

Additional file 2

Supplementary Figures S1-S9

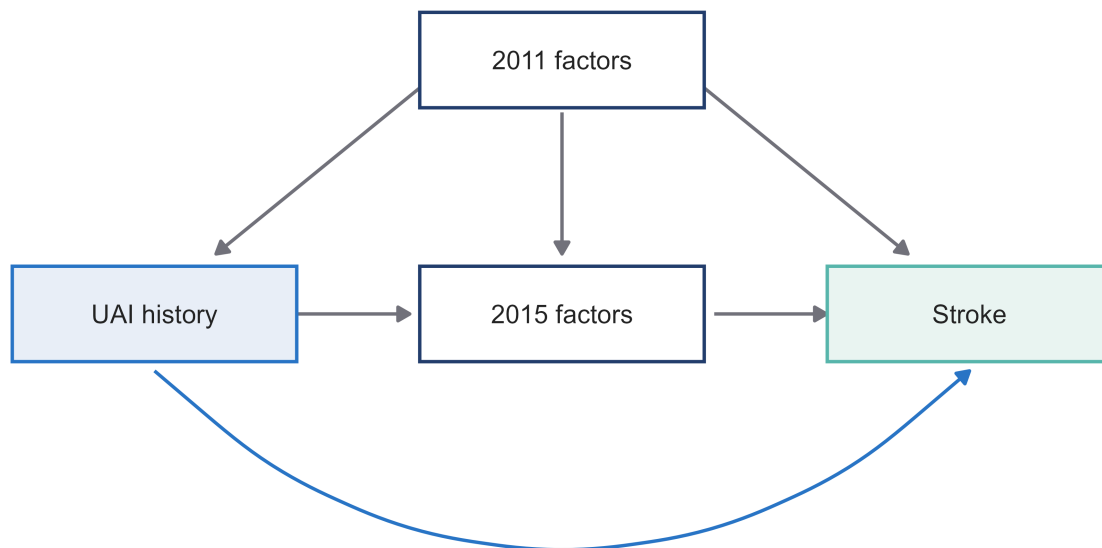
Long-term triglyceride glucose index (TyG)-uric acid burden and incident stroke in the China Health and Retirement Longitudinal Study (CHARLS): repeated-exposure and transition analyses

Cardiovascular Diabetology

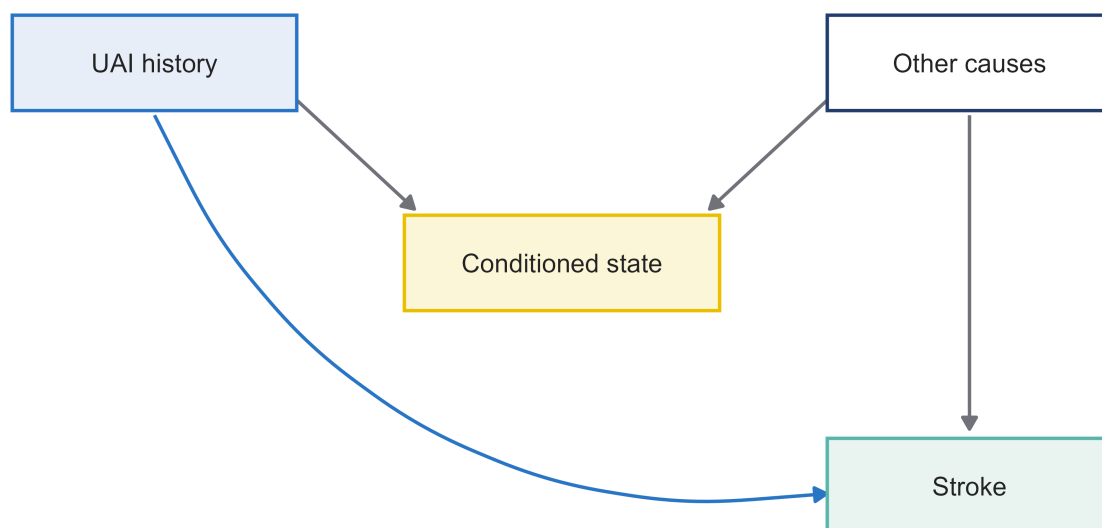
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Supplementary Figure S1. Assumed covariate timing and conditioning structures

A Covariate timing

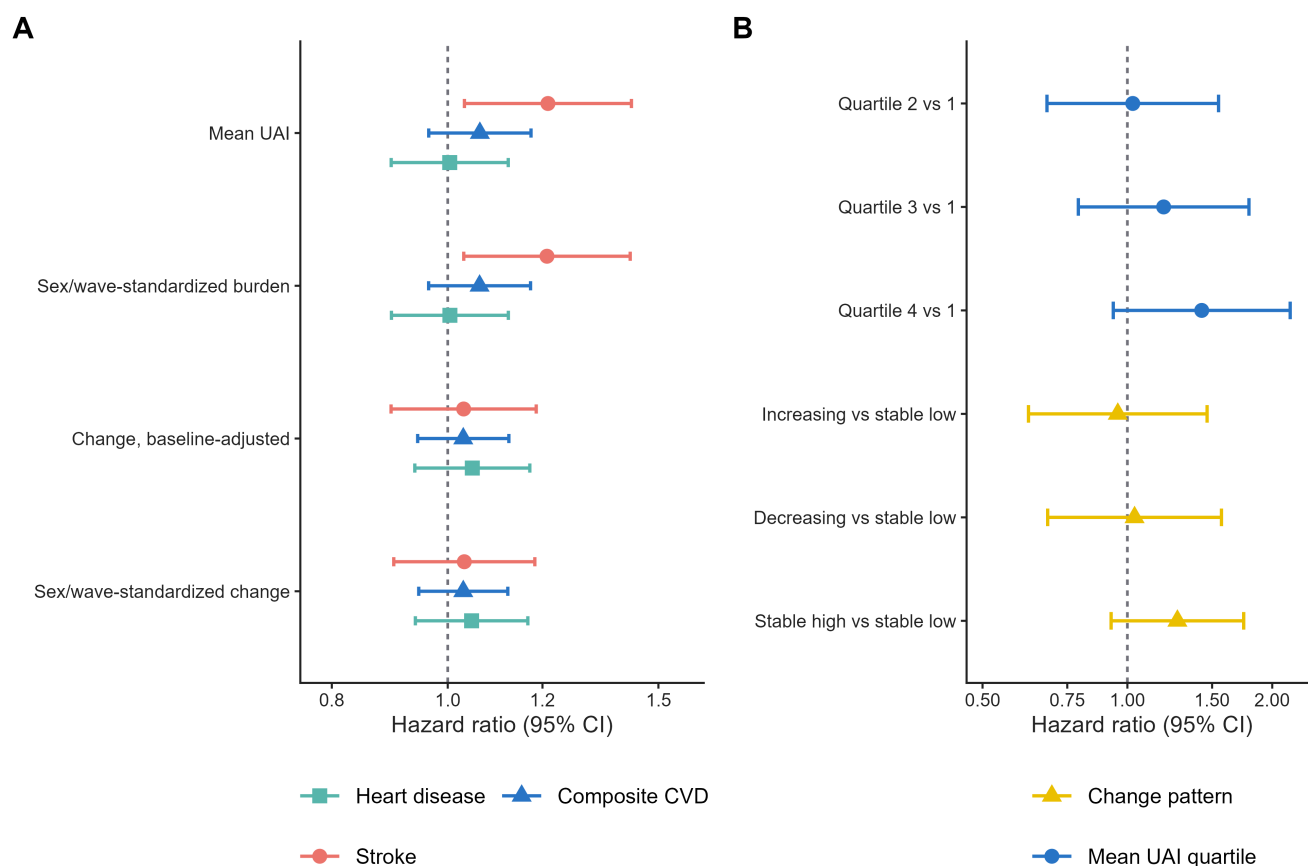


B Conditioning and selection



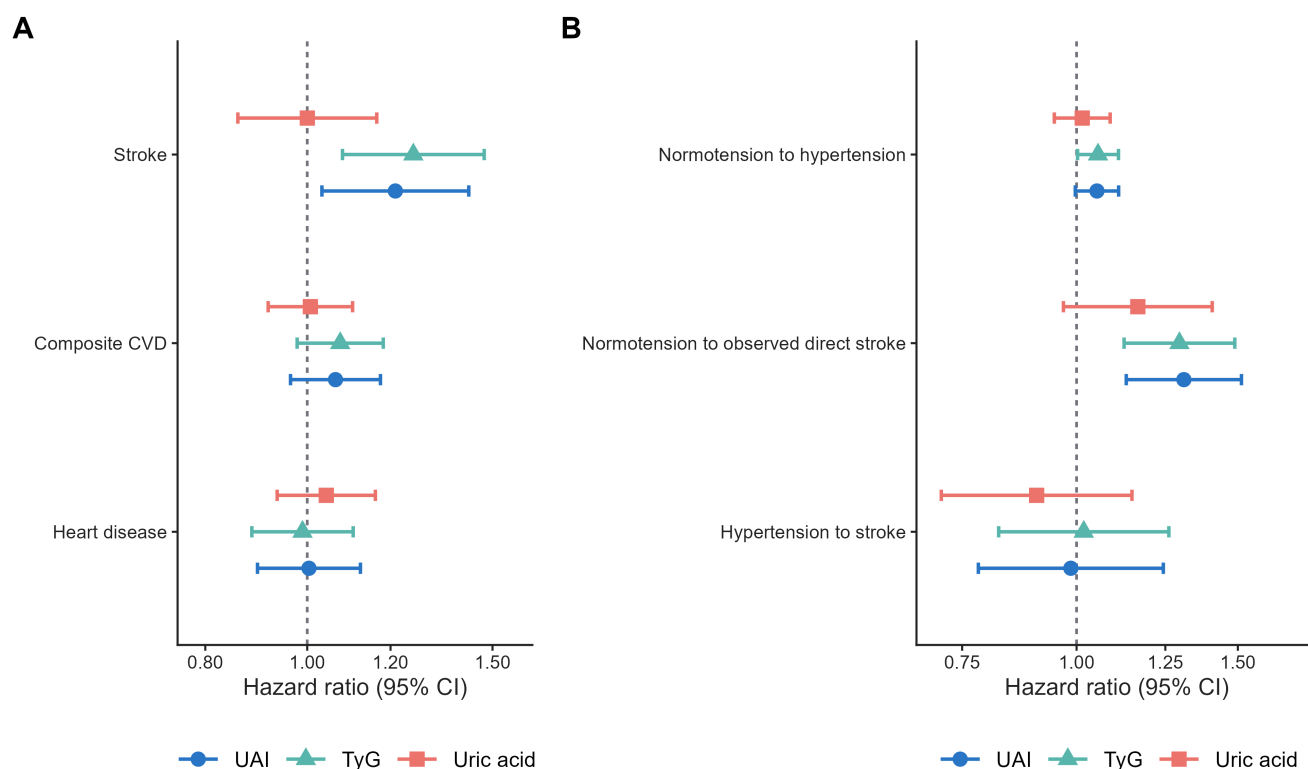
These schematic directed acyclic graphs illustrate assumptions, not identified causal effects. (A) Earlier factors may affect UAI history, factors measured in 2015, and stroke. Factors measured in 2015 may partly reflect earlier exposure or confounding; replacing or adding them changes the conditional association. UAI history is represented in this study by an arithmetic mean of two measurements, not a continuously observed exposure trajectory. (B) Conditioning on a common consequence of UAI history and other causes of stroke can open a noncausal path. The highlighted node illustrates this collider pattern separately for restriction to a recorded hypertension state or selection into an observed analysis sample; these are distinct processes, not one combined variable. Other plausible paths are omitted for clarity. Neither the diagrams nor attenuation after adjustment establish hypertension mediation, and recorded states do not identify biological ordering. UAI, uric acid index.

Supplementary Figure S2. Alternative two-examination UAI specifications



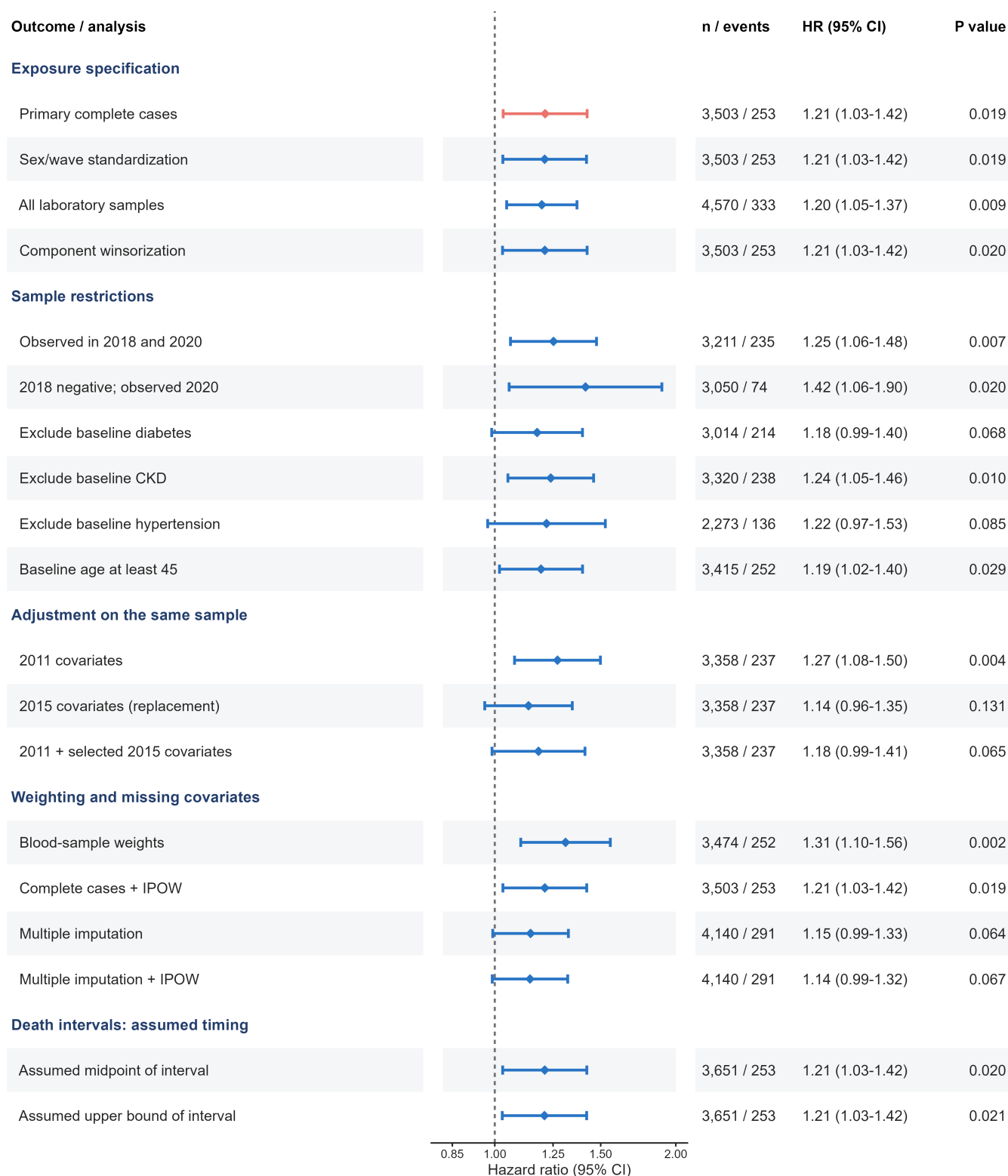
(A) Fully adjusted associations for the arithmetic mean, sex/wave-standardized average, and change measures. The displayed standardized burden is an operational summary of two examinations, not a measured continuous cumulative exposure. (B) Fully adjusted stroke associations for UAI quartiles and longitudinal change patterns; the reference categories were quartile 1 and stable-low UAI. Error bars denote 95% confidence intervals. These alternative specifications are exploratory, and their relative effect sizes do not establish biological superiority. UAI, uric acid index.

Supplementary Figure S3. Separate associations of UAI and its component biomarkers



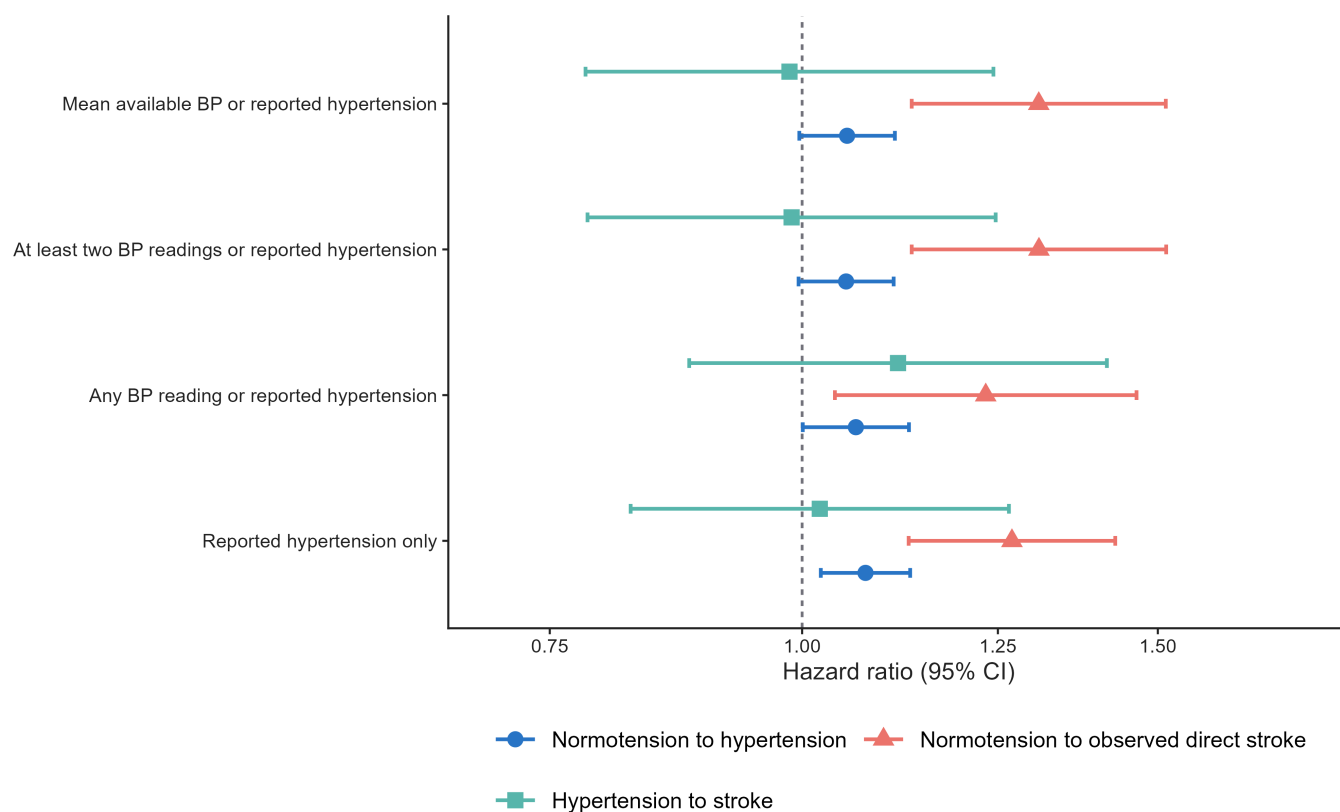
(A) Fully adjusted separate-model associations of mean UAI, triglyceride-glucose index (TyG), and uric acid with outcomes in the repeated-measure cohort. (B) Fully adjusted separate-model associations of baseline biomarkers with recorded hypertension-stroke state sequences. Effects are expressed per 1-SD higher biomarker using the corresponding reference scaling; error bars denote 95% confidence intervals. These separate-model comparisons do not test the incremental information from uric acid beyond TyG. The same-sample joint-component models and formal incremental tests are reported separately in Supplementary Table S4. Recorded sequence labels do not establish biological ordering or mediation.

Supplementary Figure S4. Selected stroke sensitivity analyses



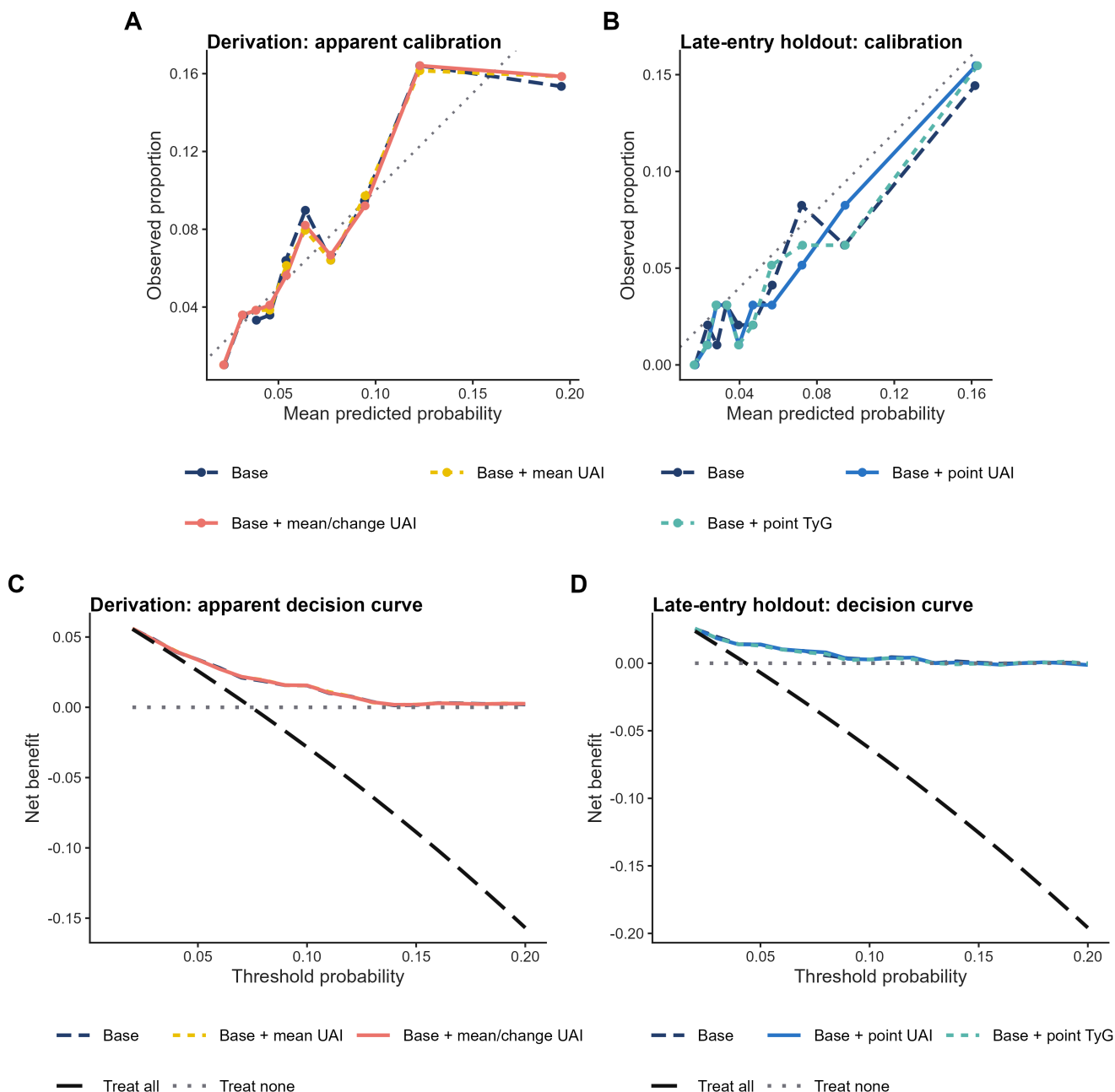
Diamonds and bars denote complementary log-log hazard ratios (HRs) and 95% confidence intervals; the primary complete-case estimate is coral. The main mean-UAI scale is the fixed 4,140-person reference SD (0.659 units); alternative exposure specifications use their corresponding reference standardization. The three adjustment rows use the identical 3,358 participants and 237 events. The strict 2020 analysis requires observed stroke-negative status in 2018 and observed status in 2020, with a two-year interval. Multiple imputation (MI; 30 imputations) applies to covariates, not exposure or outcome. Inverse-probability-of-observation weighting (IPOW) is shown separately from MI; its confidence intervals are conditional on estimated weights. Death-interval rows add recovered death information under assumed event-free follow-up until an assumed interval midpoint or upper bound, using the whole 2015-2020 interval when a narrower interval is unavailable. These rows assume no unreported pre-death stroke and do not estimate a competing-risk cumulative incidence. CKD, chronic kidney disease. Complete specifications and additional scenarios are in Supplementary Table S7.

Supplementary Figure S5. Alternative definitions of recorded hypertension



Fully adjusted associations per 1-SD higher baseline UAI for recorded hypertension-stroke state sequences under four hypertension definitions based on original-wave blood pressure readings and self-report. Bars denote 95% confidence intervals. These sensitivity analyses assess dependence on the observed hypertension definition; they do not establish biological sequence, time of hypertension onset, or a mediated effect. BP, blood pressure; CI, confidence interval; UAI, uric acid index.

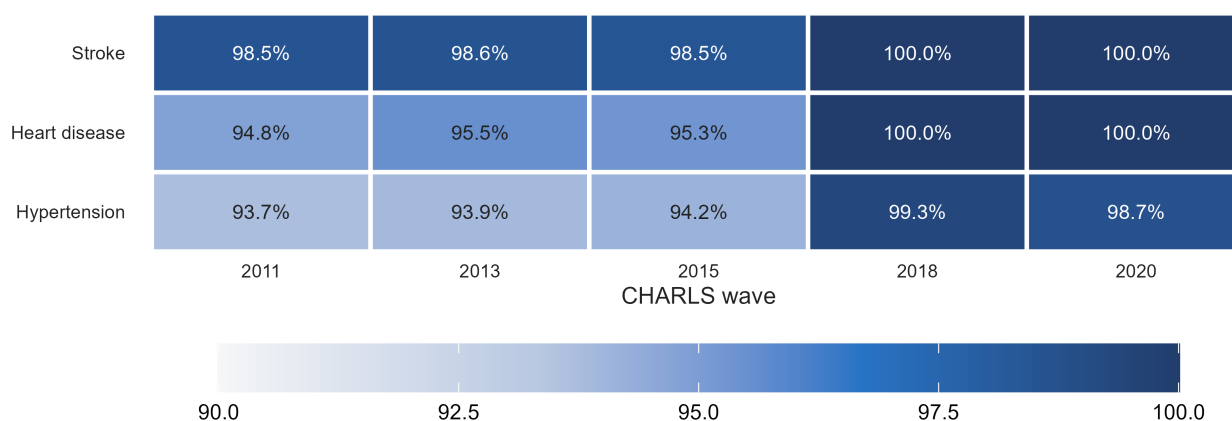
Supplementary Figure S6. Calibration and decision-curve diagnostics for stroke prediction



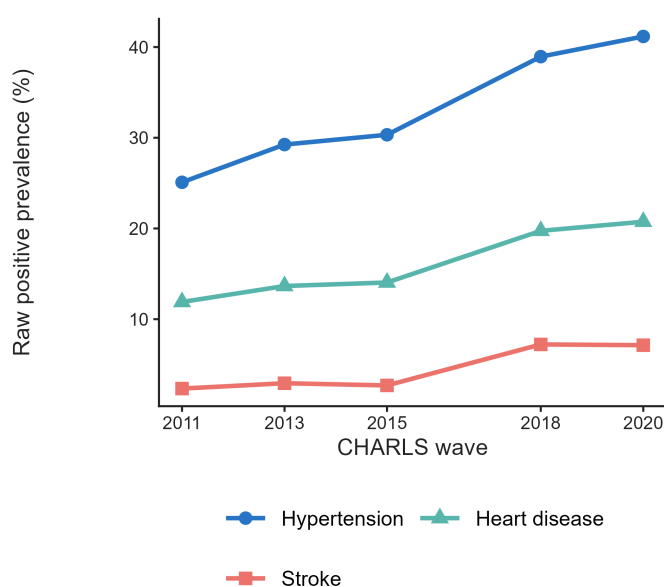
(A) Apparent grouped calibration in the repeated-measure derivation sample for the clinical base model, base plus mean UAI, and base plus mean/change UAI. (B) Grouped calibration of frozen point-biomarker models in the late-entry holdout. Points indicate the mean predicted probability and observed event proportion within deciles of predicted risk; the dotted diagonal indicates ideal calibration. (C) Apparent derivation decision curves. (D) Frozen-model decision curves in the late-entry holdout. Black long-dashed and gray dotted lines denote treating everyone and treating no one, respectively. Base denotes the 2015 clinical model. The derivation and holdout samples comprised 3,904 participants with 291 events and 969 participants with 42 events. Derivation plots are descriptive apparent displays; optimism-corrected performance and calibration estimates are reported in Supplementary Table S11. Holdout predictions use coefficients, imputation values, and scaling parameters frozen in the derivation cohort. Decision curves are exploratory and do not establish clinical implementation benefit. Mean-exposure models could not be evaluated in the late-entry cohort because 2011 biomarkers were unavailable.

Supplementary Figure S7. Original-wave endpoint audit

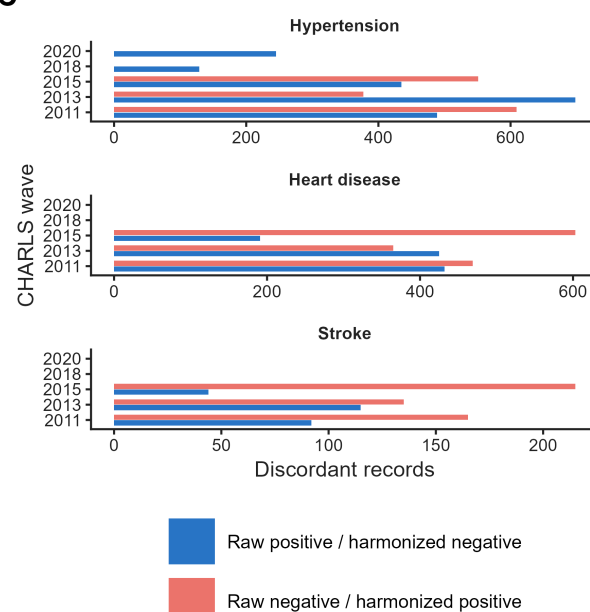
A



B

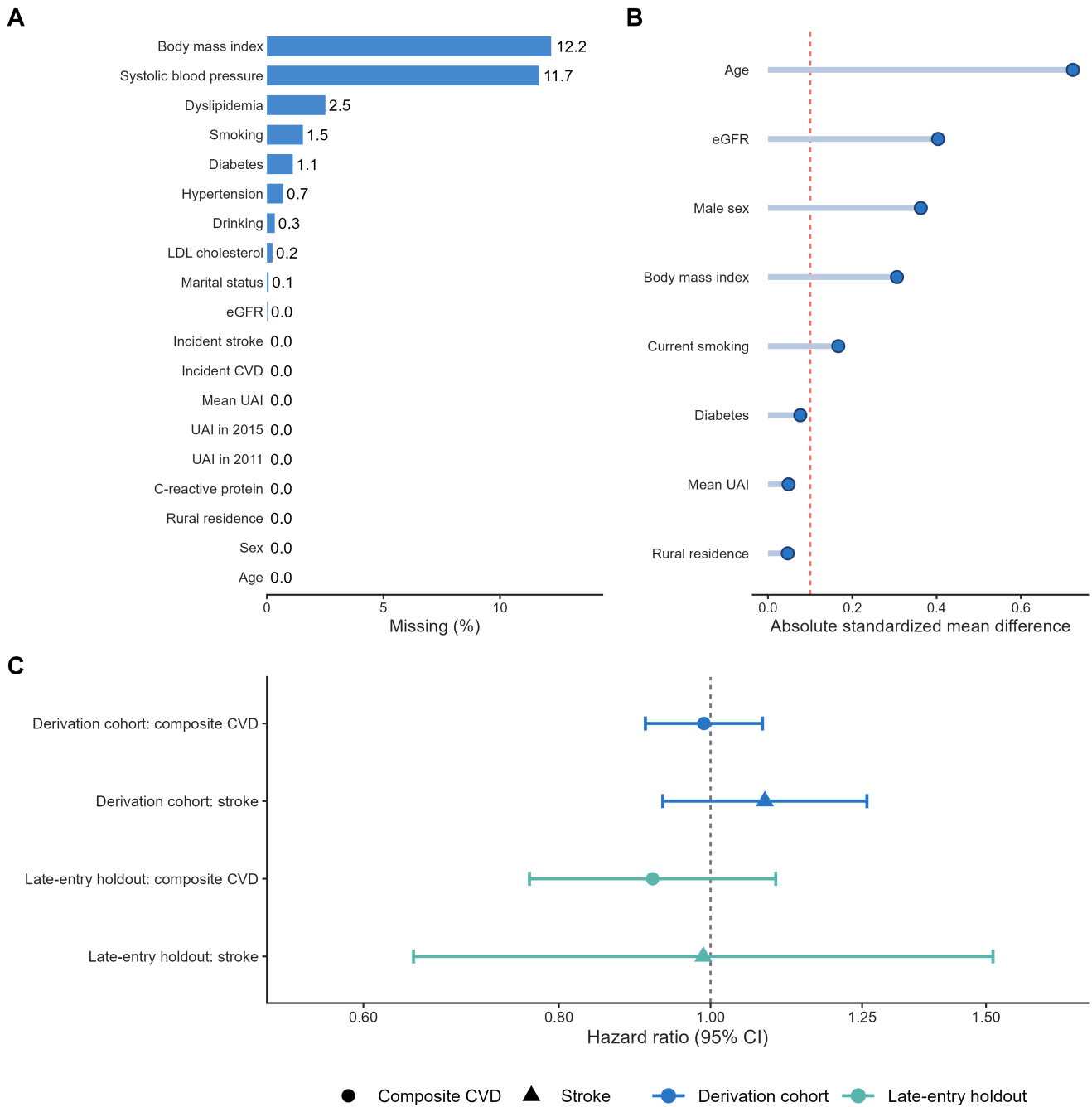


C



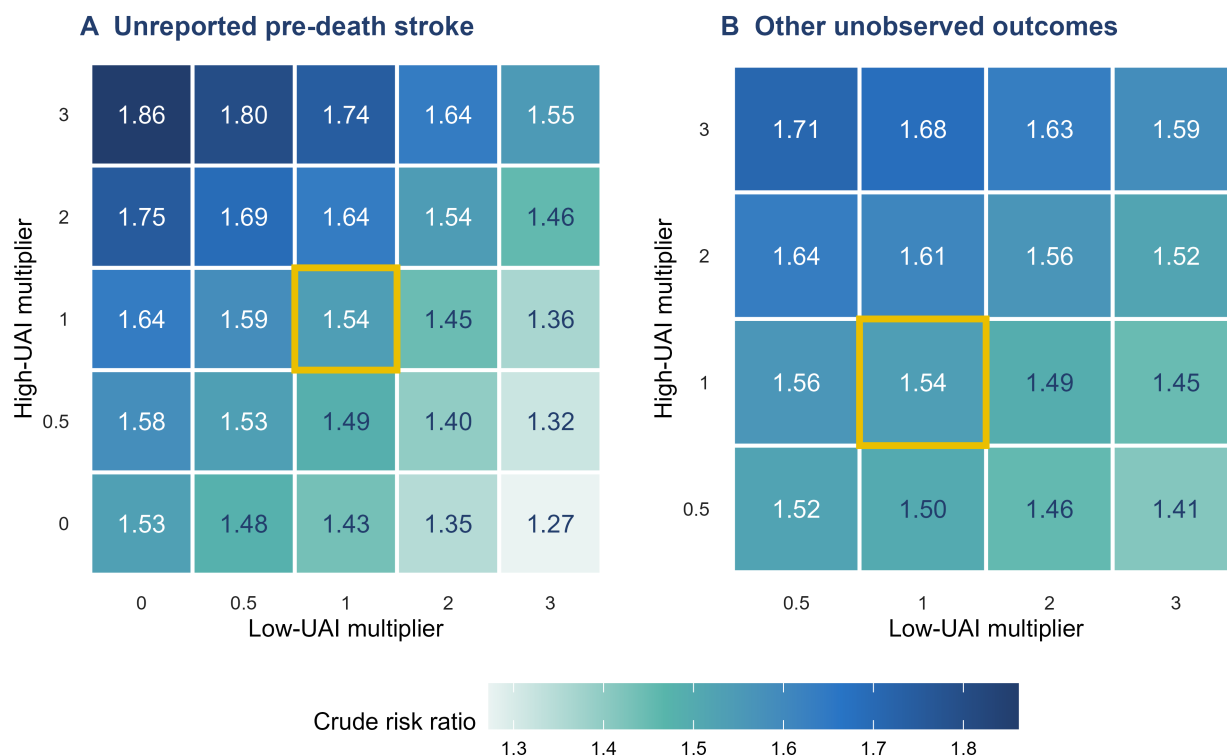
(A) Agreement between original-wave and consolidated endpoints among records observed in both sources. (B) Original-wave positive prevalence at each CHARLS examination, calculated within the wave-specific observed population. These changing wave populations do not form a fixed risk set, and the displayed prevalence is not incident stroke risk. (C) Direction and number of discordant records. Original-wave endpoints took precedence whenever observed and discordant, with the documented consolidated fallback for missing original-wave values. This audit evaluates agreement and reproducibility between data-processing sources, not clinical validation against medical records. Split-file, fixed-panel, and correction-branch audits are detailed in Supplementary Table S14; correction-sensitive model results are in Supplementary Table S7G.

Supplementary Figure S8. Selection and late-entry cohort diagnostics



(A) Variable-level missingness in the repeated-UAI cohort. Outcome availability at this selection step means at least one post-landmark observation, not necessarily complete outcome ascertainment through 2020. (B) Absolute standardized mean differences between included and otherwise eligible participants without any subsequent outcome observation; the dashed line marks 0.10. Of the 219 participants in this excluded group, 175 had recorded post-landmark deaths and 44 had other unconfirmed loss, so the group must not be interpreted as exclusively living participants lost to follow-up. (C) Associations of point UAI measured in 2015 in the derivation and late-entry cohorts, with scaling parameters from the derivation cohort. This point-exposure comparison does not validate the two-examination mean in the late-entry sample. Observation weighting, MI, and fixed-horizon outcome-availability analyses are reported separately. UAI, uric acid index; MI, multiple imputation.

Supplementary Figure S9. Death-stratified scenarios for unobserved stroke outcomes



Each cell is a scenario-based crude risk ratio comparing high versus low mean UAI, divided at the observed-cohort median, among all 4,359 otherwise eligible participants. Known horizon outcomes were available for 3,904 participants; the remaining 455 comprised 284 recorded deaths with unknown pre-death stroke and 171 other unknown outcomes. Multipliers scale the group-specific stroke probability among participants with known outcomes. (A) The probability of an unreported stroke before recorded death varies independently in the low- and high-UAI groups; other-unknown multipliers equal 1. (B) Other-unknown outcome multipliers vary while both pre-death multipliers equal 1. Gold outlines mark the common all-multipliers-equal-1 reference, displayed in both panels (25 plus 16 scenario rows). Death scenarios assign possible pre-death stroke and do not assume survival after death. These illustrative fixed scenarios are not calibrated CHARLS misclassification rates, have no sampling confidence intervals, and neither correct the primary adjusted continuous-exposure HR nor estimate a competing-risk cumulative incidence. Results depend on the stated assumptions; a risk ratio above 1 within this grid does not establish robustness to all selection mechanisms.