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Continuous CKM Severity Score: Longitudinal Associations and Treatment-Related Interpretability

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Research Article

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Continuous CKM Severity Score: Longitudinal Associations and Treatment-Related Interpretability

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Abstract

Background

Initial evaluation of the continuous cardiovascular-kidney-metabolic syndrome severity score (cCKMS-S), including analyses in NHANES, linked the score to mortality. Its outcome associations in an independent longitudinal setting and the interpretation of within-person change remain uncertain because treatment indicators contribute positively to the score.

Methods

Published sex-specific equations were applied without recalibration. In CHARLS, associations of the 2015 score and 2011–2015 change with incident cardiovascular disease were evaluated using weighted complementary log-log models. NHANES served as a survey-aware benchmark for associations with all-cause and heart-disease mortality. Covariates were multiply imputed with outcomes and follow-up included as auxiliary predictors. Secondary analyses examined dose–response, medication and nonmedication change, ordered-indicator one-factor structure, and prespecified robustness checks.

Results

Among 2,807 CHARLS participants, 534 developed cardiovascular disease. Each 1-SD higher 2015 cCKMS-S was associated with incident cardiovascular disease (hazard-ratio analogue 1.39, 95% confidence interval [CI] 1.29–1.50); each SD greater score change was also associated with the outcome (1.29, 95% CI 1.20–1.39). Among 18,592 NHANES participants, 2,385 all-cause and 605 heart-disease deaths occurred; corresponding hazard ratios per 1-SD were 1.19 (95% CI 1.11–1.27) and 1.50 (95% CI 1.35–1.68). Mutually adjusted nonmedication and medication-score changes were each associated with incident cardiovascular disease (1.19 for both), but this decomposition was noncausal. Ordered-indicator loading patterns were similar, whereas global one-factor fit was mixed. Alternative score equations attenuated the CHARLS estimates, but positive directions were retained across sensitivity analyses.

Conclusions

In CHARLS, cCKMS-S level and two-time-point increase were associated with subsequent cardiovascular disease; NHANES provided a consistent survey-aware mortality benchmark. Medication-related scoring and incomplete one-factor fit constrain interpretation of change

and cross-population comparability. Any clinical application would require independent calibration and utility-focused validation.

Keywords

Cardiovascular-kidney-metabolic syndrome; cCKMS-S; cardiovascular disease; mortality; longitudinal change; treatment intensity; NHANES; CHARLS

Research Insights

Required question	**Highlights**
What is currently known about this topic?	cCKMS-S combines physiological, smoking, and treatment information. Its longitudinal interpretation remains uncertain.
What is the key research question?	Is cCKMS-S level and change associated with incident CVD in an independent cohort?
What is new?	CHARLS estimates were 1.39 for score level and 1.29 for score change. NHANES benchmark estimates were 1.19 and 1.50 for mortality. Treatment and nonmedication changes contributed separately; one-factor fit was mixed.
How might this study influence clinical practice?	Treat cCKMS-S as a research descriptor pending calibration and utility testing.

Introduction

Cardiovascular disease remains the leading cause of death and disability-adjusted life-years worldwide, with metabolic risk exposures contributing importantly to its continuing burden [1-3]. The American Heart Association cardiovascular-kidney-metabolic (CKM) framework formalizes the reciprocal links among excess adiposity, metabolic risk factors, chronic kidney disease, and cardiovascular disease along a clinical continuum [4]. These conditions frequently overlap in population settings rather than occurring in isolation [5]. CKM staging offers a practical vocabulary for this continuum,[6-8] but threshold-based categories inevitably compress heterogeneity within stages and may be insensitive to modest changes over time [9]. A continuous measure may therefore complement staging by quantifying gradations of CKM burden and their longitudinal evolution.

Continuous metabolic syndrome severity scores derived from confirmatory factor analysis provided an earlier framework for representing clustered metabolic abnormalities on a single scale [10-11]. Such scores have been associated with future coronary heart disease across sex and racial groups [12]. More recently, Masoumi and colleagues developed the continuous cardiovascular-kidney-metabolic syndrome severity score (cCKMS-S), which combines systolic blood pressure, waist circumference, fasting glucose, triglycerides, high-density lipoprotein cholesterol, estimated glomerular filtration rate, smoking, and three treatment indicators in sex-specific equations [13]. The score discriminated CKM stages in temporal and external validation and was associated with mortality in both TLGS and NHANES [13]. However, the positive coefficients assigned to antihypertensive, glucose-lowering, and lipid-lowering therapy mean that a higher or increasing score can reflect treatment initiation as well as worsening physiology [14]. The score is also conceptually distinct from established absolute-risk equations such as PREVENT, because it measures multidomain severity rather than calibrated event probability [15-16].

The original cCKMS-S study developed the equations in the Tehran Lipid and Glucose Study. It evaluated cross-sectional CKM staging and mortality associations in the National Health and Nutrition Examination Survey (NHANES), but did not assess incident cardiovascular disease in an independent Chinese cohort or within-person score change [13]. Recent analyses, including those in the China Health and Retirement Longitudinal Study (CHARLS), have related several insulin-resistance surrogate indices to incident cardiovascular disease across CKM stages [17-21] and have examined baseline, repeated-measure burden, and two-time-point patterns of the triglyceride-glucose index–visceral lipid

ratio [22]. These studies support longitudinal assessment of composite metabolic burden, yet they do not resolve how cCKMS-S treatment components affect change interpretation or how consistently its heterogeneous components behave across populations. It therefore remains unclear whether cCKMS-S retains outcome-based meaning in an independent longitudinal setting and whether within-person changes can be interpreted as changes in underlying CKM burden without accounting for treatment intensity.

We addressed these questions with CHARLS as an independent longitudinal setting and NHANES as a survey-aware mortality benchmark. First, we evaluated 2015 cCKMS-S and its 2011–2015 change in relation to incident cardiovascular disease in CHARLS, while estimating all-cause and heart-disease mortality associations in NHANES with full survey-design correction. Second, we separated medication-related from nonmedication change to clarify the treatment-intensity contribution. Third, we assessed component distributions and exploratory one-factor structure, characterized dose–response and subgroup patterns, quantified apparent incremental discrimination, and tested the sensitivity of associations to alternative score equations, kidney-function equations, weighting strategies, and outcome definitions. The aim was not to establish a universal scale, treatment target, or standalone risk calculator, but to define the prognostic information and interpretive boundaries of cCKMS-S in longitudinal application.

Methods

Study design and data sources

This study used two complementary population-based data sources. Ten cycles of the National Health and Nutrition Examination Survey (NHANES; 1999–2018), a stratified multistage survey of the noninstitutionalized US population, were linked to the 2019 public-use mortality file [23-25]. The China Health and Retirement Longitudinal Study (CHARLS) is a multistage probability sample of Chinese adults aged ≥45 years [26-27]. CHARLS scores were measured in 2011 and 2015, and cardiovascular disease (CVD) was assessed in 2018 and 2020. Cohort-specific associations were not pooled because the outcomes and estimands differed. Supplementary methods and outputs are reported in Figs. S1–S4 and Tables S1–S11.

Study populations

The initial NHANES pool included 101,316 participants. Sequential exclusions for age outside 20–80 years (n=47,860), pregnancy (n=1,541), nonpositive fasting weight

(n=30,784), incomplete physiological score components (n=1,531), unavailable smoking or treatment indicators (n=985), undefined mortality linkage/follow-up (n=22), and zero follow-up (n=1) left 18,592 adults. From 25,586 harmonized CHARLS records, exclusions were no eligible 2011 interview at age ≥45 years (n=8,655), age >80 years at either score wave or no living 2015 interview (n=3,525), incomplete two-wave fasting physiological components (n=8,923), unavailable two-wave smoking or treatment indicators (n=673), prevalent or indeterminate CVD through 2015 (n=841), no definable 2018/2020 CVD status (n=140), and nonpositive 2015 blood-sample weight (n=22), leaving 2,807 adults. No participant failed the valid-sex/design step. Fig. 1 presents both funnels. Fig. S2 compares post-landmark participants with and without observed outcomes; Table S11 compares participants eligible and ineligible for two-wave fasting-biomarker analysis within the age-, interview-, and sex-eligible reference population. Because no common sampling weight was available across these groups, standardized differences in the latter comparison were unweighted [28].

cCKMS-S construction

The continuous cardiovascular-kidney-metabolic syndrome severity score (cCKMS-S) was calculated without recalibration using published sex-specific equations for adults aged 20–80 years [13]. For men,

$$\text{cCKMS-S (men)} = -0.62 + 0.0014(\text{SBP}) + 0.0021(\text{WC}) + 0.0034(\text{FPG}) + 0.0001(\text{TG}) - 0.0011(\text{HDL-C}) - 0.0016(\text{eGFR}) + 0.0017(\text{Smoking}) + 0.4874(\text{AntiDM}) + 0.0631(\text{AntiHTN}) + 0.1194(\text{LipidRx}).$$

For women,

$$\text{cCKMS-S (women)} = -1.62 + 0.0065(\text{SBP}) + 0.0086(\text{WC}) + 0.0042(\text{FPG}) + 0.0011(\text{TG}) - 0.0040(\text{HDL-C}) - 0.0054(\text{eGFR}) + 0.0199(\text{Smoking}) + 0.4486(\text{AntiDM}) + 0.2335(\text{AntiHTN}) + 0.2251(\text{LipidRx}).$$

SBP was in mmHg; waist circumference (WC) in cm; fasting plasma glucose (FPG), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) in mg/dL; and estimated glomerular filtration rate (eGFR) in mL/min/1.73 m². Smoking and current antidiabetic (AntiDM), antihypertensive (AntiHTN), and lipid-lowering therapy (LipidRx) were binary. eGFR used the 2009 CKD-EPI creatinine equation [29]. Primary scaling was per cohort-specific standard deviation (SD); cohort-specific quartiles used Q1 as reference. Tables S1 and S3 provide coding and formula checks.

Longitudinal score measures and treatment decomposition

In CHARLS, 2015 cCKMS-S was the landmark exposure and ΔcCKMS-S = cCKMS-S_{2015} − cCKMS-S_{2011}. The score was partitioned into physiological (six biomarkers), behavioral (smoking), and medication (three therapies) components; the first two formed the nonmedication component. Medication and nonmedication changes were examined jointly. Therapies were classified as never, initiated, continued, or discontinued. Direction patterns used a prespecified 0.2-SD buffer for the 2011 score to define concordant improvement, medication-related discordance, concordant worsening, or other/stable; zero threshold was tested secondarily. These were score-decomposition, not treatment-effect, estimands.

Outcomes

CHARLS incident CVD was defined as the first self-report in 2018 or 2020 of physician-diagnosed heart disease (including myocardial infarction, coronary disease, angina, heart failure, or other heart problems) or stroke after a disease-free 2015 landmark. Refusal, unknown, and unexplained skips were not coded negative. First reports were assigned to 2015–2018, 2018–2020 after a negative 2018 response, or 2015–2020 when 2018 was missing; exact onset dates were not imputed. Heart disease and stroke were secondary outcomes. Ascertainment was self-reported and not independently adjudicated [30-31]. Participants without definable post-landmark CVD status were excluded; the available analysis did not distinguish death from other reasons for absent outcome ascertainment and therefore estimated associations among participants with ascertainable follow-up status rather than a competing-risk CVD estimand for the full landmark cohort.

NHANES all-cause death was MORTSTAT=1; heart-disease death was UCOD_LEADING=1 among decedents, not participant-level ICD-10 coding [24]. Follow-up (PERMTH_EXM/12) ended at death or December 31, 2019.

Covariates

Covariates were selected using subject-matter knowledge and a directed acyclic graph (Fig. S1). CHARLS covariates were age, sex, rural residence, education, partnership, log per-capita economic resources, drinking, physical activity, sleep duration, CES-D-10 score, and non-CKM comorbidity count [32]. NHANES covariates were age, sex, race/ethnicity, education, partnership, poverty-income ratio, cycle, drinking, physical activity, baseline CVD, cancer, and non-CKM comorbidity count. Score components, overlapping diagnoses,

and body mass index were excluded to avoid overadjustment. Change models additionally adjusted for 2011 cCKMS-S.

Missing data and weighting

Assuming covariates were conditionally missing at random, we imputed them separately by cohort using chained equations (30 datasets; 20 iterations), predictive mean matching for continuous/ordinal variables, and logistic regression for binary variables [33]. Score components, exposures, outcomes, and follow-up were not imputed. To preserve exposure–outcome associations, imputation predictors included score measures and design-related weights together with incident-CVD status and observed follow-up in CHARLS, and both mortality indicators plus a Nelson–Aalen cumulative-hazard estimate for follow-up in NHANES[34]. Rubin's rules combined estimates; no logged imputation events occurred, and Table S2 reports missingness and convergence diagnostics.

NHANES analyses incorporated fasting weights, strata, and primary sampling units; 1999–2002 four-year weights were divided by 5 and subsequent two-year weights by 10, with design identifiers nested by cycle. CHARLS models multiplied the 2015 blood-sample weight by stabilized inverse-probability-of-observation weights estimated from age, sex, residence, education, partnership, 2015 score, smoking, and therapies [35]. Combined weights were truncated at the 1st/99th percentiles (Table S10).

Statistical analyses

Continuous characteristics were reported as weighted means (standard errors) when compatible with normality and otherwise as weighted medians (interquartile ranges); categorical variables were unweighted counts and weighted percentages. Across quartiles, design-based Wald and Rao–Scott tests were used [36]. CHARLS person-period data were analyzed using weighted complementary log-log models with interval indicators, a log interval-length offset, and community/individual clustering [37-38]. NHANES mortality was analyzed using survey-weighted Cox models [39-40]. Hazard-ratio analogues or hazard ratios with 95% confidence intervals were estimated per 1-SD, by quartile, and for ordinal quartile trend.

Model 1 included exposure and follow-up interval in CHARLS (change models also included 2011 score) and exposure alone in NHANES. CHARLS Model 2 added age, sex, rural residence, education, partnership, and log per-capita economic resources; Model 3 further added current drinking, physical activity, sleep duration, CES-D-10, and non-CKM

comorbidity count. NHANES Model 2 added age, sex, race/ethnicity, education, partnership, poverty-income ratio, and cycle; Model 3 further added current drinking, physical activity, baseline CVD, cancer, and non-CKM comorbidity count.

Restricted cubic splines used four knots at the 5th, 35th, 65th, and 95th percentiles and the median as reference; overall and nonlinear Wald tests were reported [41]. Model 3 subgroup interactions were tested for sex, age (<60/≥60 years), and baseline treatment, plus NHANES race/ethnicity; Benjamini–Hochberg false-discovery-rate q values and stratum events were reported [42]. The four continuous-exposure outcome associations were the prespecified primary estimands. Apart from false-discovery-rate control within the subgroup-interaction families, no global multiplicity correction was applied across secondary and exploratory analyses, which were interpreted as supportive rather than independently confirmatory. Exploratory weighted one-factor models standardized continuous physiological components and treated smoking and the three treatment indicators as ordered variables, using weighted least squares with mean- and variance-adjusted estimation and theta parameterization [43]. Models were fitted separately in NHANES and each CHARLS wave; loading-pattern congruence was descriptive and did not constitute a test of measurement invariance [44-45]. Robust-maximum-likelihood models treating all indicators as continuous were retained as an estimator-sensitivity analysis. Incremental discrimination and calibration after adding cCKMS-S were described as first-imputation, non-resampled apparent performance rather than validation or clinical-utility evaluation [46-48].

Sensitivity analyses

Sensitivity analyses used complete cases; age-by-sex score equations; the 2021 race-free CKD-EPI equation [49]; alternative CHARLS weights; exclusion of first-interval CHARLS events; exclusion of baseline CVD in NHANES; three- and five-knot splines and 1st–99th-percentile trimming; zero-threshold treatment-pattern classification; and separate CHARLS heart-disease and stroke outcomes. NHANES proportional hazards were assessed using weighted Schoenfeld residual tests;[50] 0–5-year and >5-year effects characterized departures. Weighted generalized estimating equations tested the CHARLS interval model, and an unweighted first-imputation Fine–Gray model treated other death as competing with heart-disease death [51]. Tables S5–S9 provide the corresponding estimates.

Software, reporting, and ethics

Analyses used R 4.5.2 with survey 4.5, survival 3.8.6, mice 3.19.0, rms 8.1.1, lavaan 0.7.2, geepack 1.3.13, cmprsk 2.2.12, and timeROC 0.4.1; versions were frozen using renv. Tests were two-sided with $P < 0.05$. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies[52]. NHANES protocols were approved by the NCHS review board (98-12, 2005-06, 2011-17, and 2018-01), with documented consent [53]. CHARLS household and blood collection were approved by the Peking University Biomedical Ethics Review Committee (IRB00001052-11015 and IRB00001052-11014), with written consent [54]. No new participant contact or data collection occurred. The submitting authors must add their institution's determination for this deidentified secondary analysis and the final code-repository citation before submission.

Results

Study population and baseline characteristics

The analytic samples comprised 18,592 of 101,316 screened NHANES participants and 2,807 of 25,586 screened CHARLS records (Fig. 1). During a median follow-up of 9.1 years (178,185.9 person-years), 2,385 NHANES participants (12.8%) died from any cause and 605 (3.3%) died from heart disease, corresponding to crude rates of 13.4 and 3.4 deaths per 1,000 person-years, respectively. In CHARLS, 534 participants (19.0%) developed CVD during a median nominal follow-up of 5.0 years, representing 13,059 nominal person-years because onset was assigned to survey intervals rather than exact dates.

Higher score quartiles were accompanied by older age and a generally less favorable cardiometabolic profile (Table 1). In NHANES, the weighted median age increased from 35 years in Q1 to 62 years in Q4, while systolic blood pressure increased from 109.33 to 130.67 mmHg. The corresponding CHARLS values were 56 versus 62 years and 115.67 versus 139.00 mmHg. Within the 13,406-person CHARLS age-, interview-, and sex-eligible reference population, 4,483 participants met the two-wave fasting-physiology requirement. Across 16 available baseline descriptors, the largest absolute standardized mean difference between biomarker-eligible and ineligible participants was 0.096; this unweighted comparison does not address unmeasured selection (Table S11). Compared with the 2,807 included CHARLS participants, the 137 otherwise eligible participants without an observed eligible outcome were older (60.7 vs 56.7 years; standardized mean difference, 0.467 in absolute value) and had lower eGFR (90.3 vs 94.7 mL/min/1.73 m^2; absolute standardized

mean difference, 0.335) (Fig. S2). Stabilized observation weights remained centered near 1.00, and truncation increased the effective sample size of the combined person-period weights from 1,635 to 3,780 (Table S10).

Distribution and measurement structure of cCKMS-S

The standardized score distributions overlapped across NHANES and the two CHARLS waves, whereas the primary ordered-indicator one-factor models showed heterogeneous global fit (Fig. 2 and Table S4). CFI/RMSEA values were 0.825/0.119 for NHANES, 0.876/0.053 for CHARLS 2011, and 0.740/0.040 for CHARLS 2015; all models converged without negative residual variances. The strongest absolute standardized loading was antidiabetic therapy in NHANES (0.970), CHARLS 2011 (0.734), and CHARLS 2015 (0.740). Loading-pattern congruence was 0.963 between NHANES and CHARLS 2011, 0.963 between NHANES and CHARLS 2015, and 0.993 between the two CHARLS waves. Despite the high descriptive loading similarity, these models did not establish measurement invariance, particularly given their mixed global fit. Robust-maximum-likelihood sensitivity models were less stable and also had limited fit. Alternative-equation score shifts are displayed in Fig. S3 and quantified with the sensitivity analyses below.

Prospective associations in CHARLS

Both the 2015 cCKMS-S level and its 2011–2015 change were positively associated with subsequent incident CVD after full adjustment (Table 2). Each 1-SD higher 2015 score was associated with a hazard-ratio analogue of 1.39 (95% CI 1.29–1.50, $P < 0.001$), and each 1-SD greater change was associated with a hazard-ratio analogue of 1.29 (95% CI 1.20–1.39, $P < 0.001$). Compared with Q1, the Q4 estimates were 2.46 (95% CI 1.85–3.28) for the 2015 score and 2.20 (95% CI 1.62–2.99) for score change (both P for trend < 0.001). Q2 estimates were null for both exposures, whereas Q3 and Q4 estimates were elevated, indicating a step-like rather than evenly graded quartile pattern. The longitudinal decomposition underlying the change-score estimate is presented in Fig. 3 and reported below.

Mortality associations in NHANES

Higher baseline cCKMS-S was associated with both mortality outcomes in fully adjusted survey-weighted models (Table 3). Per 1-SD higher score, the HR was 1.19 for all-cause mortality (95% CI 1.11–1.27, $P < 0.001$) and 1.50 for heart-disease mortality (95% CI 1.35–1.68, $P < 0.001$). The Q4-versus-Q1 HR was 1.41 (95% CI 1.07–1.86, $P = 0.015$) for all-cause mortality and 4.61 (95% CI 2.30–9.25, $P < 0.001$) for heart-disease mortality (both P

for trend < 0.001). For all-cause mortality, Q2 and Q3 were null; for heart-disease mortality, Q2 was null but Q3 and Q4 were elevated. Thus, the quartile results did not show an evenly spaced gradient despite significant ordinal trends.

Dose–response associations

The fully adjusted spline analyses were overall significant for all four exposure–outcome pairs (all P for overall < 0.001) (Fig. 4). The associations were approximately linear for the CHARLS 2015 score (P for nonlinearity = 0.191), CHARLS score change (P for nonlinearity = 0.069), and NHANES all-cause mortality (P for nonlinearity = 0.772). In contrast, the association with heart-disease mortality was nonlinear (P for nonlinearity = 0.013), with wider uncertainty at the distribution tails. The heart-disease mortality result remained nonlinear with three knots, five knots, and 1st–99th-percentile trimming (P for nonlinearity = 0.028, 0.011, and 0.003, respectively) (Fig. S4). Evidence for nonlinearity of CHARLS score change was specification-sensitive, ranging from P = 0.890 with three knots to P = 0.050 with five knots and P = 0.004 after tail trimming; it was therefore not treated as stable nonlinearity.

Treatment-related interpretability, score decomposition, and component outcomes

Longitudinal score change reflected both nonmedication change and treatment escalation (Fig. 3 and Table S8). Before mutual adjustment, the hazard-ratio analogues per 1-SD were 1.26 (95% CI 1.15–1.38) for nonmedication change and 1.23 (95% CI 1.14–1.33) for medication-score change. With both components in the same model, the corresponding estimates were 1.19 (95% CI 1.09–1.30) and 1.19 (95% CI 1.10–1.29), respectively (all P < 0.001). The medication and nonmedication changes summed exactly to total change. Their blood-weighted correlation was 0.016 (approximate two-predictor variance-inflation factor, 1.000), indicating that the mutually adjusted estimates were not driven by collinearity; the decomposition nevertheless remained noncausal. After adjustment for nonmedication change, initiation of any treatment was associated with incident CVD (hazard-ratio analogue = 2.10, 95% CI 1.68–2.62, P < 0.001). The prespecified medication-related discordance pattern comprised only 48 participants (weighted 1.51%) and had an imprecise estimate (hazard-ratio analogue = 1.38, 95% CI 0.81–2.33, P = 0.233); it was not interpreted as a positive subgroup finding. Associations were also positive for the component outcomes: for the 2015 score, estimates were 1.36 for heart disease and 1.46 for stroke; for score change, they were 1.32 and 1.31, respectively (all P < 0.001) (Table S9).

Subgroup analyses

No CHARLS interaction survived false-discovery-rate correction (all q values ≥ 0.299) (Fig. 5 and Table S7). In NHANES, the all-cause mortality association was stronger in men than women (HR = 1.40 vs 1.11; P for interaction = 0.001, q = 0.006) and in participants aged <60 versus ≥60 years (HR = 1.43 vs 1.10; P for interaction < 0.001, q < 0.001). The heart-disease mortality association was likewise stronger at age <60 than ≥60 years (HR = 1.85 vs 1.35; P for interaction < 0.001, q < 0.001). Its nominal sex interaction did not survive correction (P for interaction = 0.039, q = 0.137). The "Other race/ethnicity" stratum included only 18 heart-disease deaths and yielded HR = 1.56 (95% CI 0.56–4.37), warranting the prespecified sparse-event caution rather than a claim of subgroup absence or excess.

Exploratory incremental prediction

Adding cCKMS-S produced small changes in apparent discrimination in NHANES (Fig. 6 and Table S9). The C-index changed from 0.853 to 0.855 for all-cause mortality (Δ = 0.0015) and from 0.893 to 0.898 for heart-disease mortality (Δ = 0.0057). In CHARLS, the apparent weighted AUC increased from 0.641 for the base model to 0.679 after adding the 2015 score and to 0.679 after adding score change together with the baseline score (Δ = 0.0376 and 0.0378). These first-imputation, non-resampled results were reported as exploratory apparent performance; no external validation or clinical utility inference was made.

Sensitivity analyses and model diagnostics

The direction of all four primary associations remained positive across complete-case analyses, the 2021 race-free eGFR equation, alternative CHARLS weighting, exclusion of first-interval CHARLS events, and exclusion of baseline CVD in NHANES (Fig. S3 and Table S5). The age-by-sex score equations attenuated the two CHARLS estimates to 1.25 (95% CI 1.19–1.32) for the 2015 score and 1.19 (95% CI 1.11–1.26) for score change, compared with primary estimates of 1.39 and 1.29; alternative-equation correlations with the primary score ranged from 0.735 to 0.802 across CHARLS waves (Fig. S3). Across alternative CHARLS weights, estimates ranged from 1.32 to 1.46 for the 2015 score and from 1.22 to 1.36 for score change; excluding first-interval events yielded 1.51 and 1.37, respectively. Excluding baseline CVD yielded HRs of 1.17 for all-cause and 1.49 for heart-disease mortality in NHANES. Weighted GEE estimates reproduced the CHARLS primary values (1.39 and 1.29), while the first-imputation unweighted Fine–Gray estimate for heart-disease death was 1.40 (95% CI 1.29–1.52) (Table S6). Schoenfeld tests indicated

nonproportionality for cCKMS-S in both mortality models (P = 0.006 and P = 0.015). Nevertheless, the period-specific HRs remained above 1 during 0–5 years and >5 years for all-cause mortality (1.11 and 1.23) and heart-disease mortality (1.34 and 1.59); time-interaction P values were 0.056 and 0.080, respectively. The primary Cox estimates were therefore treated as average associations over follow-up rather than constant effects.

Discussion

The cCKMS-S was developed to complement categorical CKM staging by representing severity on a continuous scale, and its initial evaluation established important evidence for stage discrimination and mortality associations [13]. Building on that contribution, the present study used CHARLS to evaluate whether the score retained prospective meaning in an independent longitudinal setting. We also examined whether within-person change was informative and remained interpretable when treatment indicators were embedded in the score. Survey-aware NHANES analyses provided a mortality benchmark rather than a second independent validation, because NHANES contributed to the original score evaluation. Higher cCKMS-S level and two-time-point increase were associated with incident CVD in CHARLS, while the NHANES mortality estimates were directionally consistent. However, longitudinal change reflected both nonmedication components and treatment escalation, and the one-factor measurement results did not support an unqualified common latent scale. The score may therefore summarize outcome-relevant CKM burden, but its longitudinal interpretation requires more caution than its use as a cross-sectional severity descriptor.

The mortality findings broadly align with the original cCKMS-S report, although differences in outcome coding, survey estimation, and covariate adjustment preclude direct comparison of association magnitudes [13]. In our survey-weighted NHANES benchmark, the fully adjusted HRs per 1-SD higher score were 1.19 for all-cause mortality and 1.50 for heart-disease mortality. Evidence from CHARLS has linked several insulin-resistance surrogates with incident CVD and suggested that repeated metabolic exposure can add information beyond a single measurement [17,22]. Our corresponding hazard-ratio analogues were 1.39 for the 2015 score and 1.29 for 2011–2015 change. Unlike those studies, which examined insulin-resistance or adiposity-lipid indices, the present analysis focused on a multidomain CKM severity score and explicitly separated medication from nonmedication change. Accordingly, the principal contribution is the independent CHARLS outcome analysis and clarification of what change in this newly proposed score represents.

The pattern across outcomes is compatible with the integrated nature of CKM syndrome [55]. The AHA framework emphasizes interdependent metabolic, renal, and cardiovascular domains rather than isolated risk factors [4], and the cCKMS-S combines anthropometry, glycaemia, blood pressure, lipids, kidney function, smoking, and treatment indicators [56-58]. Positive associations with both CHARLS component outcomes argue against the overall CVD result being attributable to only heart disease or only stroke. The largely near-linear associations are also consistent with a graded burden marker rather than a single universal threshold. By contrast, the larger association with heart-disease mortality and its nonlinear shape (P for nonlinearity = 0.013) may indicate concentration of risk at the upper end of the score, where several adverse domains co-occur [59]. Because uncertainty widened in the tails and no biological intermediates were measured, this interpretation remains a result-compatible hypothesis rather than evidence for a specific pathway.

The treatment analyses highlight the most important interpretive tension. When nonmedication and medication-score changes were entered together, each remained associated with incident CVD (hazard-ratio analogue = 1.19 for both), while initiation of any treatment had an estimate of 2.10 after accounting for nonmedication change. The two change components summed exactly to total score change, and their weighted correlation was only 0.016 (approximate variance-inflation factor, 1.000), making collinearity an unlikely explanation for the mutually adjusted estimates. These results do not indicate that treatment increased cardiovascular risk. In observational data, treatment commonly marks the condition that prompted prescribing, producing confounding by indication even after adjustment [60-61]. The positive medication coefficients in the published cCKMS-S formula create an additional measurement issue: a score can increase when disease is recognized and therapy is intensified, even if subsequent physiological control improves [13]. The prespecified medication-related discordance group was too uncommon for a stable conclusion (48 participants; weighted prevalence 1.51%; estimate 1.38, 95% CI 0.81–2.33). Longitudinal cCKMS-S change may therefore contain two associated signals—physiological burden and treatment intensity—but their decomposition does not identify treatment effects.

Structural validity must be distinguished from outcome association. In the primary ordered-indicator models, loading-pattern congruence was 0.963 for both NHANES–CHARLS comparisons and 0.993 between CHARLS waves, but global fit was mixed: CFI/RMSEA values were 0.825/0.119 in NHANES, 0.876/0.053 in CHARLS 2011, and 0.740/0.040 in CHARLS 2015. The separate models were admissible, yet they were descriptive fits rather than formal tests of configural, metric, or scalar invariance; MLR sensitivity models were

less stable and also showed limited fit. The original development study likewise reported incomplete support for sex-based metric and scalar invariance and derived subgroup-specific equations [13]. In our analyses, replacing the primary equations with age-by-sex-specific equations attenuated the CHARLS estimates to 1.25 for the 2015 score and 1.19 for score change, although both remained positive. Thus, outcome-relevant information can coexist with incomplete one-factor representation. Similar score distributions or loading patterns should not be mistaken for measurement equivalence, and a universal scale or cut point should not be assumed without dedicated invariance testing and local recalibration.

The components of cCKMS-S are available from routine history, anthropometry, blood pressure, and laboratory assessment, so repeated calculation is feasible. Feasibility alone, however, does not demonstrate clinical utility. Adding the score changed the NHANES apparent C-index by only 0.0015 for all-cause mortality and 0.0057 for heart-disease mortality. The CHARLS apparent AUC increased from 0.641 to 0.679, but these calculations used only the first imputed dataset and no resampling. Such performance can be optimistic without internal and external evaluation [62-63]. These analyses should therefore be viewed as descriptive support for future prediction research, not evidence that cCKMS-S improves clinical decisions or replaces validated absolute-risk systems such as PREVENT [15]. Future evaluations of repeated use should preserve the component values and treatment history; any clinical application would require independent validation, calibration, and evidence of net benefit.

This study has three principal strengths. First, it paired an independent longitudinal CHARLS analysis of incident CVD with a survey-aware NHANES mortality benchmark while retaining each data source's design and estimand. Second, the CHARLS landmark analysis moved beyond a single baseline measurement and directly evaluated two-time-point change, including prespecified separation of medication and nonmedication components. Third, the main estimates were challenged through alternative score and eGFR equations, weighting strategies, early-event exclusions, dose–response specifications, component outcomes, competing-risk analysis, and time-varying mortality checks. Together, these features allowed outcome associations and limitations in measurement or interpretation to be evaluated in the same study.

Several limitations concern design, outcomes, and exposure measurement. First, the observational analyses remain vulnerable to residual confounding and reverse directionality, especially for treatment initiation;[64] randomized evaluations, natural experiments, or carefully specified target-trial emulations would be needed to evaluate treatment-related

questions. Second, CHARLS CVD was based on self-reported physician diagnosis and could be located only to interview intervals, so outcome misclassification and imprecise timing are possible; linkage to medical records or adjudicated registries with exact dates should be prioritized. Participants without ascertainable post-landmark CVD status were excluded, and the analysis could not separate death from other causes of absent ascertainment; observation weighting addressed measured predictors of observation but did not recover a full-cohort competing-risk estimand. Third, two laboratory waves characterize change but not a long-term trajectory and remain susceptible to regression to the mean and within-person measurement error; cohorts with at least three repeated assessments could apply time-updated or trajectory models [65-66]. Fourth, therapy variables were binary indicators without drug class, dose, adherence, treatment indication, or timing within the interval; future pharmacoepidemiologic datasets should reconstruct these details before medication-score change is interpreted clinically.

Additional limitations affect generalizability and model performance. Fifth, the CHARLS analytic sample narrowed from 13,406 age-, interview-, and sex-eligible participants to 4,483 with two-wave fasting physiology and ultimately 2,807 in the outcome analysis. Measured baseline differences between biomarker-eligible and ineligible participants were small (maximum absolute standardized difference, 0.096), but the comparison was unweighted because a common sampling weight was unavailable, and unmeasured selection remains possible. The smaller post-landmark group without observed outcomes differed in age and kidney function; observation weighting addressed measured predictors only. Replication in cohorts with broader biomarker completeness is needed. Sixth, although ordered-indicator estimation respected the binary treatment and smoking variables, one-factor fit remained incomplete and separate cohort fits did not test invariance; future work should use formal multi-group or longitudinal invariance designs, alternative measurement models, and local recalibration. Seventh, the NHANES proportional-hazards diagnostics were significant, so the Cox estimates represent averages over follow-up rather than constant associations; flexible time-varying models and adjudicated cause-specific outcomes should examine how associations evolve. Finally, incremental prediction was evaluated only in the first imputed dataset, without resampling or external validation, and it did not assess decision consequences; optimism-corrected validation, independent testing, calibration updating, and decision-curve analysis are required before clinical implementation.

Overall, these findings define where cCKMS-S may be informative and where its interpretation is limited. In CHARLS, the score behaved as an outcome-associated

longitudinal descriptor, while NHANES supplied a survey-aware mortality benchmark. Medication-related scoring and incomplete one-factor fit mean that serial or cross-population values should not be assumed to represent untreated physiological change on a common scale. cCKMS-S should remain a research descriptor until independent calibration and utility-focused validation establish an appropriate clinical role.

Conclusions

In CHARLS, higher cCKMS-S level and greater two-time-point increase were associated with subsequent CVD; survey-aware NHANES analyses provided a consistent mortality benchmark. Medication-related scoring and incomplete one-factor fit constrain interpretation of change and cross-population comparability. Any clinical-risk or monitoring role requires prior independent calibration and utility-focused validation.

Abbreviations

AntiDM, antidiabetic therapy;
AntiHTN, antihypertensive therapy;
AUC, area under the receiver operating characteristic curve;
CES-D-10, 10-item Center for Epidemiologic Studies Depression Scale;
CFA, confirmatory factor analysis;
CHARLS, China Health and Retirement Longitudinal Study;
CI, confidence interval;
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration;
CKM, cardiovascular-kidney-metabolic;
cCKMS-S, continuous cardiovascular-kidney-metabolic syndrome severity score;
CVD, cardiovascular disease;
eGFR, estimated glomerular filtration rate;
FPG, fasting plasma glucose;
HDL-C, high-density lipoprotein cholesterol;
HR, hazard ratio;
LipidRx, lipid-lowering therapy;
MICE, multiple imputation by chained equations;
NHANES, National Health and Nutrition Examination Survey;
PSU, primary sampling unit;
RCS, restricted cubic spline;
SBP, systolic blood pressure;
SD, standard deviation;
TG, triglycerides;
WC, waist circumference;

Declarations

Ethics approval and consent to participate

NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board (protocols 98-12, 2005-06, 2011-17, and 2018-01), and participants provided documented consent. CHARLS household and biomarker data collection were approved by the Peking University Biomedical Ethics Review Committee (IRB00001052-11015 and IRB00001052-11014), and participants provided written informed consent. This study used deidentified secondary data and involved no new participant contact or data collection.

Consent for publication

Not applicable.

Availability of data and materials

NHANES public-use data and linked mortality documentation are available from the National Center for Health Statistics. CHARLS data are available to registered users through the CHARLS data portal subject to its data-use terms. Reproducible R scripts, frozen package versions, analytic specifications, and machine-readable result tables accompany the project.

Competing interests

Author declaration required before submission.

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Authors' contributions

Conceptualization, methodology, supervision, and project administration: YL and WX;

Software: YL;

Formal analysis and validation: YL;

Data curation: YL;

Investigation, resources and material collection: YL;

Writing-original draft preparation: YL;

Writing-reviewing and editing: WX.

All authors read and approved the final manuscript.

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Tables

Table 1. Selected baseline characteristics of the NHANES and CHARLS analytic cohorts by quartiles of cCKMS-S

Cohort	Characteristic	Q1	Q2	Q3	Q4	P
NHANES	Age, years	35.00 (26.00, 45.00)	38.00 (29.00, 49.00)	54.00 (44.00, 64.00)	62.00 (52.00, 71.00)	<0.001
NHANES	Male	565 (11.4)	3763 (81.2)	3298 (69.9)	1595 (32.1)	<0.001
NHANES	Poverty-income ratio	3.08 (1.46, 5.00)	3.00 (1.52, 5.00)	3.45 (1.81, 5.00)	2.51 (1.37, 4.36)	<0.001
NHANES	Current smoking	898 (20.6)	1275 (26.9)	924 (19.5)	747 (16.4)	<0.001
NHANES	SBP, mmHg	109.33 (103.00, 116.00)	117.33 (111.33, 125.33)	124.67 (116.67, 136.00)	130.67 (120.00, 144.67)	<0.001
NHANES	Waist, cm	83.70 (77.00, 91.70)	94.90 (87.70, 103.00)	104.70 (96.50, 113.80)	109.00 (98.50, 120.20)	<0.001
NHANES	FPG, mg/dL	91.00 (86.00, 97.00)	97.00 (92.00, 102.00)	103.60 (97.00, 110.00)	115.90 (102.00, 144.00)	<0.001
NHANES	TG, mg/dL	75.00 (56.00, 101.00)	99.00 (72.00, 142.00)	127.00 (90.00, 187.00)	144.00 (100.00, 203.00)	<0.001
NHANES	HDL-C, mg/dL	61.00 (51.00, 73.00)	49.00 (41.00, 59.00)	46.00 (39.00, 56.00)	48.00 (40.00, 58.00)	<0.001
NHANES	eGFR, mL/min/1.73 m²	107.62 (94.76, 119.58)	101.44 (89.39, 112.50)	87.98 (75.58, 99.36)	81.46 (64.15, 97.12)	<0.001
NHANES	Non-CKM comorbidities	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 2.00)	<0.001
NHANES	Baseline CVD	76 (1.5)	124 (2.1)	604 (10.8)	1163 (23.9)	<0.001
NHANES	Cancer	204 (5.4)	195 (4.7)	545 (11.7)	711 (16.8)	<0.001
NHANES	Antidiabetic therapy	0 (0.0)	2 (0.0)	18 (0.2)	2075 (40.0)	<0.001
NHANES	Antihypertensive therapy	101 (2.2)	286 (5.5)	2112 (42.2)	3666 (77.7)	<0.001
NHANES	Lipid-lowering therapy	29 (0.8)	54 (1.4)	1049 (23.5)	2439 (52.9)	<0.001
NHANES	cCKMS-S	-0.46 (-0.60, -0.30)	-0.13 (-0.16, -0.10)	0.03 (-0.02, 0.10)	0.57 (0.33, 0.86)	<0.001
CHARLS	Age, years	56.00 (52.00, 61.00)	60.00 (53.00, 66.00)	62.00 (56.00, 69.00)	62.00 (58.00, 68.00)	<0.001
CHARLS	Male	75 (9.9)	521 (76.9)	501 (72.6)	186 (27.0)	<0.001
CHARLS	Rural residence, yes	498 (63.9)	504 (64.8)	459 (55.9)	432 (51.4)	<0.001
CHARLS	Per-capita resources	8740.00 (5370.50, 14014.00)	8555.67 (4726.00, 15360.00)	8850.00 (5200.00, 14430.00)	9326.67 (5112.50, 15655.00)	0.780
CHARLS	Current smoking	68 (9.0)	323 (45.2)	275 (35.3)	106 (16.8)	<0.001
CHARLS	SBP, mmHg	115.67 (106.67, 126.00)	120.00 (112.00, 131.33)	134.33 (120.33, 147.33)	139.00 (125.67, 151.33)	<0.001
CHARLS	Waist, cm	80.80 (75.00, 85.50)	82.50 (76.00, 87.00)	88.60 (82.70, 94.20)	91.40 (86.00, 98.50)	<0.001
CHARLS	FPG, mg/dL	90.09 (82.88, 95.50)	90.09 (84.68, 95.50)	97.30 (91.89, 106.31)	106.31 (97.30, 131.53)	<0.001
CHARLS	TG, mg/dL	92.92 (71.68, 117.70)	98.23 (71.68, 125.66)	119.47 (88.50, 167.26)	152.21 (113.27, 233.63)	<0.001
CHARLS	HDL-C, mg/dL	56.37 (49.81, 64.48)	52.12 (45.56, 59.07)	47.10 (41.70, 54.83)	47.49 (40.93, 53.67)	<0.001
CHARLS	eGFR, mL/min/1.73 m²	97.70 (91.11, 103.24)	94.08 (84.63, 99.82)	88.69 (77.07, 97.15)	89.40 (78.46, 98.30)	<0.001
CHARLS	Non-CKM comorbidities	1.00 (0.00, 1.00)	1.00 (0.00, 2.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.068
CHARLS	Antidiabetic therapy	0 (0.0)	0 (0.0)	2 (0.2)	136 (20.2)	<0.001

Cohort	Characteristic	Q1	Q2	Q3	Q4	P
CHARLS	Antihypertensive therapy	5 (0.4)	29 (3.6)	152 (19.1)	369 (51.0)	<0.001
CHARLS	Lipid-lowering therapy	6 (1.3)	3 (0.3)	17 (2.0)	121 (18.1)	<0.001
CHARLS	2015 cCKMS-S	-0.37 (-0.47, -0.29)	-0.17 (-0.20, -0.15)	-0.06 (-0.10, -0.03)	0.22 (0.08, 0.51)	<0.001
CHARLS	2011–2015 cCKMS-S change	-0.03 (-0.11, 0.08)	-0.02 (-0.06, 0.02)	0.01 (-0.04, 0.07)	0.10 (-0.02, 0.32)	<0.001

Notes

Values are unweighted n (survey-weighted %) for categorical variables and survey-weighted median (Q1, Q3) for continuous variables. The compact table retains core demographics, all physiological score components, treatment indicators, and primary score measures; additional adjustment variables are defined in Methods. NHANES estimates use fasting subsample weights with nested strata and primary sampling units; CHARLS estimates use 2015 blood-sample weights. Quartiles are cohort-specific quartiles of baseline cCKMS-S (NHANES baseline or CHARLS 2015); P values compare Q1–Q4 using design-based Wald or Rao–Scott tests as appropriate. CKM indicates cardiovascular-kidney-metabolic; cCKMS-S, continuous CKM syndrome severity score; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Q, quartile; SBP, systolic blood pressure; TG, triglycerides.

Table 2. Baseline and longitudinal cCKMS-S measures in relation to incident cardiovascular disease in CHARLS

Section	Contrast	Model 1	Model 2	Model 3
2015 cCKMS-S	Per 1 SD	1.43 (1.33, 1.53); P <0.001	1.39 (1.29, 1.49); P <0.001	1.39 (1.29, 1.50); P <0.001
2015 cCKMS-S	Q1	Reference	Reference	Reference
2015 cCKMS-S	Q2	1.18 (0.87, 1.60); P 0.297	1.20 (0.87, 1.65); P 0.278	1.20 (0.87, 1.66); P 0.258
2015 cCKMS-S	Q3	1.58 (1.19, 2.11); P 0.002	1.58 (1.16, 2.17); P 0.004	1.66 (1.22, 2.27); P 0.001
2015 cCKMS-S	Q4	2.60 (1.97, 3.43); P <0.001	2.37 (1.78, 3.15); P <0.001	2.46 (1.85, 3.28); P <0.001
2015 cCKMS-S	P for trend	P trend <0.001	P trend <0.001	P trend <0.001
2011–2015 change in cCKMS-S	Per 1 SD	1.32 (1.23, 1.41); P <0.001	1.30 (1.21, 1.41); P <0.001	1.29 (1.20, 1.39); P <0.001
2011–2015 change in cCKMS-S	Q1	Reference	Reference	Reference
2011–2015 change in	Q2	1.12 (0.83, 1.49); P 0.462	1.11 (0.82, 1.50); P 0.503	1.18 (0.87, 1.61); P 0.292

Section	Contrast	Model 1	Model 2	Model 3
cCKMS-S				
2011–2015 change in cCKMS-S	Q3	1.81 (1.37, 2.39); P <0.001	1.83 (1.38, 2.43); P <0.001	1.87 (1.40, 2.50); P <0.001
2011–2015 change in cCKMS-S	Q4	2.25 (1.67, 3.03); P <0.001	2.19 (1.62, 2.98); P <0.001	2.20 (1.62, 2.99); P <0.001
2011–2015 change in cCKMS-S	P for trend	P trend <0.001	P trend <0.001	P trend <0.001

Notes

Values are hazard-ratio analogues from survey-weighted discrete-time complementary log-log models, shown as HR (95% CI); P. Q1 is the reference quartile, and P for trend treats quartile as an ordinal variable scored 1–4. Model 1 includes exposure and follow-up interval; change models additionally adjust for 2011 cCKMS-S. Model 2 additionally adjusts for age, sex, rural residence, education, partnership, and log per-capita economic resources. Model 3 additionally adjusts for current drinking, physical activity, sleep duration, CES-D-10 score, and non-CKM comorbidity count. All models use 2015 blood-sample weights combined with stabilized inverse observation weights, cluster on community and individual, and pool 30 multiple imputations. Exposure and outcome variables were not imputed. Abbreviations: CES-D-10, 10-item Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; cCKMS-S, continuous CKM syndrome severity score; CVD, cardiovascular disease; HR, hazard ratio; Q, quartile; SD, standard deviation.

Table 3. Survey-weighted associations of cCKMS-S with all-cause and heart-disease mortality in NHANES

Section	Contrast	Model 1	Model 2	Model 3
All-cause death	Per 1 SD	1.76 (1.62, 1.91); P <0.001	1.28 (1.20, 1.36); P <0.001	1.19 (1.11, 1.27); P <0.001
All-cause death	Q1	Reference	Reference	Reference
All-cause death	Q2	2.38 (1.86, 3.04); P <0.001	1.07 (0.80, 1.44); P 0.651	1.09 (0.81, 1.46); P 0.576
All-cause death	Q3	6.78 (5.31, 8.64); P <0.001	1.15 (0.86, 1.54); P 0.356	1.08 (0.80, 1.46); P 0.600
All-cause death	Q4	12.58 (9.89, 16.00); P <0.001	1.66 (1.26, 2.20); P <0.001	1.41 (1.07, 1.86); P 0.015

Section	Contrast	Model 1	Model 2	Model 3
All-cause death	P for trend	P trend <0.001	P trend <0.001	P trend <0.001
Heart-disease death	Per 1 SD	1.88 (1.69, 2.09); P <0.001	1.64 (1.48, 1.82); P <0.001	1.50 (1.35, 1.68); P <0.001
Heart-disease death	Q1	Reference	Reference	Reference
Heart-disease death	Q2	5.10 (2.46, 10.57); P <0.001	1.72 (0.80, 3.69); P 0.167	1.81 (0.83, 3.91); P 0.134
Heart-disease death	Q3	20.01 (10.23, 39.17); P <0.001	2.65 (1.28, 5.47); P 0.009	2.51 (1.20, 5.22); P 0.014
Heart-disease death	Q4	46.98 (24.36, 90.60); P <0.001	5.66 (2.82, 11.36); P <0.001	4.61 (2.30, 9.25); P <0.001
Heart-disease death	P for trend	P trend <0.001	P trend <0.001	P trend <0.001

Notes

Values are hazard ratios from fasting-subsample-weighted survey Cox models, shown as HR (95% CI); P. Q1 is the reference quartile, and P for trend treats quartile as an ordinal variable scored 1–4. Model 1 includes cCKMS-S only. Model 2 adjusts for age, sex, race/ethnicity, education, partnership, poverty-income ratio, and survey cycle. Model 3 additionally adjusts for current drinking, physical activity, baseline cardiovascular disease, cancer, and non-CKM comorbidity count. All estimates account for nested strata and primary sampling units and pool 30 multiple imputations. Exposure, mortality status, and follow-up time were not imputed. Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; cCKMS-S, continuous CKM syndrome severity score; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; Q, quartile; SD, standard deviation.

Figure legends

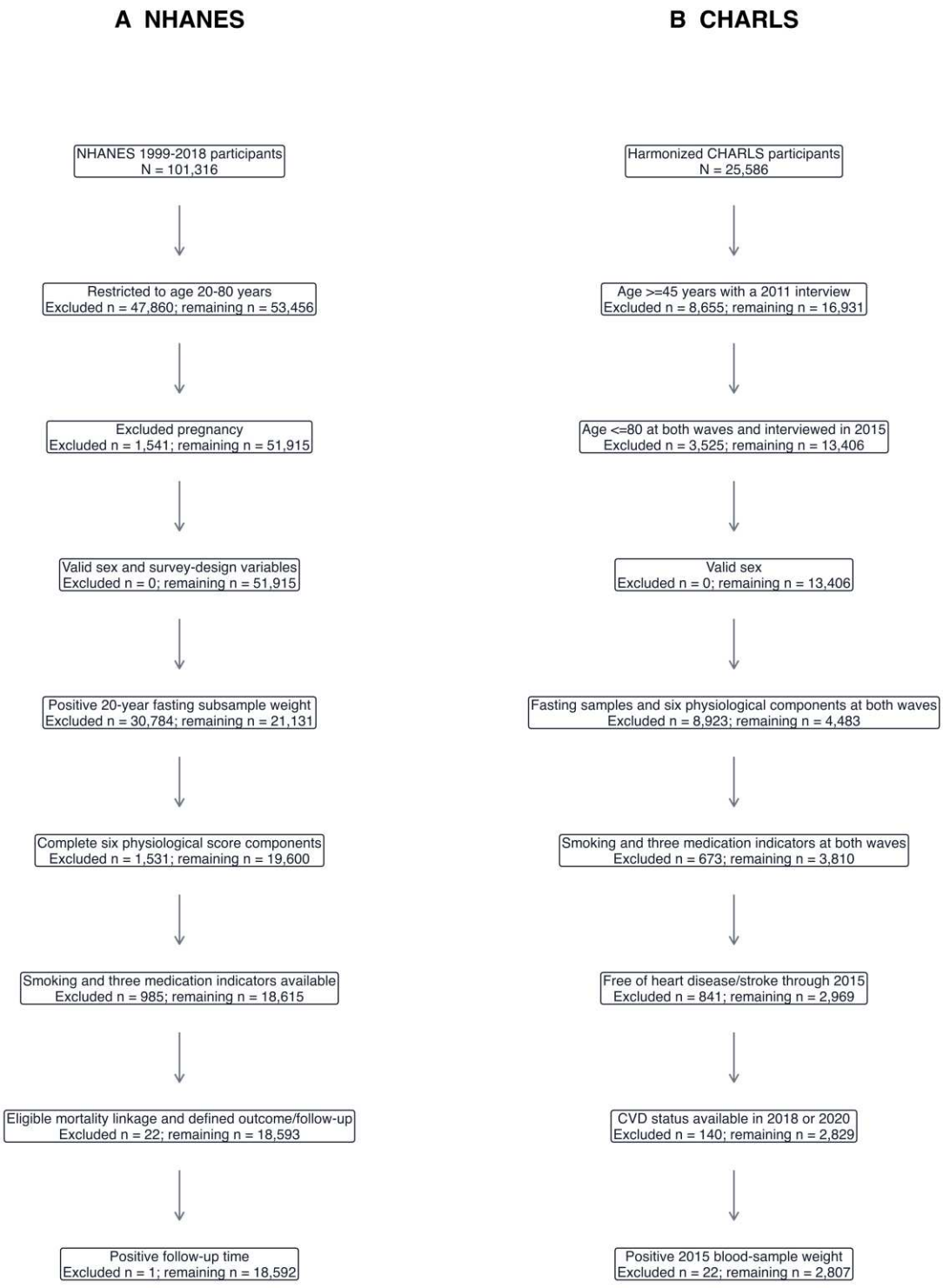


Fig. 1. Flowchart of the NHANES and CHARLS analytic cohorts

Panel A shows sequential eligibility criteria for the pooled 1999–2018 NHANES fasting subsample linked to mortality. Panel B shows sequential eligibility criteria for the longitudinal CHARLS cohort with complete fasting score components in 2011 and 2015 and ascertainable cardiovascular disease status after the disease-free 2015 baseline. Counts at each box are unweighted participants. NHANES indicates National Health and Nutrition Examination Survey; CHARLS, China Health and Retirement Longitudinal Study; CVD, cardiovascular disease.

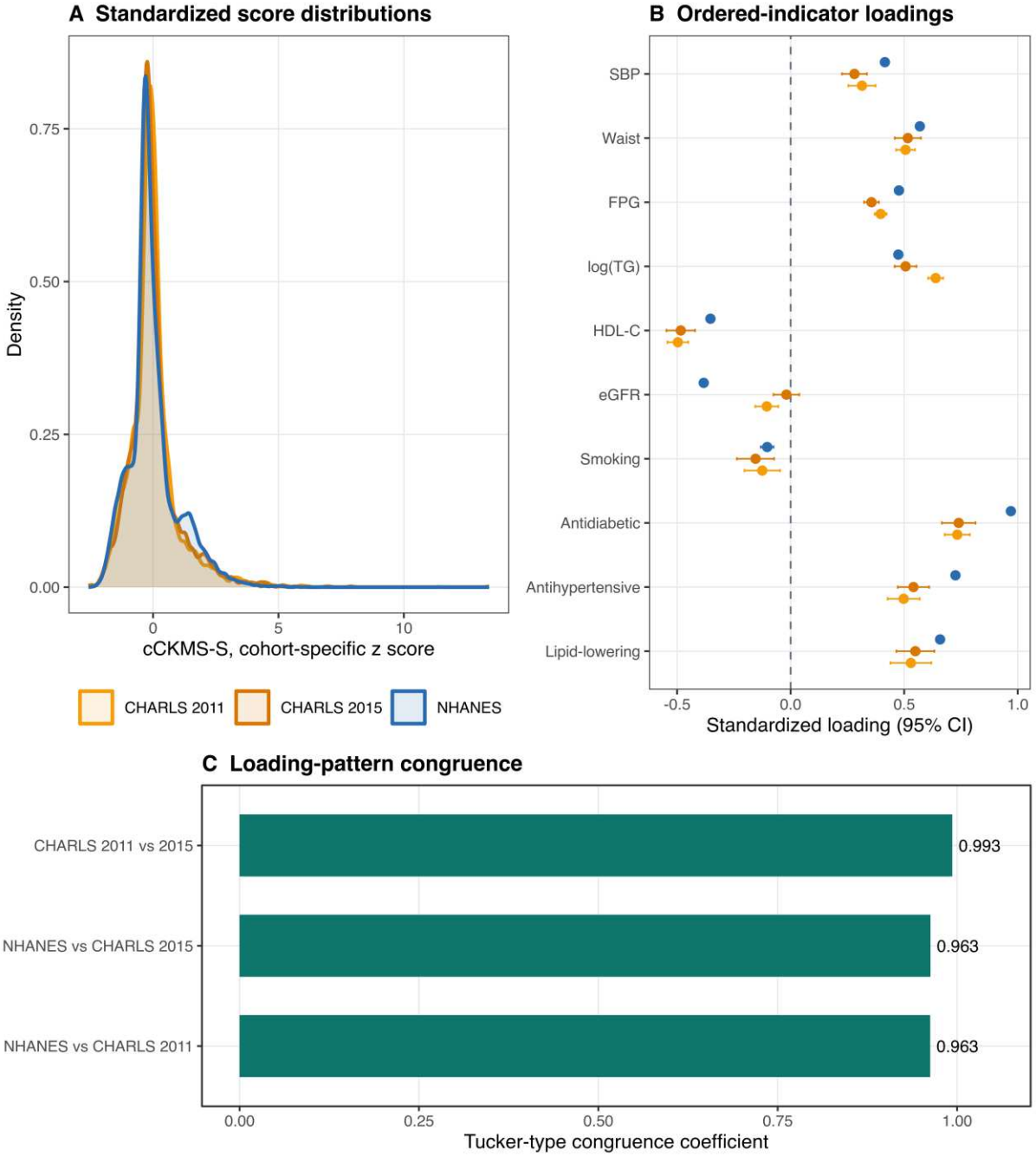
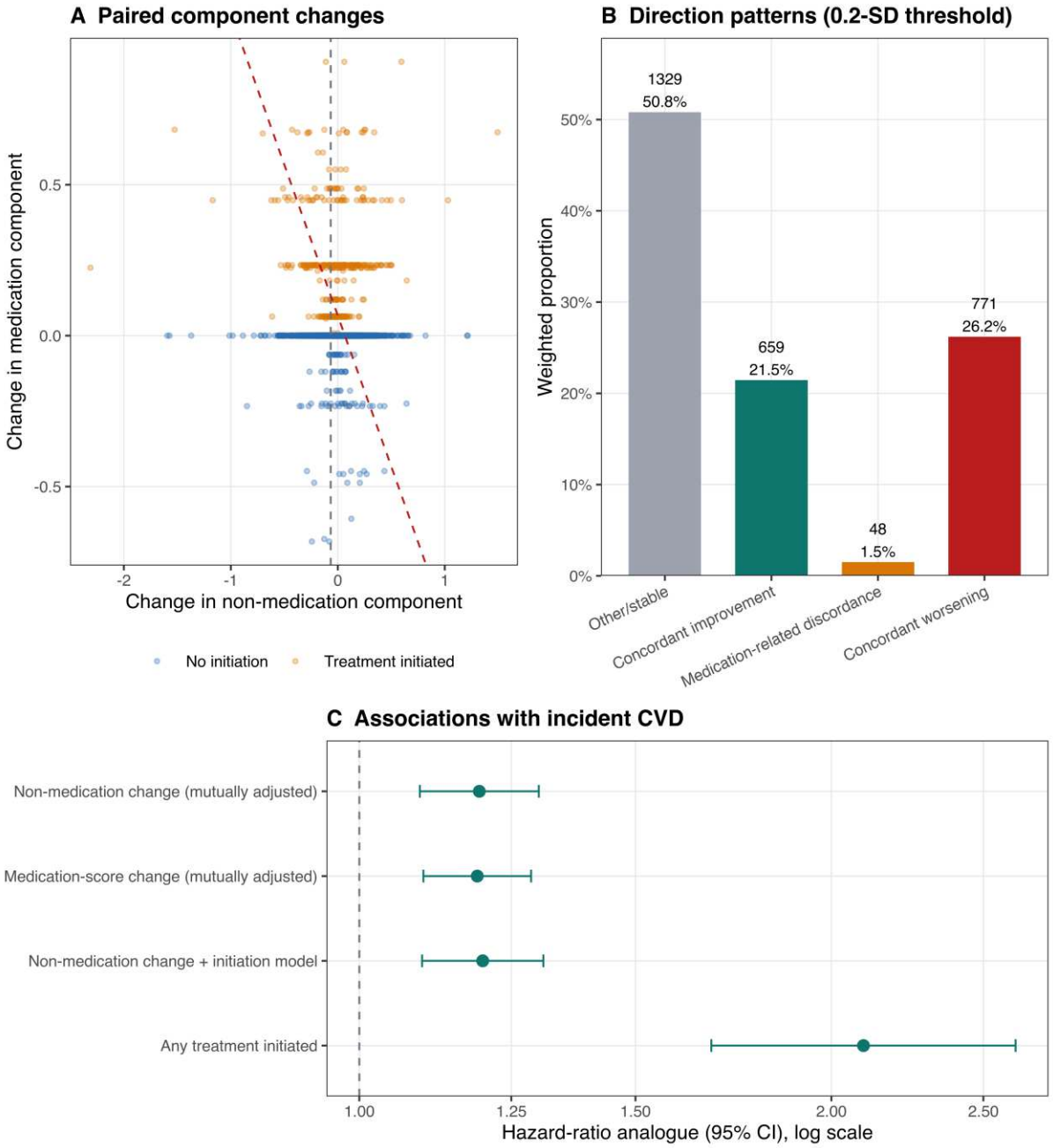


Fig. 2. Distribution and cross-cohort measurement structure of cCKMS-S

Panel A shows kernel-density estimates of cohort-specific standardized cCKMS-S in NHANES and at the 2011 and 2015 CHARLS waves. Panel B shows standardized loadings and 95% confidence intervals from exploratory weighted one-factor models of the ten score components. Panel C shows Tucker-type loading-pattern congruence coefficients between cohorts and waves. The factor analysis characterizes the score structure but does not establish strict measurement invariance; global fit indices are reported in Table S4. cCKMS-S indicates continuous cardiovascular-kidney-metabolic syndrome severity score; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.



653

654 **Fig. 3. Decomposition of longitudinal changes in total, non-medication, and medication components of**
655 **cCKMS-S in CHARLS**

656 Panel A plots each participant's 2011–2015 change in the non-medication component against
657 the change in the medication component; color identifies initiation of at least one antidiabetic,
658 antihypertensive, or lipid-lowering treatment. Dashed boundaries represent the prespecified
659 0.2 baseline-SD threshold. Panel B shows weighted prevalence and unweighted counts of
660 direction patterns. Panel C shows Model 3 hazard-ratio analogues and 95% confidence
661 intervals for mutually adjusted component changes and for the model containing non-
662 medication change plus any treatment initiation. Model 3 includes follow-up interval, age,

sex, rural residence, education, partnership, log per-capita economic resources, current drinking, physical activity, sleep duration, CES-D-10 score, non-CKM comorbidity count, and 2011 cCKMS-S where applicable; estimates use the 2015 blood-sample weight combined with stabilized inverse observation weights and pool 30 imputations. Medication-pattern results are descriptive and are not causal treatment effects. CI indicates confidence interval; CVD, cardiovascular disease; SD, standard deviation.

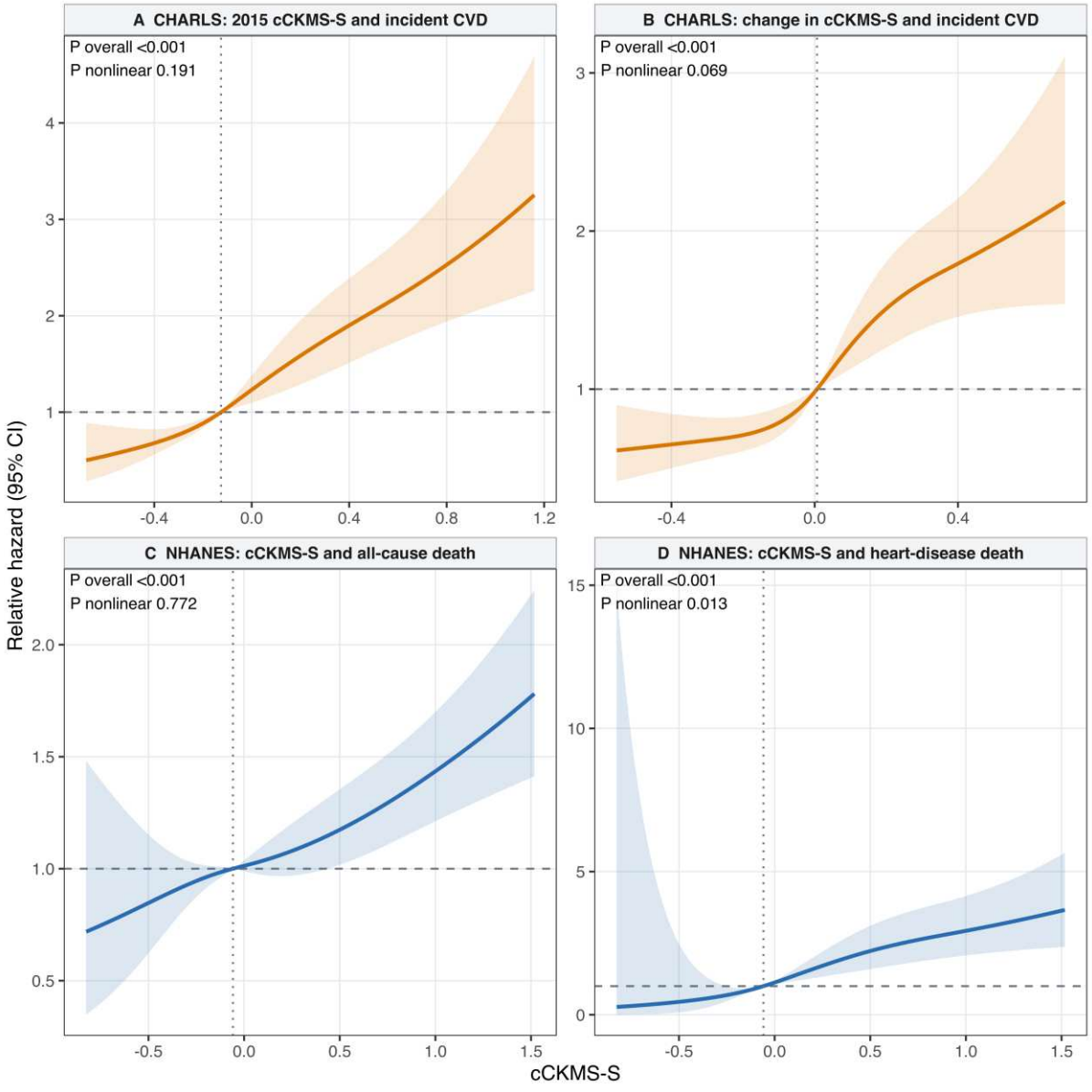
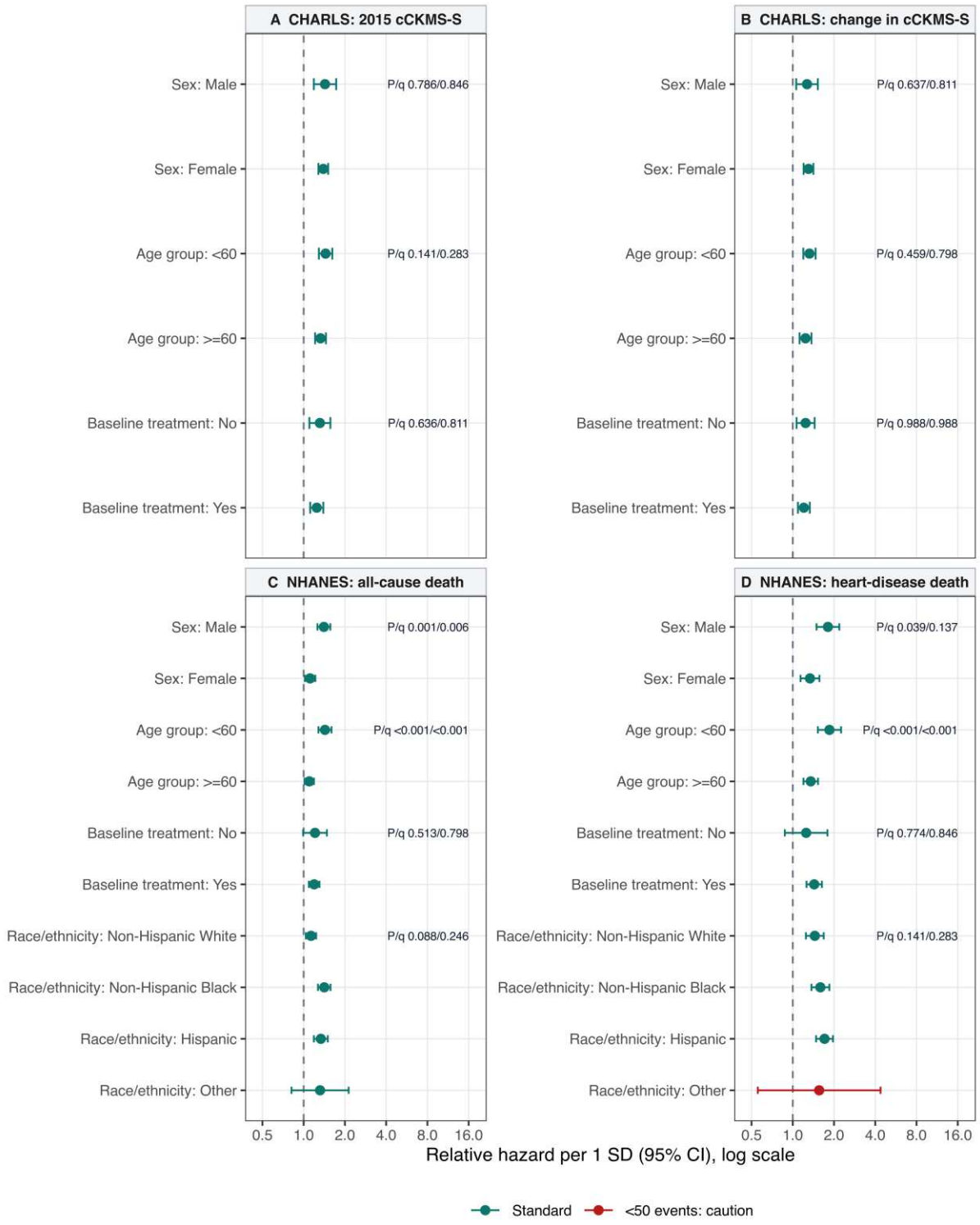


Fig. 4. Dose–response associations of cCKMS-S with incident CVD and mortality

Restricted cubic spline curves show fully adjusted relative hazards and 95% confidence intervals for 2015 cCKMS-S and subsequent incident CVD in CHARLS (A), 2011–2015

change in cCKMS-S and incident CVD in CHARLS (B), baseline cCKMS-S and all-cause mortality in NHANES (C), and baseline cCKMS-S and heart-disease mortality in NHANES (D). Four knots were placed at the prespecified 5th, 35th, 65th, and 95th percentiles; the median is the reference. Overall and nonlinearity P values pool 30 imputations. Panels use separate vertical scales to preserve the visibility of confidence intervals. CHARLS estimates are survey-weighted complementary log-log hazard-ratio analogues; NHANES estimates are fasting-subsample-weighted survey Cox hazard ratios. CI indicates confidence interval; CVD, cardiovascular disease.



685

686 **Fig. 5. Prespecified subgroup analyses of cCKMS-S and clinical outcomes**

687 Points and bars show fully adjusted relative hazards per 1-SD higher exposure and 95%
688 confidence intervals across prespecified strata for 2015 cCKMS-S (A) and its 2011–2015
689 change (B) in relation to incident CVD in CHARLS, and baseline cCKMS-S in relation to
690 all-cause (C) and heart-disease (D) mortality in NHANES. P/q annotations give the

interaction P value and Benjamini–Hochberg false-discovery-rate q value once per subgroup variable. Red denotes a stratum with fewer than 50 events and therefore requiring caution. Differences in within-stratum significance are not evidence of interaction. CI indicates confidence interval; SD, standard deviation.

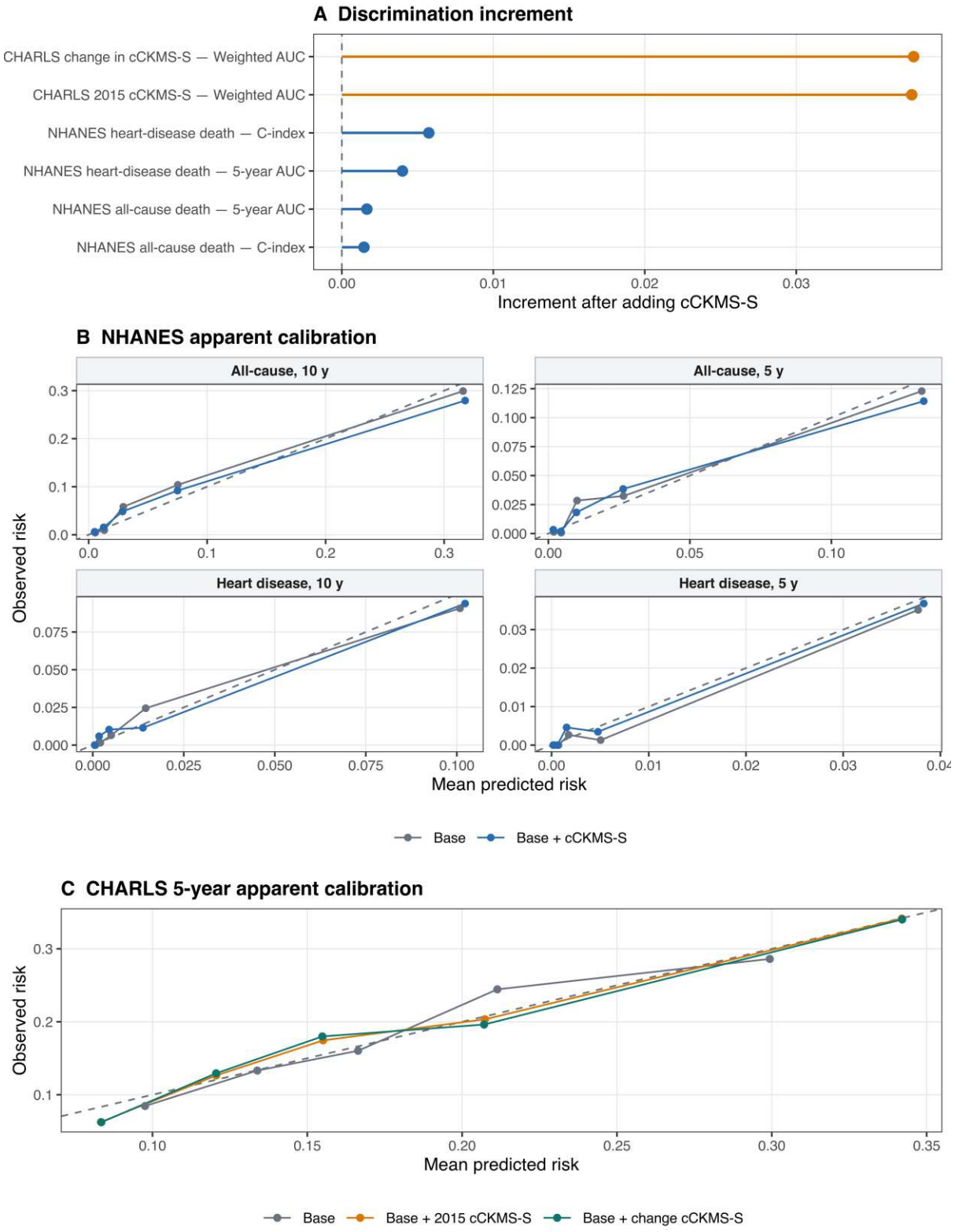


Fig. 6. Exploratory apparent discrimination and calibration after adding cCKMS-S

Panel A shows the apparent change in discrimination after addition of cCKMS-S to the prespecified base models. Panel B shows quintile-based apparent calibration for 5- and 10-year all-cause and heart-disease mortality in NHANES. Panel C shows quintile-based

apparent 5-year calibration for incident CVD in CHARLS. The dashed line denotes perfect calibration. These analyses use only the first imputed dataset and no resampling or external validation. NHANES C-index values come from weighted Cox models, whereas time-dependent AUC is an unweighted inverse-probability-of-censoring estimate because the selected implementation has no complex-survey interface; CHARLS uses a combined-weight person-level binary approximation. The results are exploratory apparent performance and do not establish clinical utility, transportability, or a deployable risk tool. AUC indicates area under the receiver operating characteristic curve; CVD, cardiovascular disease.

Additional files

Additional file 1 contains Figs. S1–S4 and Tables S1–S11 with their legends, notes, and machine-readable source tables. The accompanying supplementary file contains the complete inventory.

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