated symptom burden but do not replace diagnostic assessment, and screening evidence remains heterogeneous [10–13]. Identifying clinically recognizable groups with increased symptom burden may therefore support more deliberate care coordination while not replacing universal attention to mood.

Stroke commonly coexists with cardiovascular, metabolic, musculoskeletal, pulmonary, renal, and digestive diseases. Multimorbidity creates interacting treatment burden and functional consequences that a total disease count cannot fully describe [14]. Yet definitions, condition lists, and analytical approaches vary widely, and recent reviews call for transparent measurement, longitudinal evaluation, and systematic validation of data-derived patterns [15–17]. Large cohort work suggests that latent multimorbidity clusters may carry different risks even after accounting for disease count, although transportability is not uniform across datasets [18–20]. Chinese studies have repeatedly recovered relatively healthy, cardiometabolic or vascular, respiratory–digestive–musculoskeletal, and multisystem patterns and linked them with service use, costs, disability, and depressive symptoms [21–31]. Broader reviews and observational studies also support a close relationship between physical multimorbidity and depression [32–34]. However, evidence focused specifically on reproducible physical multimorbidity phenotypes among people with a history of stroke remains limited.

Three methodological problems weaken many phenotype studies. First, psychiatric disorders may be included among the indicators used to construct a class and then analysed again as an outcome, creating conceptual circularity [32]. Second, class solutions derived in one sample are often interpreted without resampling, classification-uncertainty analysis, or testing in different participants, despite explicit calls for transparent validation [15–18]. Third, a phenotype model is rarely compared with the simpler disease-count alternative, so interpretability may be mistaken for incremental statistical performance. Moderate classification entropy further means that analyses based only on the most likely class can understate uncertainty.

We therefore aimed to (1) derive physical multimorbidity phenotypes in a 2011 CHARLS sample with self-reported physician-diagnosed stroke; (2) quantify class-solution stability and propagate posterior classification uncertainty; (3) freeze the derivation model and evaluate profile transportability and class–symptom associations in non-overlapping participants from later CHARLS waves; and (4) compare the

class model with physical disease count. We hypothesized that a high-complexity phenotype would be associated with elevated depressive symptoms in both samples, whereas we did not assume that the phenotype model would outperform disease count.

2. Methods

2.1 Data source and study samples

We conducted a secondary analysis of the Harmonized CHARLS, a nationally based longitudinal survey of community-dwelling Chinese adults aged 45 years or older [35]. The derivation sample included 486 unique participants who reported a physician diagnosis of stroke in the 2011 baseline wave. Participants with partial physical-condition information remained eligible for LCA because their likelihood contributions were calculated from observed indicators.

For participant-level temporal validation, we screened waves 2–4 (2013, 2015, and 2018). At each wave, we selected participants whose stroke indicators in every earlier available wave equalled zero, whose current-wave stroke indicator equalled one, and for whom at least 9 of the 11 physical-condition indicators were observed. Thus, the validation sample excluded all derivation participants and comprised individuals with a first study report of physician-diagnosed stroke in a later wave. This definition does not establish the clinical date or adjudicated incidence of stroke. The validation cohort contained 918 participants: 93 in 2013, 159 in 2015, and 666 in 2018. Exposure, covariates, and depressive symptoms were taken from the same wave, so each wave-specific association remained cross-sectional. Figure 1 summarizes the design.

2.2 Physical multimorbidity indicators

Eleven self-reported physician-diagnosed physical conditions were modelled as binary indicators: hypertension, diabetes, heart disease, chronic lung disease, liver disease, kidney disease, digestive disease, arthritis or rheumatism, dyslipidaemia, memory-related disease, and cancer. Stroke defined the study population and was not an indicator. A diagnosis of an emotional, nervous, or psychiatric problem was excluded from the class indicators to avoid constructing the exposure partly from the depressive-symptom domain.

2.3 Depressive symptoms

Depressive symptoms were measured with the CES-D-10, which assesses symptom frequency during the preceding week and has demonstrated reliability and validity in Chinese older adults [36]. Scores range from 0 to 30; scores ≥ 10 were classified as elevated depressive symptoms. This threshold identifies symptom burden and is not a clinical diagnosis of major depressive disorder or adjudicated post-stroke depression. The primary analysis used the harmonized total when available. Sensitivity analyses required documentation of no missing CES-D-10 items and excluded participants reporting a prior psychiatric diagnosis.

2.4 Covariates

Prespecified covariates were age, sex, education (primary or less, secondary, or college or higher), partnered status, ever smoking, ever drinking, and number of basic activities-of-daily-living (ADL) limitations. Validation models additionally included indicators for the 2015 and 2018 waves, with 2013 as the reference, to account for period differences.

2.5 Latent class derivation and stability

Bernoulli LCA models containing two through five classes were estimated by maximum likelihood in the 2011 sample. For each class count, 100 random initializations were evaluated using reproducibility seed 20260816, and the solution with the greatest log likelihood was retained. Selection considered Akaike information criterion (AIC), Bayesian information criterion (BIC), normalized entropy, smallest assigned class size, separation of conditional response profiles, parsimony, and clinical interpretability. Participants were assigned to the class with the greatest posterior probability for descriptive analyses.

We assessed class-solution stability in 200 nonparametric bootstrap samples. In each sample the three-class model was re-estimated, class labels were aligned with the derivation profiles by minimum squared distance, and class prevalence, profile root-mean-square error (RMSE), and Pearson profile correlation were recorded. These analyses assess sampling stability; they do not convert a data-derived class into a biological entity.

2.6 Fixed-model temporal validation

The 2011 class prevalences and condition-response probabilities were frozen before outcome validation. For each later-wave participant, posterior class probabilities were computed from the fixed model using the available condition indicators, and modal class assignment was used for primary validation analyses. We summarized mean maximum posterior probability. The class model used for outcome analysis was not re-estimated in the validation participants.

As a separate structural replication analysis, we independently re-estimated a three-class LCA in the full validation sample using 100 random starts. Validation classes were aligned with derivation classes by minimum squared profile distance. We then calculated Pearson correlation and RMSE between the independently estimated 11-condition profiles. This check was kept separate from the fixed-model outcome analysis to avoid treating assignment-induced similarity as independent evidence of profile replication.

2.7 Association models and sensitivity analyses

Multivariable logistic regression estimated adjusted odds ratios (aORs) and 95% confidence intervals for elevated depressive symptoms, with the low-comorbidity class as reference. Derivation and validation analyses used complete outcome and covariate observations. To propagate classification uncertainty in the derivation sample, 300 pseudo-class datasets were drawn from individual posterior probabilities; coefficients and variances were combined using within- and between-draw variance. A 1,000-sample

regression bootstrap provided percentile confidence intervals for the class coefficients and optimism-corrected area under the receiver-operating-characteristic curve (AUC) and Brier score.

Response-weighted sensitivity models used wave-specific respondent weights and sandwich standard errors. These were robustness analyses rather than full design-based survey estimates because clustering and stratification variables were not incorporated. In participants with all 11 condition indicators and all model variables observed, we replaced class membership with physical disease count and compared AIC, AUC, and Brier score on the identical sample. Additional validation sensitivities required complete CES-D-10 items and excluded prior psychiatric diagnosis. Two-sided $P < 0.05$ was considered statistically significant. Analyses were performed in Python 3.12 with NumPy and pandas. Reproducibility files include the fixed seed, analysis scripts, numerical outputs, and derived class assignments.

2.8 Ethics and reporting

The original CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and participants provided written informed consent. This analysis used de-identified secondary data and is reported in accordance with the STROBE statement [54].

3. Results

3.1 Derivation sample and class enumeration

The derivation sample contained 486 participants. CES-D-10 scores were available for 415, and 409 had complete outcome and covariate data for the primary adjusted model. BIC supported the three-class solution (BIC 4541.40). Although the four-class solution had a marginally lower AIC, it generated an assigned class of seven participants; the five-class solution generated a class of six. The three-class solution was retained for stability, parsimony, and clinical interpretability (Table 1).

Table 1
Fit statistics for two- through five-class latent class models

Classes	Log likelihood	AIC	BIC	Entropy	Smallest class, n
2	-2204.52	4455.04	4551.33	0.497	193
3	-2162.44	4394.88	4541.40	0.632	61
4	-2149.89	4393.79	4590.54	0.684	7
5	-2139.74	4397.48	4644.47	0.701	6

The selected three-class model minimized BIC. Very small assigned classes made the four- and five-class solutions clinically fragile.

3.2 Phenotypes, bootstrap stability, and transportability

The high-complexity class contained 61 participants (12.6%) and combined high arthritis/rheumatism with digestive, cardiovascular, pulmonary, hepatic, and renal disease. The cardiometabolic class contained 144 (29.6%) and was dominated by hypertension, dyslipidaemia, diabetes, and heart disease. The low-comorbidity class contained 281 (57.8%) and had lower probabilities except for hypertension and arthritis/rheumatism (Table 2 and Supplementary Table S1).

Table 2
Selected derivation-sample characteristics by latent class

Class	n (%)	Age, mean (SD)	Female, n (%)	Partnered, n (%)	ADL, mean (SD)	CES-D-10, mean (SD)	CES-D-10 ≥ 10, n/N (%)
High-complexity	61 (12.6)	62.0 (11.6)	34 (55.7)	42 (68.9)	1.51 (1.94)	14.8 (7.1)	38/52 (73.1)
Cardiometabolic	144 (29.6)	64.1 (9.1)	70 (48.6)	111 (77.1)	1.71 (2.22)	11.2 (6.9)	68/121 (56.2)
Low-comorbidity	281 (57.8)	64.2 (11.0)	129 (45.9)	219 (77.9)	1.56 (2.10)	10.6 (6.8)	122/242 (50.4)

CES-D-10 summaries use participants with an available harmonized score. ADL, activities of daily living; SD, standard deviation.

Across 200 bootstrap samples, median aligned profile correlations were 0.966 for the high-complexity class, 0.982 for the cardiometabolic class, and 0.985 for the low-comorbidity class; corresponding median RMSEs were 0.087, 0.063, and 0.030. Bootstrap class-prevalence intervals were wider for the high-complexity class (median 17.1%, 95% empirical interval 8.5%–31.5%), indicating that its prevalence was less precise than its disease-profile shape.

When a three-class model was independently refitted in the 918 later-wave participants, the aligned high-complexity profile correlated strongly with its derivation counterpart ($r = 0.958$; $RMSE = 0.116$). Correlations were lower for the cardiometabolic ($r = 0.846$; $RMSE = 0.239$) and low-comorbidity profiles ($r = 0.839$; $RMSE = 0.126$), indicating partial rather than complete structural replication (Fig. 2). Under the frozen 2011 classification model used for outcome validation, mean maximum posterior probability was 0.807 overall.

3.3 Derivation-sample associations and internal validation

Among 415 participants with CES-D-10 scores, 228 (54.9%) met the threshold for elevated depressive symptoms. Prevalence was 73.1% in the high-complexity class, 56.2% in the cardiometabolic class, and 50.4% in the low-comorbidity class ($\chi^2=8.99$, $df = 2$, $P = 0.011$). In the adjusted complete-case model, the high-complexity class had higher odds than the low-comorbidity class (aOR 2.59, 95% CI 1.30–5.16; $P =$

0.007), whereas the cardiometabolic estimate was compatible with no association (aOR 1.36, 0.84–2.20; $P = 0.211$).

Posterior pseudo-class inference attenuated the high-complexity estimate but retained the association (aOR 2.35, 95% CI 1.09–5.03; $P = 0.029$). The response-weighted derivation model was similar (aOR 2.44, 1.20–4.99; $P = 0.014$). Across 1,000 regression bootstrap samples, the percentile interval for the high-complexity coefficient corresponded to an OR of 1.34–5.72. Apparent AUC was 0.710 and declined to 0.679 after optimism correction; the Brier score changed from 0.217 to 0.229. These values do not support use as a stand-alone prediction model.

3.4 Temporal validation

The fixed model assigned 228 of 918 validation participants (24.8%) to the high-complexity class, 338 (36.8%) to the cardiometabolic class, and 352 (38.3%) to the low-comorbidity class. Among those with an available outcome, elevated depressive symptoms occurred in 130/201 (64.7%), 144/290 (49.7%), and 132/291 (45.4%), respectively (Table 3).

Table 3
Temporal validation class characteristics

Fixed-model class	n (%)	Mean maximum posterior	Independent-refit profile correlation	CES-D-10 ≥ 10 , n/N (%)
High-complexity	228 (24.8)	0.782	0.958	130/201 (64.7)
Cardiometabolic	338 (36.8)	0.819	0.846	144/290 (49.7)
Low-comorbidity	352 (38.3)	0.813	0.839	132/291 (45.4)

Class counts, posterior probabilities, and symptom frequencies use the frozen 2011 model. Profile correlation comes from a separate three-class model independently refitted in validation participants and aligned to the 2011 profiles.

In the wave-adjusted complete-case validation model ($n = 782$; 406 events), the high-complexity class was associated with elevated depressive symptoms (aOR 1.74, 95% CI 1.17–2.60; $P = 0.006$); the cardiometabolic class was not (1.14, 0.81–1.62; $P = 0.452$). Results were similar in the response-weighted model (1.93, 1.22–3.06), when no CES-D-10 item was missing (1.89, 1.21–2.95), and after excluding prior psychiatric diagnosis (1.80, 1.19–2.72). Table 4 and Fig. 3 summarize the class estimates.

Table 4
Class associations with elevated depressive symptoms across analyses

Analysis	n	High-complexity vs low, aOR (95% CI)	P	Cardiometabolic vs low, aOR (95% CI)	P
Derivation: modal assignment	409	2.59 (1.30–5.16)	0.007	1.36 (0.84–2.20)	0.211
Derivation: posterior pseudo-class	409	2.35 (1.09–5.03)	0.029	1.20 (0.67–2.13)	0.536
Derivation: response-weighted	409	2.44 (1.20–4.99)	0.014	1.25 (0.73–2.17)	0.417
Temporal validation: main	782	1.74 (1.17–2.60)	0.006	1.14 (0.81–1.62)	0.452
Temporal validation: response-weighted	768	1.93 (1.22–3.06)	0.005	1.01 (0.67–1.52)	0.968
Temporal validation: complete CES-D items	662	1.89 (1.21–2.95)	0.005	1.11 (0.76–1.63)	0.592
Temporal validation: exclude psychiatric diagnosis	741	1.80 (1.19–2.72)	0.005	1.14 (0.80–1.63)	0.478

All models adjusted for age, sex, education, partnered status, ever smoking, ever drinking, and ADL limitations. Temporal validation models additionally adjusted for wave.

3.5 Comparison with physical disease count

In the 392 derivation participants with all 11 condition indicators and model variables observed, each additional physical condition was associated with elevated depressive symptoms (aOR 1.22, 95% CI 1.06–1.41; $P = 0.004$). The count model had slightly lower AIC and slightly higher AUC than the class model on the identical sample (Table 5). Therefore, the empirical value of the class solution lies primarily in describing clinically recognizable patterns rather than improving statistical discrimination over disease burden alone.

Table 5
Class-versus-count model comparison on an identical complete-case sample (n = 392)

Exposure representation	Parameters for exposure	AIC	AUC	Brier score	Exposure estimate
Three latent classes	2	507.24	0.715	0.215	See class estimates
Physical disease count	1	503.16	0.720	0.213	1.22 (1.06–1.41)

Lower AIC and Brier score and higher AUC indicate better in-sample performance. The disease-count estimate is per additional condition.

4. Discussion

4.1 Principal findings

This study adds four forms of evidence that were absent from the initial single-sample analysis. First, the three disease-profile shapes were stable in bootstrap samples even though the high-complexity class prevalence remained imprecise. Second, the high-complexity association persisted after posterior classification uncertainty was propagated. Third, an independently refitted validation model strongly recovered the high-complexity profile but showed some shift in the other two profiles; nevertheless, the fixed-model high-complexity association replicated with a smaller effect estimate in non-overlapping participants. Fourth, the count model performed marginally better statistically, clarifying that LCA contributes pattern interpretability rather than superior prediction.

The null cardiometabolic-class estimates are also informative. Hypertension, dyslipidaemia, diabetes, and heart disease in isolation from broader multisystem burden did not identify higher depressive-symptom odds after covariate adjustment. By contrast, the high-complexity profile combined musculoskeletal, digestive, cardiopulmonary, hepatic, and renal burden. The findings therefore support an association with multisystem complexity rather than a unique effect of any single organ-system cluster.

4.2 Relation to previous evidence

The derived profiles resemble those in international and Chinese studies. Systematic and cross-cohort evidence most consistently identifies cardiometabolic, respiratory, musculoskeletal or pain-related, and multisystem patterns, but also shows dataset-dependent heterogeneity [16, 18–20]. Chinese studies have reported vascular or cardiometabolic, stomach–arthritis, respiratory, relatively healthy, and multisystem patterns [21–23, 27–29]. Multisystem patterns have been linked to higher service use and costs, disability, functional decline, and out-of-hospital care needs [22, 24, 25, 28–30]. Recent CHARLS analyses further associate multimorbidity burden or specific patterns with depression [26, 31]. Our count-model result agrees with graded burden evidence, while the phenotype analysis shows which co-occurring systems characterize the group with the largest symptom burden among adults reporting stroke. Differences in indicators, ages, waves, and class-selection rules preclude assuming that similarly named classes are identical biological entities [15–17].

4.3 Potential mechanisms

Several non-exclusive pathways may contribute. Multisystem disease can increase treatment burden, fragmented care, pain, fatigue, dyspnoea, dietary restriction, sleep disruption, and loss of perceived control; contextual stressors and functional loss may then compound neurological limitations [33, 34]. Biological reviews describe interacting neuroinflammatory, monoaminergic, glutamatergic, neurotrophic,

epigenetic, and gut–brain pathways in depressive states after stroke [37, 38]. Meta-analyses report associations with circulating cytokines, acute-phase C-reactive protein, high-sensitivity C-reactive protein, homocysteine, and leptin, although biomarker heterogeneity and observational designs limit causal interpretation [39–42]. The present data contain no biomarkers, medication burden, pain, sleep, stroke severity, or time since stroke; these explanations are therefore hypotheses rather than demonstrated mechanisms.

4.4 Clinical and research implications

Mood assessment should remain broadly available after stroke because 45% of validation participants in the low-comorbidity class also screened positive, and contemporary reviews support systematic attention to symptoms across the stroke pathway [10, 11]. Multisystem complexity may nevertheless identify patients who warrant especially deliberate review of mood, ADL limitations, pain, sleep, treatment burden, and coordination across specialties. The current findings do not justify a class-specific intervention or a clinical prediction rule. Systematic reviews of non-pharmacological, psychological, behavioural-activation, mindfulness, exercise, home-based, telehealth, and dyadic approaches show potential benefit in selected settings but variable certainty, heterogeneity, and limited long-term evidence [43–53]. A next-stage study should prospectively record stroke timing and severity, ascertain depressive disorders clinically, and test whether phenotype information adds value beyond disease count and functional status in an external cohort.

4.5 Strengths and limitations

Strengths include removal of psychiatric disease from the class indicators, 100 random starts, explicit rejection of tiny higher-class solutions, 200 LCA bootstrap samples, posterior pseudo-class inference, 1,000 regression bootstrap samples, fixed-model outcome validation, a separate independently refitted structural replication model, non-overlapping participants, response-weighted and outcome-definition sensitivities, direct comparison with disease count, and reproducible analysis files.

Limitations remain important. The validation participants came from later waves of the same CHARLS study and share its sampling frame, measures, and potential biases; this is not external validation in an independent clinical or administrative cohort and does not satisfy a requirement for biological validation. Exposure and depressive symptoms were measured concurrently within each wave, so temporal validation of transportability does not establish whether multimorbidity preceded symptoms. A first study report of stroke is not an adjudicated incident event, and stroke subtype, lesion location, severity, recurrence, and time since stroke were unavailable. Diseases and stroke were self-reported as physician diagnosed. CES-D-10 is a screening instrument rather than a diagnostic interview. Complete-case analyses may be selected, the high-complexity derivation class was small, and moderate entropy indicates residual classification uncertainty despite pseudo-class analysis. Weighted sensitivities did not incorporate the complete complex survey design. Finally, the count model performed slightly better in sample, and data through 2018 may not reflect current treatment patterns.

5. Conclusions

A high-complexity physical multimorbidity phenotype showed a reproducible association with elevated depressive symptoms among Chinese adults with a history of stroke, including non-overlapping participants from later CHARLS waves. The cardiometabolic phenotype did not. The phenotype model offers a clinically interpretable description of multisystem burden but did not outperform simple disease count for statistical fit. External prospective validation with adjudicated stroke and depression measures is required before clinical risk-stratification claims are warranted.

Declarations

Ethics approval and consent to participate: The original CHARLS study was conducted in accordance with the Declaration of Helsinki and was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015); all participants provided written informed consent. The present study used de-identified secondary data.

Clinical trial number: not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Harmonized CHARLS data are available through the Gateway to Global Aging Data subject to registration and applicable data-use conditions. Reproducible analysis code, numerical outputs, and de-identified derived class assignments are provided with the submission materials, subject to the source-data agreement.

Competing interests: The authors declare no competing interests.

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Figures

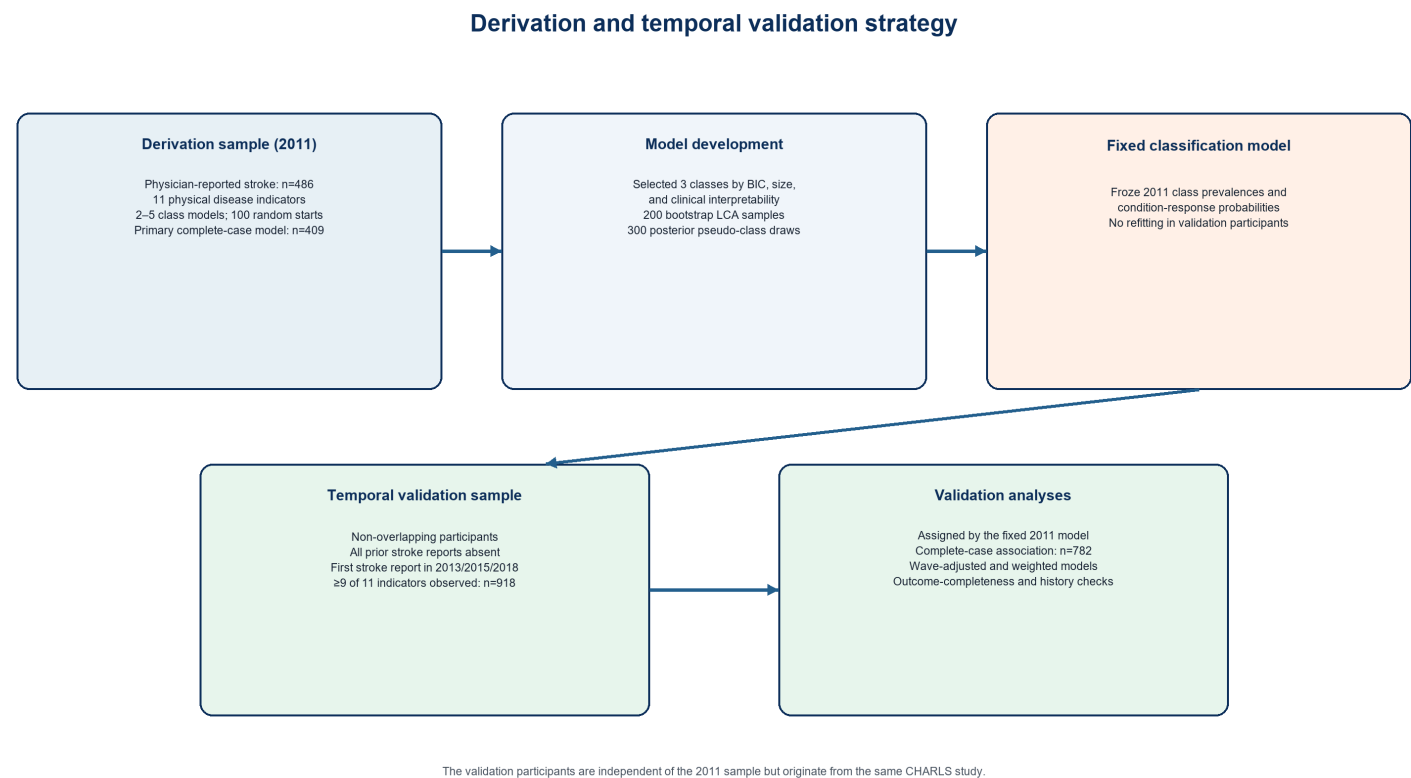


Figure 1

Derivation and temporal validation strategy.



Figure 2

Physical-condition profiles estimated independently in the derivation and validation samples.

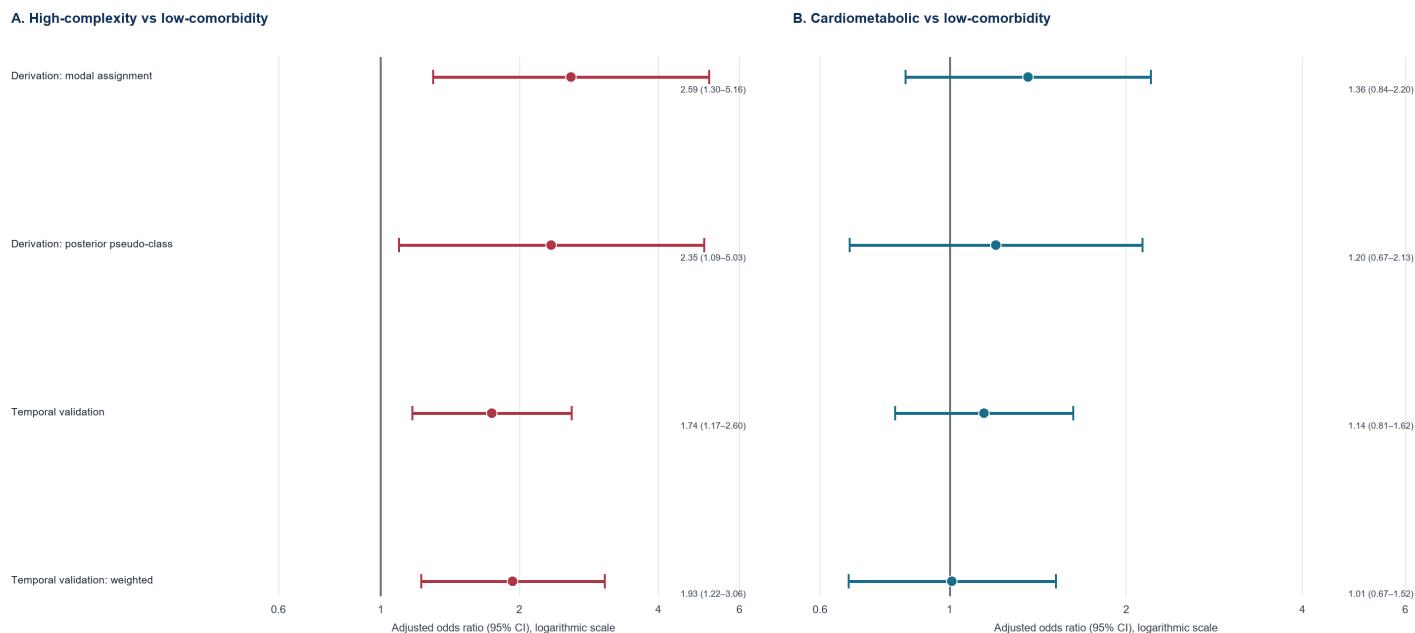


Figure 3

Adjusted class associations in derivation and temporal validation analyses.

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