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Article

Keywords: cardiovascular-kidney-metabolic syndrome, metabolic index, adiposity index, cardiovascular disease, CHARLS, NHANES

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11424125/v1

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Additional Declarations: No competing interests reported.

Comparison of 16 metabolic-adiposity composite indices and cardiovascular risk in adults with cardiovascular-kidney-metabolic stages 0-3: cohort evidence from CHARLS and NHANES

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Abstract

Background: Stage 0-3 of cardiovascular-kidney-metabolic (CKM) syndrome identifies a population characterized by the interaction of obesity, abnormal glucose metabolism, dyslipidemia and chronic inflammation. Composite indices built from routine anthropometric and laboratory measurements are convenient tools for characterizing this shared burden, but metabolic indices and adiposity indices are usually evaluated separately and are rarely compared head-to-head across multiple populations.

Methods: This study constructed all 16 multiplicative combinations of 4 metabolic indices (triglyceride-glucose index, TyG; C-reactive protein-triglyceride glucose index, CTI; cholesterol-high-density lipoprotein-glucose index, CHG; atherogenic index of plasma, AIP) and 4 adiposity indices (waist-to-height ratio, WHtR; body roundness index, BRI; Chinese visceral adiposity index, CVAI; a body shape index, ABSI). The China Health and Retirement Longitudinal Study (CHARLS) provided 5,304 adults aged 45 years or older with CKM stages 0-3 and 1,366 incident self-reported cardiovascular disease (CVD) events, plus a separate 2,811-participant wave 3 landmark cohort for cumulative-exposure and two-point exposure pattern analyses. The US National Health and Nutrition Examination Survey (NHANES) provided 5,487 participants and 431 cardiovascular deaths across six cycles from 1999-2010, with mortality linkage. Analyses used Cox models, restricted cubic splines, in-sample incremental performance metrics and a direction-constrained weighted quantile sum (WQS) extension, all fitted within source, retaining their respective weights and sampling designs.

Results: Per 1 source-sample standard deviation (SD) increase, CTI-CVAI was associated with incident CVD in CHARLS (hazard ratio, HR 1.213, 95% confidence interval, CI 1.147-1.282) and with cardiovascular death in NHANES (HR 1.270, 1.053-1.533), and CHG-CVAI with 1.221 (1.154-1.292) and 1.226 (1.009-1.490), respectively. The two cohorts were consistent for the metabolic component, with CTI and CHG both higher than TyG and AIP, but the best adiposity index differed: CVAI combinations were highest in CHARLS, whereas CTI-WHtR (1.331, 1.127-1.572), CTI-BRI (1.323, 1.128-1.552) and CTI-ABSI (1.318, 1.139-1.526) were highest in NHANES, and AIP combinations were unassociated in NHANES. In CHARLS, cumulative CTI-CVAI and CHG-CVAI were associated with incident CVD (HR 1.079, 1.034-1.127; 1.081, 1.034-1.130), and in the two-point pattern the highest mean-level WHtR group had HRs of 1.517-1.822. In neither cohort did the discrimination improvement of any index pass the multiple-correction threshold, although some indices improved reclassification metrics. The six-component positive WQS associations in the internal validation samples were positive in both cohorts (CHARLS 1.263, 1.139-1.401; NHANES 1.544, 1.125-2.121), with weights concentrated mainly on waist circumference, CRP, fasting glucose and total cholesterol, but component weights were unstable across repeated splits.

Conclusions: In adults with CKM stages 0-3, combinations of CTI or CHG with adiposity indices showed the strongest and most consistent associations with two different cardiovascular endpoints, and cumulative exposure provided additional information in CHARLS; the optimal adiposity index varied by cohort, and AIP combinations were weakest in both cohorts. Because no discrimination improvement was observed, these indices are better suited as convenient summaries of existing risk and should not be used directly for screening until absolute risk has been externally validated.

Keywords: cardiovascular-kidney-metabolic syndrome; metabolic index; adiposity index; cardiovascular disease; CHARLS; NHANES

Introduction

Cardiovascular disease remains the leading cause of death worldwide, and its risk increasingly reflects the coexistence of obesity, metabolic abnormalities, kidney disease and vascular injury(1-4). The cardiovascular-kidney-metabolic (CKM) framework divides this continuum into different stages and identifies early adults as a population with a remaining window for prevention(4-8). Therefore, risk summary indicators applicable to CKM stages 0-3

should be easy to measure routinely while covering information such as insulin resistance, inflammation, lipid metabolism and central obesity.

Existing indices reflect these domains separately. The triglyceride-glucose (TyG) index summarizes insulin resistance(9-11); the C-reactive protein-triglyceride glucose (CTI) and cholesterol-high-density lipoprotein-glucose (CHG) indices further add information on inflammation and cholesterol metabolism(12-14); the atherogenic index of plasma (AIP) reflects the ratio of triglycerides to high-density lipoprotein cholesterol(15, 16). Waist-to-height ratio (WHtR), body roundness index (BRI), Chinese visceral adiposity index (CVAI) and a body shape index (ABSI) provide different summaries of central or visceral obesity(17-24). These signals overlap, and their relative performance may vary with population, exposure distribution and outcome definition(25-27).

Previous studies have mostly evaluated a single index or a single cohort, leaving two questions unresolved: whether the ranking of metabolic-adiposity combinations can be reproduced across populations, and whether repeated measurements can provide information beyond baseline values. CHARLS provides repeated biomarker measurements and incident self-reported CVD, while NHANES provides standardized physical examinations, a complex sampling design and cardiovascular mortality linkage(28-30). Because the outcome ascertainment pathways of the two cohorts differ, consistency of results indicates the reproducibility of associations across contexts rather than equivalence of endpoints.

This study compared the 16 combinations formed by 4 metabolic indices and 4 adiposity indices in adults with CKM stages 0-3, evaluating incident CVD in CHARLS and cardiovascular death in NHANES; it also analyzed cumulative exposure and two-point patterns in CHARLS, and examined incremental discrimination, reclassification and mixture stability. The study aimed to identify the most consistently associated combinations and to determine whether their information exceeds that of conventional risk factors.

Materials and Methods

Study design and population

The two cohorts provide complementary rather than equivalent evidence: CHARLS provides repeated exposure measurements and incident self-reported CVD, and NHANES provides cardiovascular death based on a probability sampling design. All models were fitted within source, without pooling individual records, weights or effect estimates. Figure 1 shows

the construction of each analytic sample, and the stepwise exclusion counts are given in Supplementary Table S1.

CHARLS is a nationally representative cohort of Chinese adults aged 45 years or older that began in 2011-2012 with follow-up every two years(28). This study used wave 1 as baseline and evaluated outcomes through wave 5, requiring complete demographic data, fasting biomarkers and the components needed to construct the 16 indices, and applying the established ±3 SD screening rule for baseline measurements and the wave 5 participation requirement. Cumulative-exposure and two-point pattern analyses used the wave 3 (2015) landmark cohort, additionally requiring complete fasting exposure data at waves 1 and 3 and no definite CVD at waves 2 and 3; follow-up began at wave 3, with no further exclusion of extreme values. Participants with prevalent CVD at baseline were excluded.

NHANES uses a stratified multistage probability sampling design and provides mortality-linked follow-up(29, 30). This study combined six cycles from 1999-2000 to 2009-2010, requiring a positive official fasting subsample weight, complete exposure measurements, eligible mortality linkage and positive follow-up time; in cycles with publicly available fasting duration, participants with a fasting time of less than 8 hours or reaching 24 hours were excluded.

Exposure assessment

The 4 metabolic indices and 4 adiposity indices were multiplied pairwise to obtain 16 composite indices. TyG was the natural logarithm of the product of triglycerides and fasting glucose divided by 2(9); CTI was 0.412 multiplied by the natural logarithm of CRP plus TyG(12); CHG was the natural logarithm of the product of total cholesterol and fasting glucose divided by twice high-density lipoprotein cholesterol(14); and AIP was the base-10 logarithm of the molar ratio of triglycerides to high-density lipoprotein cholesterol(15). Lipids and glucose were in mg/dL and CRP in mg/L. WHtR was waist circumference divided by height, CVAI used the published sex-specific formula(21), BRI used the published eccentricity formula(19), and ABSI was used in its original unscaled form(23). Formulas, units and sex coding are given in Supplementary Table S2.

Baseline exposure was calculated in both cohorts. Cumulative exposure in CHARLS was the trapezoidal area between waves 1 and 3, that is, the mean of the two index values multiplied by the individual's actual inter-visit interval in years; the two-point pattern applied k-means clustering to the two standardized measurements by Euclidean distance, retaining K=3 and

ordering by the two-wave mean level. Elbow diagnostics and the cluster means for each combination are shown in Supplementary Figs. S1 and S2, and the landmark cohort characteristics, actual measurement intervals and derived exposure distributions in Supplementary Table S3. Because two measurements cannot identify latent trajectories, this paper consistently calls this the two-point pattern.

Outcome ascertainment

Incident CVD in CHARLS was defined as the first self-reported physician diagnosis of heart disease or stroke during follow-up. Baseline analyses were counted from wave 1 and cumulative and two-point pattern analyses from wave 3; the year of the first positive visit was used to approximate event time, and participants without events were censored at the last valid CVD assessment. Because the true onset time lies between the last negative visit and the first positive visit, we additionally used a complementary log-log visit-interval model to address the effect of this interval length.

NHANES used the 2019 public-use mortality linkage, with follow-up through December 31, 2019. Cardiovascular death required MORTSTAT equal to 1 and UCOD_LEADING equal to 001 or 005 in the linked record, and follow-up time was determined by PERMTH_EXM from examination to death or censoring. Other causes of death were censored in cause-specific Cox models and treated as competing events in cumulative incidence functions.

A comparison of source-specific outcome definitions, sampling designs and time axes is given in Supplementary Table S4, and the available risk-set support at each evaluation time point and the boundaries of the CHARLS mortality fields in Supplementary Table S5.

Covariates and operational CKM staging

Covariates included age, sex, marital status, education, smoking, drinking, systolic blood pressure, diastolic blood pressure and self-reported hypertension, with urban-rural residence additionally included in CHARLS. Marital status was coded as married versus other in both cohorts; education was coded as junior high school or below in CHARLS and as less than high school in NHANES. Questionnaire definitions of drinking and self-reported diseases retained the original coding of their respective sources and were not forcibly harmonized; blood pressure was the mean of available positive readings. The main models used complete cases.

CKM stage was assigned according to the highest stage met. Stage 1 required overweight or central obesity, with BMI thresholds of 23 kg/m^2 in CHARLS and 25 kg/m^2 in NHANES and

waist circumference thresholds by sex of 80/90 cm and 88/102 cm, respectively; or prediabetes, that is, fasting glucose of 100 to less than 126 mg/dL or HbA1c of 5.7% to less than 6.5%. Stage 2 required diabetes, hypertension, triglycerides ≥135 mg/dL, at least 3 components of metabolic syndrome(31), or a single estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m². Stage 3 used an eGFR below 30 mL/min/1.73 m² or a Framingham 10-year general CVD risk ≥20% as a proxy for subclinical disease(32). Diabetes integrated glucose, HbA1c, self-reported diagnosis and treatment criteria(33), and hypertension integrated blood pressure ≥130/80 mmHg, self-reported diagnosis or treatment(34). Participants who could not be classified because of non-fasting status or incomplete data and who did not meet subsequent stages were not assigned a stage rather than being placed in a particular stage. eGFR used the 2021 race-free CKD-EPI creatinine equation(35, 36), and early NHANES cycles used the corresponding creatinine calibration(37). Thresholds and ascertainment rules are given in Supplementary Table S6. Because urine albumin and imaging data were lacking and eGFR was measured only once, the staging used here is operational and is not equivalent to full clinical CKM or chronic kidney disease staging.

Statistical analysis

Continuous variables are presented as mean and SD, and categorical variables as counts and percentages. CHARLS analyses were unweighted and are not national estimates. NHANES means, SDs and proportions used fasting subsample weights, with pooled weights of WTSAF4YR×4/12 for 1999-2002 and WTSAF2YR×2/12 for 2003-2010, and the strata and primary sampling units (PSUs) of the parent design were retained before defining the analytic domain, with counts as unweighted counts. Baseline characteristics are shown in Table 1 and covariate missingness in Supplementary Table S7.

Cox proportional hazards models were fitted by source, retaining the survey design in NHANES. Model 1 was unadjusted, model 2 added demographic covariates, and model 3 further added smoking, drinking, blood pressure and self-reported hypertension. Continuous exposures were standardized by the source- and dimension-specific sample SD, and hazard ratios (HRs) per SD with 95% confidence intervals (CIs) are reported; quartiles used the lowest group as the reference with trend tested by quartile ordinal, and the two-point pattern used the lowest mean-level group as the reference. NHANES inference used design degrees of freedom, and the 16 primary continuous tests per source and dimension each formed a Benjamini-Hochberg (BH)

correction family(38). Each index entered the model separately. Collinearity and proportional hazards diagnostics are shown in Supplementary Figs. S3-S6 and Supplementary Table S8, and unadjusted Kaplan-Meier curves in Supplementary Figs. S7-S9.

Nonlinearity was modeled with restricted cubic splines (knots at the 25th, 50th and 75th percentiles, with the 10th percentile as the reference and a plotting range from the 1st to the 99th percentile), and the overall and nonlinear tests each formed a 16-item BH family(39) (Supplementary Figs. S10-S12; Supplementary Table S9). Incremental performance was evaluated by adding each index to model 3: CHARLS used the Uno inverse-probability-of-censoring weighted concordance index at 8.9 and 4.9 years together with time-dependent area under the curve (AUC), continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI), and NHANES used the survey-weighted Harrell concordance index; intervals for changes in the concordance index were obtained from 1,000 paired refits, with each metric family corrected separately(40, 41). All results are in-sample apparent values without optimism correction (Supplementary Tables S10-S12; Supplementary Fig. S13).

Mixture associations were assessed with a direction-constrained Cox weighted quantile sum (WQS) extension, with the main model being the positive six-component model (waist circumference, BMI, triglycerides, fasting glucose, CRP and total cholesterol), and the reverse configuration and a configuration adding low-density lipoprotein cholesterol as exploratory analyses(42, 43). Cutpoints and weights were estimated in one half of the sample and frozen, after which associations were estimated in the other half; 300 full-process resamples provided HR and weight intervals, and the 9 configurations underwent an additional 100 random splits (Supplementary Tables S13-S16; Supplementary Figs. S14 and S15). Weights are within-model relative weights and do not represent causal contributions.

Eight prespecified subgroup dimensions covered all 16 indices, and interaction tests were corrected within source for 128 items (Supplementary Fig. S16; Supplementary Table S17). In the two-point pattern, groups with fewer than 30 participants or fewer than 10 events were not used for grouped inference, and the reproducibility of K=3 is shown in Supplementary Fig. S17 and Supplementary Table S18.

In NHANES, survey-weighted Aalen-Johansen cumulative incidence functions of cardiovascular death were estimated by CTI-CVAI and CHG-CVAI quartiles, with other deaths as competing events(44-46) (Supplementary Fig. S18; Supplementary Table S19). Non-

cardiovascular death and a 2-year event-free landmark were analyzed separately (Supplementary Fig. S19; Supplementary Table S20), and age restriction and an alternative AIP definition are given in Supplementary Table S21; covariate missingness is shown in Supplementary Fig. S20 and Supplementary Table S22. CHARLS reconstructed a cohort not requiring wave 5 participation (Supplementary Table S23), and exploratory analyses included the interaction of cumulative exposure with self-reported dyslipidemia (Supplementary Fig. S21; Supplementary Tables S24 and S25) and baseline selection weights based on model 3 covariates (Supplementary Table S26).

All tests were two-sided, and a BH-corrected $P<0.05$ was regarded as corrected evidence within the corresponding family. Analyses used R 4.6.1 with the survival and survey packages, and reporting followed STROBE(47).

Results

Study participants and source-specific outcomes

The CHARLS baseline cohort included 5,304 participants and 1,366 incident self-reported CVD events, and the landmark cohort included 2,811 participants and 552 events. NHANES included 5,487 participants, 431 cardiovascular deaths and 1,115 other deaths; the model 3 complete cases were 5,294/1,361, 2,807/550 and 5,214/410, respectively (the latter with an additional 1,050 other deaths) (Fig. 1; Supplementary Tables S1-S5). Baseline characteristics are shown in Table 1, missingness in Supplementary Table S7, and complete outcome-stratified characteristics in Supplementary Table S27. The mean interval between the two CHARLS measurements was 4.005 years, and unadjusted curves are shown in Supplementary Figs. S7-S9.

CTI and CHG combinations had the strongest baseline associations

In model 3, CTI-CVAI was associated with incident CVD in CHARLS (HR 1.213; 95% CI 1.147-1.282) and with cardiovascular death in NHANES (1.270; 1.053-1.533), and the corresponding HRs for CHG-CVAI were 1.221 (1.154-1.292) and 1.226 (1.009-1.490). CVAI combinations had the highest estimates in CHARLS; in NHANES, CTI-WHtR (1.331), CTI-BRI (1.323) and CTI-ABSI (1.318) were highest. AIP combinations were weakest and were unassociated in NHANES (0.985-1.036). The ranking of the metabolic components was consistent across the two cohorts, whereas the optimal adiposity index differed. Results for the 16 indices, stepwise adjustment and quartiles are shown in Fig. 2 and Supplementary Tables

S28-S29; in NHANES, the BH-adjusted *P* values for CTI-CVAI, CHG-CVAI/TyG-CVAI and CTI-WHtR/BRI/ABSI were 0.0273, 0.0582 and 0.005, respectively.

No improvement in discrimination but improvement in reclassification

The baseline concordance index was 0.6298 in CHARLS, 0.8354 in NHANES and 0.6129 in the CHARLS landmark cohort; the largest baseline increment in CHARLS was 0.0088 for CTI-CVAI (95% CI 0.0014-0.0161), and no increment passed BH correction (Table 2; Supplementary Fig. S22). The baseline AUCs at the prespecified evaluation time points were 0.6378 and 0.6121, and the highest AUCs of the extended models were 0.6472, 0.6287 and 0.6309, respectively. The numbers of indices passing correction for AUC, continuous NRI and IDI were 0/13/9, 0/16/0 and 0/10/0 in the baseline, cumulative and two-point pattern analyses, respectively; uncertainty distributions are shown in Supplementary Fig. S23.

Dose-response shapes differed between the two cohorts

The numbers of indices whose spline overall tests passed BH correction were 15, 16 and 12 in CHARLS baseline, cumulative exposure and NHANES baseline, respectively, and those for the nonlinear tests were 0, 3 and 12; the CHARLS curves were overall close to linear, whereas the upper end of the NHANES exposure showed curvature (Fig. 3; Supplementary Figs. S10-S12; Supplementary Table S9).

Cumulative exposure and the two-point pattern in CHARLS

In the landmark cohort, cumulative CTI-CVAI and CHG-CVAI were associated with CVD (HRs per SD of 1.079 and 1.081, respectively). The highest two-wave mean WHtR group had HRs of 1.781 for TyG-WHtR, 1.822 for CTI-WHtR, 1.802 for CHG-WHtR and 1.517 for AIP-WHtR (Fig. 4). Full models are shown in Supplementary Tables S30-S31.

Subgroup associations were homogeneous

Of the 256 interaction tests, only the interactions of sex with AIP-BRI and AIP-CVAI in CHARLS passed correction (adjusted *P*=0.0450 and 0.0461), and no interaction passed in NHANES. Key estimates are shown in Supplementary Fig. S24, and full results in Supplementary Fig. S16 and Supplementary Table S17.

Mixture associations were positive but compositionally unstable

In the internal validation half-samples, the positive six-component WQS was associated with the outcomes, with HRs of 1.263 (1.139-1.401) in CHARLS and 1.544 (1.125-2.121) in NHANES (Fig. 5; Supplementary Tables S13-S16). The highest weight was waist circumference

in CHARLS (45.8%) and CRP in NHANES (57.1%); the cumulative-exposure HR in CHARLS was 1.308 (1.108-1.545). Across repeated splits, the mixture direction was more stable than the component ranking (Supplementary Figs. S14-S15).

Competing risks, cohort selection and diagnostic evidence

With other deaths treated as competing events, the survey-weighted 10-year cumulative incidence of cardiovascular death in NHANES rose from 1.8% to 4.4% and from 2.1% to 4.5% across CTI-CVAI and CHG-CVAI quartiles, respectively (Supplementary Fig. S18; Supplementary Table S19). Other-death and 2-year event-free analyses maintained the same direction (Supplementary Fig. S19; Supplementary Table S20). Sensitivity analyses for age, the risk score and the AIP definition are shown in Supplementary Table S21; covariate missingness was low in both cohorts (Supplementary Fig. S20; Supplementary Table S22). After relaxing the CHARLS wave 5 participation requirement, changing the visit interval and applying exploratory selection reweighting, the direction of estimates was consistent (Supplementary Table S23; Supplementary Table S26); the dyslipidemia interaction was not supported (Supplementary Fig. S21; Supplementary Tables S24-S25). Diagnostics showed no substantial violation of the proportional hazards assumption (Supplementary Figs. S5-S6; Supplementary Table S8), and clustering and initialization diagnostics are shown in Supplementary Fig. S17 and Supplementary Table S18. No death dates were available in CHARLS, so competing-risk analysis was not performed.

Discussion

This two-cohort comparison yielded three main findings. First, CTI and CHG combinations had the strongest and most consistent associations in both cohorts, whereas AIP combinations were weakest. Second, the optimal adiposity component differed by source: CVAI combinations were highest in CHARLS, whereas CTI combined with WHtR, BRI or ABSI was highest in NHANES. Third, cumulative exposure and the two-point WHtR pattern in CHARLS remained associated with the outcomes, but no combination improved the concordance index after conventional risk factors were included. WQS supported a positive association between the mixture and the outcome, while component weights varied considerably across repeated splits.

Recent dual-cohort studies of the stress hyperglycemia ratio, CTI, TyG-ABSI and the residual cholesterol inflammatory index likewise showed that metabolic composite indicators can be associated with outcomes in Chinese and US populations(48-51). In this study, the weaker

performance of AIP was consistent with its narrower composition of lipid ratios and with its information being attenuated after adjustment for blood pressure, smoking and obesity. The differences in the adiposity component were also consistent with recent evidence that body shape indicators may modify the apparent strength of metabolic indices(49, 52). Thus, the two-cohort results support selecting an index family according to the measurement context rather than seeking a universally optimal single index.

This study extends previous CHARLS research on baseline indices, cumulative CTI or CHG exposure and two-point metabolic patterns(48-50, 52, 53). Previous studies demonstrated that a single index can be associated with CVD; this study applied the same 4×4 combination matrix to a second national cohort with a fatal endpoint and a survey design, and incorporated longitudinal exposure, in-sample incremental performance and mixture stability evaluation within the same framework. The contribution lies in comparing reproducibility and scope across contexts rather than proposing a new biomarker.

The longitudinal results distinguish two questions. Cumulative exposure remained associated with incident CVD after integrating repeated measurements, and the strongest two-point pattern was concentrated on WHtR. When repeated measurements are available, the sustained level of central obesity merits continued observation; however, two measurements can only constitute an exposure pattern and cannot be used to infer a biological trajectory. The lack of improvement in the concordance index indicates that these combinations mainly summarize information already contained in conventional risk factors. Changes in reclassification metrics may suggest that the probability of risk grouping has changed, but the models in this study are in-sample, unvalidated apparent estimates, and clinical benefit cannot be inferred from them. The mixture results convey the same message. The direction of the WQS association was more stable than the component ranking, and weights changed both across repeated splits and after adding low-density lipoprotein cholesterol. WQS weights are influenced by component correlation structure and direction constraints and describe relative weights within the fitted mixture; they do not represent the causal or biological contribution of any single component(42, 43).

This study used a prespecified combination matrix, parallel within-source analyses, repeated measurements in CHARLS, survey-weighted inference in NHANES, multiple correction and competing-risk analysis of cardiovascular death. Interpretation remains limited by the different endpoints of the two cohorts, self-reported CVD in CHARLS, approximation of event time,

landmark participation selection and the absence of external validation. Because urine albumin and repeated kidney function measurements were lacking, CKM staging is operational; the two-point pattern also cannot determine a true trajectory. These factors limit calibration and transportability, but sensitivity analyses showed that the main directions were not caused by a single cohort selection rule.

Overall, CTI and CHG combinations are suitable as concise summaries for comparing CKM risk across populations, and the adiposity component should be selected in light of the measurement context. Their association does not equal incremental predictive value and is insufficient to support their use as an independent screening tool. Clinical application still requires calibration and external validation in independent cohorts with adjudicated outcomes.

Conclusions

In adults with CKM stages 0-3, combinations of CTI or CHG with adiposity indices showed the strongest and most consistent associations with incident self-reported cardiovascular disease in China and cardiovascular death in the United States, whereas the optimal adiposity index differed between the two cohorts and AIP combinations were weakest. Cumulative exposure and the waist-circumference-based two-point pattern provided additional information in CHARLS. Because no index improved the concordance index beyond conventional risk factors and component weights were unstable across resampling, these indices are better suited as convenient summaries of existing risk than as validated predictive tools.

Acknowledgments

The authors thank all study participants, interviewers and data management teams of the US National Health and Nutrition Examination Survey (NHANES) and the China Health and Retirement Longitudinal Study (CHARLS). The data used in this study were all derived from public databases, and we thank the relevant institutions for their work in data collection, processing and sharing.

Author contributions

Jiayang Xie was responsible for study conception and design, data curation, statistical analysis, interpretation of results, visualization and drafting of the manuscript. Ji Ouyang participated in study design, data curation, interpretation of results and manuscript revision. Wanghua Liu was responsible for study supervision, methodological guidance and interpretation

of results, and reviewed and revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for its content.

Ethics approval and consent to participate

This study is a secondary analysis of the publicly available, de-identified data of NHANES and CHARLS. Each NHANES survey cycle was approved by the NCHS Research Ethics Review Board, and CHARLS was approved by the Ethics Review Committee of Peking University (approval number IRB00001052-11015), and all participants provided written informed consent as required by each project. This study did not directly recruit study participants and did not conduct any additional intervention or data collection, and used public data only within the scope of the informed consent of the original surveys; therefore, no separate participant informed consent was obtained.

Consent for publication

This study does not involve any personally identifiable information, images or other materials requiring separate consent for publication, and is therefore not applicable.

Data availability

The NHANES data used in this study (including the public-use mortality linkage files) are publicly available from the website of the National Center for Health Statistics (https://www.cdc.gov/nchs/nhanes/ ; the public-use mortality linkage files are at https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). The CHARLS data are available after registration and application through the official website of the China Health and Retirement Longitudinal Study of Peking University (https://charls.pku.edu.cn/). The analysis code and derived datasets of this study are available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no competing interests related to this study.

Funding

This study was supported by the National Natural Science Foundation of China (No. 82574912), the Hunan Provincial Natural Science Foundation (Nos. 2023JJ30451 and 2025JJ50719), the Hunan Provincial Health Research Project (No. 20256419) and the Undergraduate Research and Innovation Fund Project of Hunan University of Chinese Medicine (No. 2025BKS082).

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Table 1 Source-specific baseline characteristics

Characteristics	CHARLS (N=5,304)	NHANES (N=5,487)
Anthropometry and blood pressure	—	—
Age (years)	57.90 (8.50)	58.28 (10.49)
SBP (mmHg)	126.80 (19.46)	127.16 (18.75)
DBP (mmHg)	74.37 (11.36)	72.15 (11.42)
Height (m)	1.58 (0.08)	1.68 (0.10)
Weight (kg)	58.54 (11.11)	81.29 (19.64)
Waist circumference (cm)	84.68 (9.72)	99.17 (14.85)
BMI (kg/m2)	23.44 (3.83)	28.55 (6.02)
Laboratory measurements	—	—
BUN (mg/dL)	15.55 (4.30)	14.06 (5.08)
Fasting glucose (mg/dL)	104.06 (17.61)	106.90 (29.84)
Creatinine (mg/dL)	0.76 (0.16)	0.89 (0.32)
Total cholesterol (mg/dL)	192.37 (34.92)	209.18 (40.53)
Triglycerides (mg/dL)	117.87 (65.19)	147.68 (133.67)
HDL cholesterol (mg/dL)	51.86 (13.98)	55.31 (16.40)
LDL cholesterol (mg/dL)	117.80 (31.64)	125.29 (34.69)
C reactive protein (mg/L)	2.38 (6.66)	4.26 (8.33)
eGFR (mL/min/1.73 m2)	97.50 (12.31)	88.06 (16.77)
HbA1c (%)	5.17 (0.46)	5.66 (0.86)
Uric acid (mg/dL)	4.36 (1.19)	5.51 (1.35)
Demographics, history and lifestyle	—	—
Female	2926 (55.2)	2874 (54.2)
Married	4781 (90.1)	3365 (68.0)
Rural residence	3592 (67.7)	Not available
Below high school	3793 (71.5)	1699 (18.1)
Self-reported hypertension	1099 (20.7)	2355 (38.8)
Self-reported diabetes	178 (3.4)	679 (9.5)
Self-reported dyslipidemia	382 (7.3)	Not available
Self-reported kidney disease	234 (4.4)	Not available
Drinking, source-specific	1771 (33.4)	4550 (88.3)
Current smoking, source-specific	1573 (29.7)	955 (18.3)
Operational hypertension	2667 (50.3)	3696 (62.8)
Operational diabetes	583 (11.0)	1020 (14.4)
Reduced eGFR <60	36 (0.7)	480 (6.0)
Metabolic-adiposity indices	—	—
TyG-WHtR	4.62 (0.71)	5.19 (0.94)
TyG-BRI	35.99 (12.59)	47.24 (18.90)
TyG-CVAI	802.54 (359.54)	1305.32 (564.33)
TyG-ABSI	0.7098 (0.0714)	0.7226 (0.0725)
CTI-WHtR	4.65 (0.79)	5.39 (1.12)
CTI-BRI	36.25 (13.20)	49.25 (20.97)
CTI-CVAI	809.44 (374.28)	1359.50 (611.30)
CTI-ABSI	0.7128 (0.0837)	0.7475 (0.0908)
CHG-WHtR	2.84 (0.44)	3.14 (0.58)
CHG-BRI	22.13 (7.80)	28.59 (11.51)
CHG-CVAI	493.50 (222.45)	790.73 (345.38)
CHG-ABSI	0.4360 (0.0446)	0.4370 (0.0457)
AIP-WHtR	-0.0177 (0.1613)	0.0152 (0.1872)

Characteristics	CHARLS (N=5,304)	NHANES (N=5,487)
AIP-BRI	-0.0646 (1.3035)	0.2486 (1.7690)
AIP-CVAI	2.2878 (30.2312)	10.8597 (51.0695)
AIP-ABSI	-0.0035 (0.0247)	0.0012 (0.0261)
Operational measured-core CKM stage	—	—
Stage 0	565 (10.7)	251 (6.7)
Stage 1	1098 (20.7)	705 (15.2)
Stage 2	2544 (48.0)	3249 (60.8)
Stage 3	1097 (20.7)	1282 (17.2)
Risk classification uncertain	233 (4.4)	851 (10.0)

Values are mean (SD) or yes n (%); CKM stages are category n (%). Counts are unweighted. CHARLS summaries are unweighted; NHANES means, SDs and percentages use pooled fasting-subsample weights. Percentages use available-case denominators. Drinking, smoking and disease history retain source-specific definitions. Not available denotes unavailable harmonized items. Self-reported kidney disease and reduced eGFR are distinct; CKM is operational, not full clinical adjudication. No pooled or cross-country *P* value is calculated. Full 52-feature outcome-stratified summaries and descriptive tests: Supplementary Table S27; variable availability: Supplementary Table S7.

Table 2 Apparent incremental baseline discrimination

Index	CHARLS ΔC (95% CI)	CHARLS BH P	NHANES ΔC (95% CI)	NHANES BH P
TyG-WHtR	0.0060 (0.0001, 0.0118)	0.079	0.0027 (-0.0034, 0.0088)	0.871
CTI-WHtR	0.0062 (0.0002, 0.0122)	0.079	0.0054 (-0.0029, 0.0137)	0.871
CHG-WHtR	0.0064 (0.0002, 0.0126)	0.079	0.0020 (-0.0036, 0.0076)	0.871
AIP-WHtR	0.0023 (-0.0014, 0.0059)	0.252	-0.0001 (-0.0031, 0.0030)	0.965
TyG-BRI	0.0065 (0.0007, 0.0123)	0.076	0.0036 (-0.0029, 0.0102)	0.871
CTI-BRI	0.0068 (0.0008, 0.0128)	0.076	0.0052 (-0.0026, 0.0129)	0.871
CHG-BRI	0.0069 (0.0009, 0.0130)	0.076	0.0033 (-0.0031, 0.0097)	0.871
AIP-BRI	0.0015 (-0.0016, 0.0046)	0.352	0.0001 (-0.0030, 0.0032)	0.965
TyG-CVAI	0.0083 (0.0011, 0.0156)	0.076	0.0016 (-0.0047, 0.0080)	0.883
CTI-CVAI	0.0088 (0.0014, 0.0161)	0.076	0.0027 (-0.0050, 0.0104)	0.871
CHG-CVAI	0.0087 (0.0013, 0.0162)	0.076	0.0013 (-0.0049, 0.0074)	0.911
AIP-CVAI	0.0018 (-0.0015, 0.0052)	0.299	0.0002 (-0.0033, 0.0037)	0.965
TyG-ABSI	0.0021 (-0.0013, 0.0056)	0.252	0.0016 (-0.0035, 0.0067)	0.871
CTI-ABSI	0.0028 (-0.0013, 0.0070)	0.252	0.0062 (-0.0020, 0.0144)	0.871
CHG-ABSI	0.0026 (-0.0015, 0.0068)	0.252	0.0013 (-0.0027, 0.0053)	0.871
AIP-ABSI	0.0027 (-0.0012, 0.0066)	0.252	-0.0001 (-0.0031, 0.0029)	0.965

CHARLS baseline Uno C=0.6298; NHANES survey-weighted Harrell C=0.8354. Fixed horizon CHARLS 8.9 years. 1,000 paired full-model refits, SE-based normal/design-df t intervals. Performance is apparent, not optimism corrected. Absolute C and ΔC across distinct endpoints/estimators are not directly compared. Full CHARLS dimensions and AUC/NRI/IDI in Supplementary Tables S10–S12. Complete-case N/events: CHARLS 5,294/1,361; NHANES 5,214/410. BH families contain 16 baseline index comparisons per source; displayed CIs are pointwise and are not multiplicity adjusted. Positive pointwise intervals can therefore coexist with BH *P* >0.05.



Figure 1. Source-specific participant construction.

Separate CHARLS and NHANES branches show eligibility, exposure availability and complete-case denominators. CHARLS contributes incident self-reported CVD and a wave-3 landmark cohort; NHANES contributes cardiovascular death. No combined analytic population is formed. Detailed exclusions are in Supplementary Table S1.

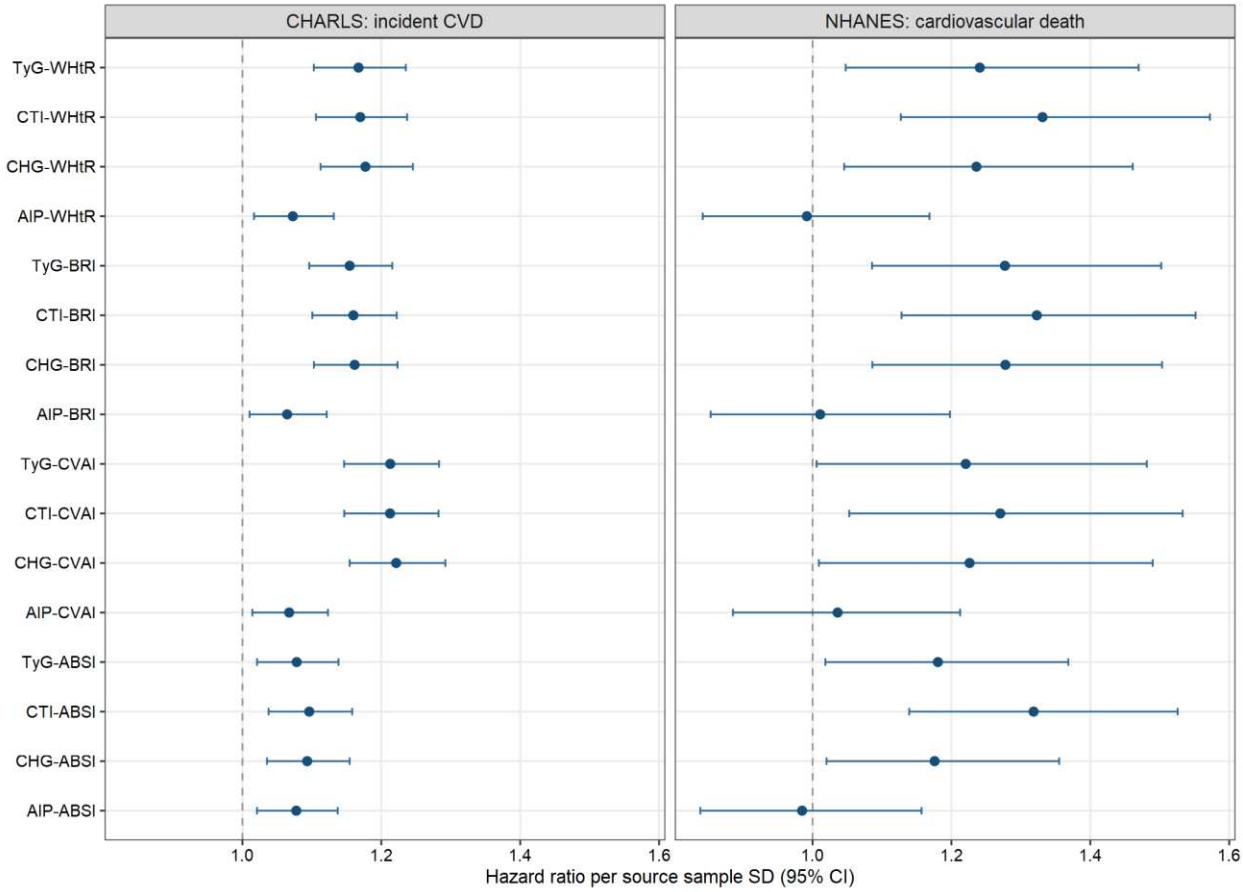


Figure 2. Baseline associations across 16 metabolic–adiposity indices. Points and horizontal bars show model-3 HRs per unweighted source sample SD and 95% CIs. CHARLS and NHANES endpoints differ. NHANES estimates retain the parent survey design and design-df inference. Supplementary Table S28 reports raw and BH adjusted *P* values; visual exclusion of unity is not the multiplicity criterion.

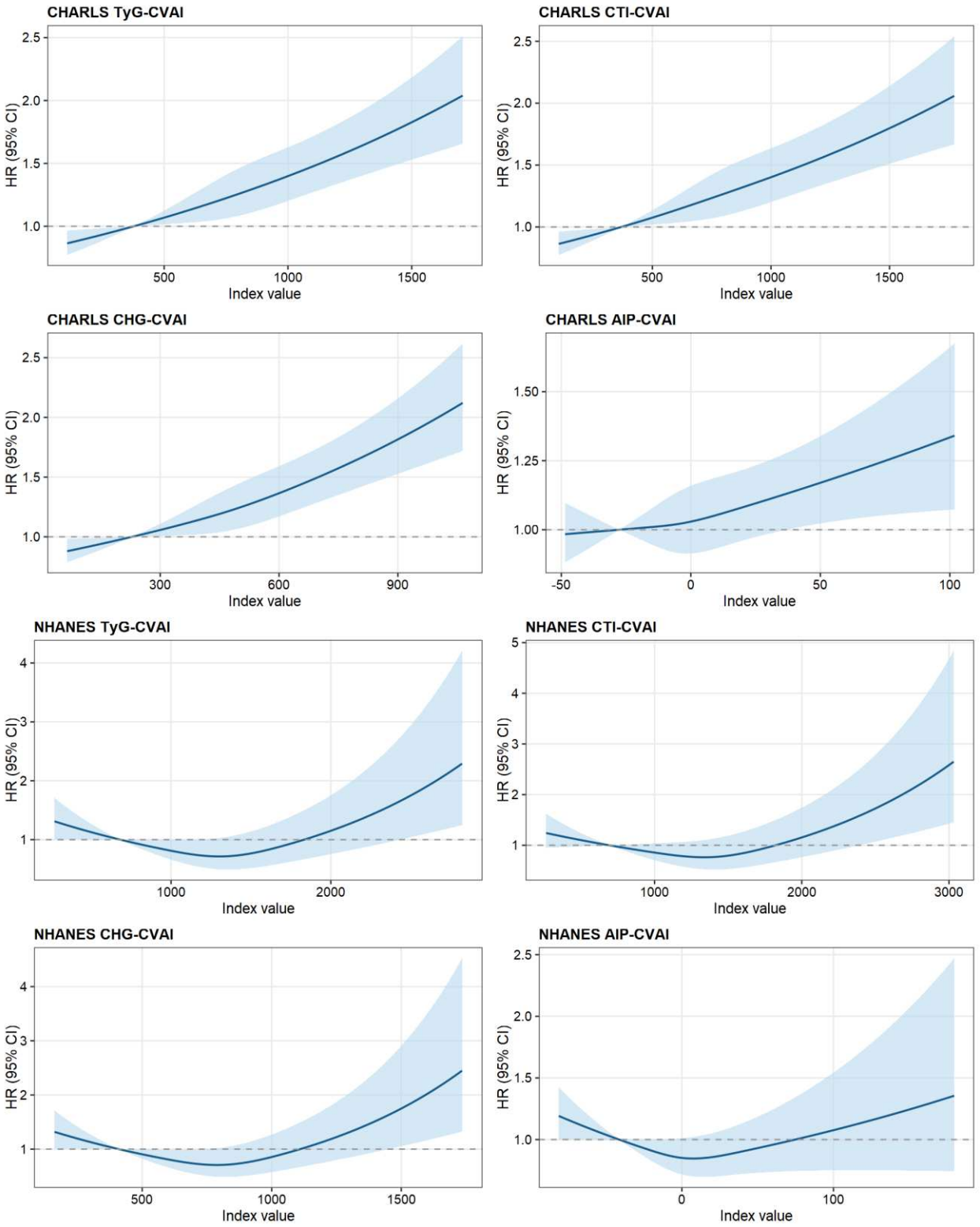


Figure 3. Baseline spline associations for CVAI-containing indices.

Curves show model-3 HRs relative to the source-specific 10th percentile, with pointwise 95% intervals. Knots are the 25th, 50th and 75th percentiles; plots cover the 1st–99th percentiles. Panels distinguish CHARLS incident CVD and NHANES cardiovascular death. All 16 indices and formal overall/nonlinear tests are available in Supplementary Figs. S10–S12 and Supplementary Table S9. Curves do not define clinical cutoffs.

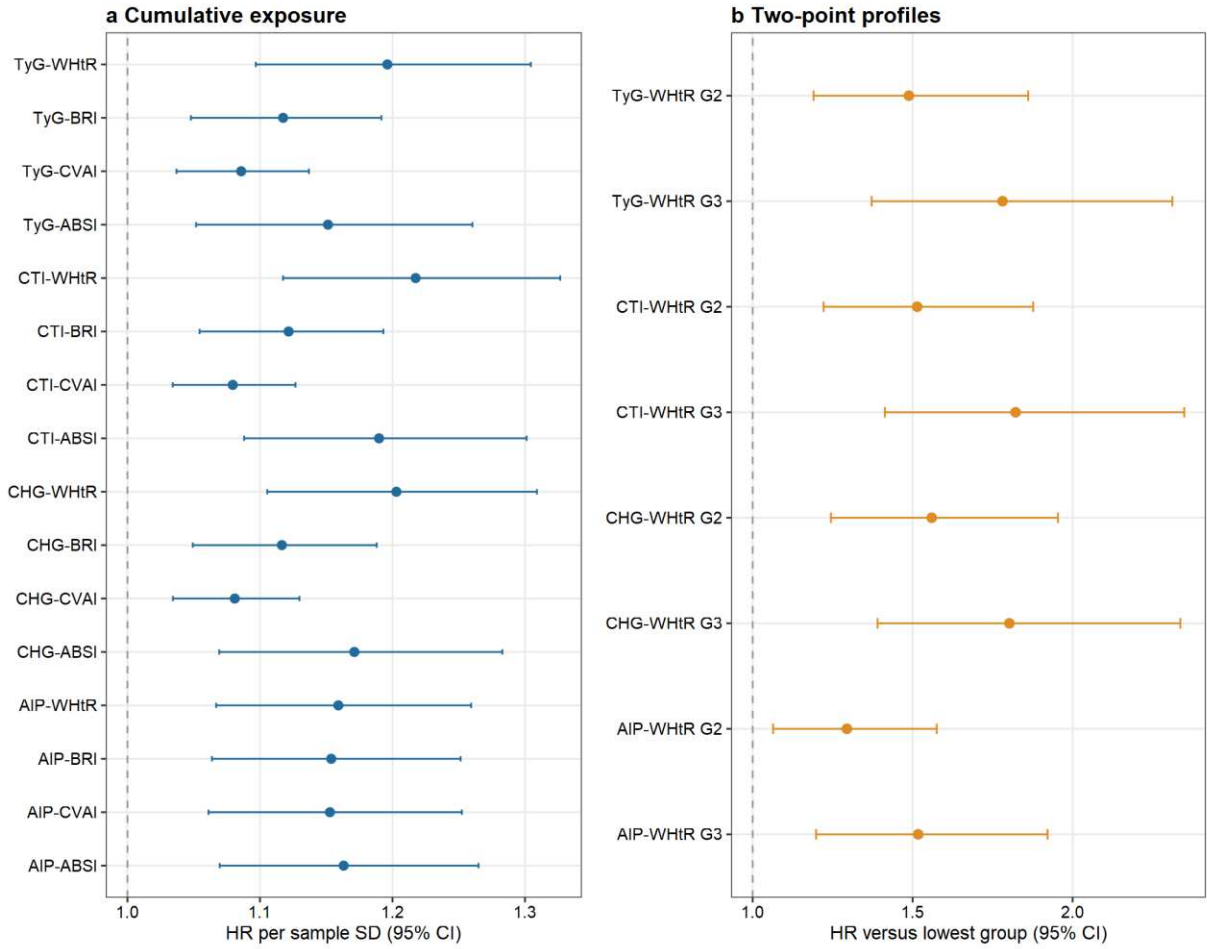


Figure 4. Cumulative exposure and two-point WHtR profiles in CHARLS.

Panel a reports model-3 HRs per cumulative-exposure SD for all 16 indices. Panel b shows groups 2 and 3 versus group 1 for the four WHtR products, ordered by two-wave mean level. Bars are 95% CIs. Follow-up begins at wave 3 among participants previously free of reported CVD. Groups summarize two measurements and do not represent latent trajectories. Sparse profiles for other indices are excluded from grouped inference.

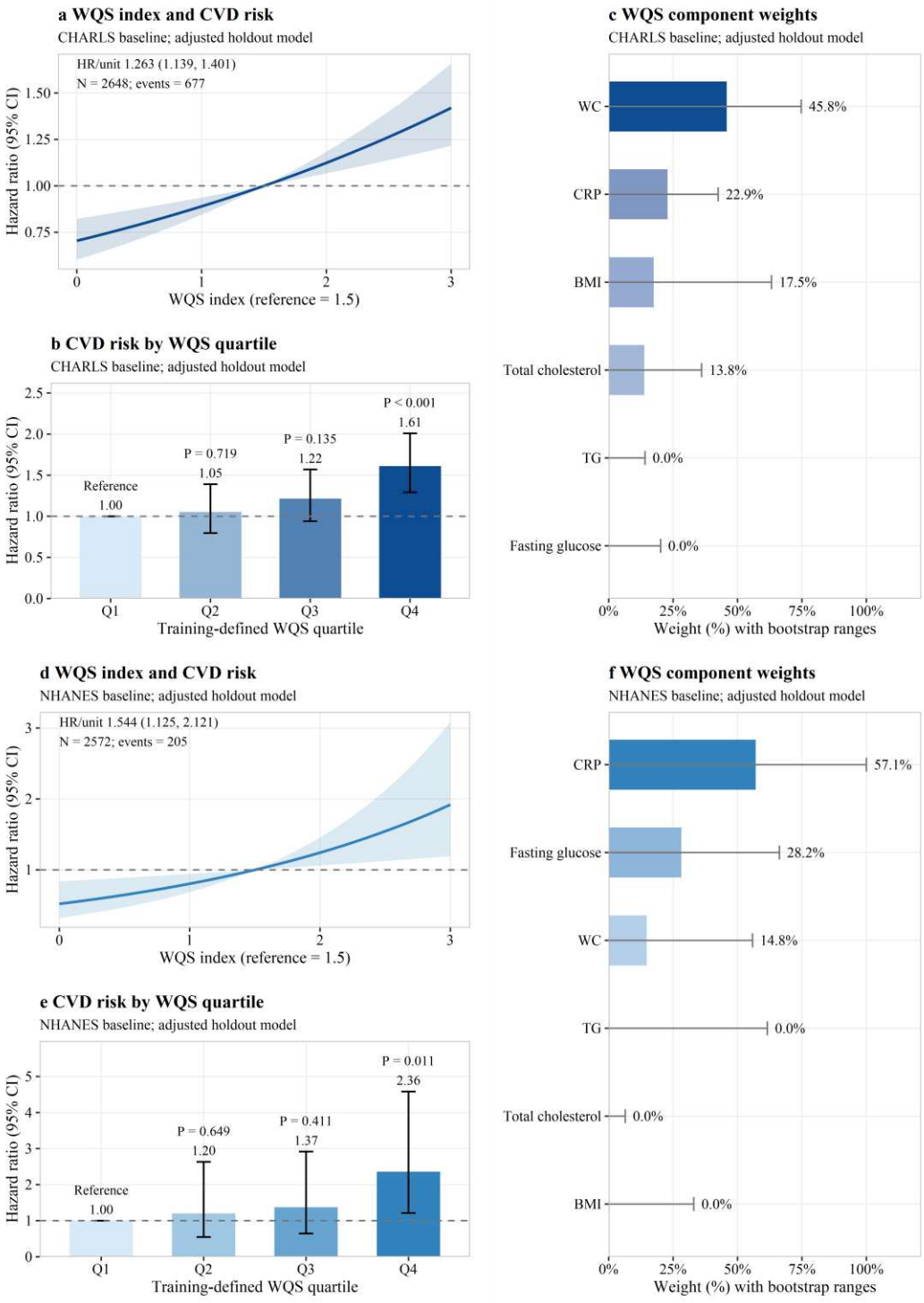


Figure 5. Positive six-component WQS baseline associations and composition.
The fixed training/validation analysis shows log-linear validation associations, training-defined WQS groups and normalized component weights with bootstrap uncertainty in each source. Components are waist circumference, BMI, TG, glucose, CRP and total cholesterol. CHARLS validation includes 2,648 participants/677 events; NHANES includes 2,572/205 cardiovascular deaths. Three hundred full-process resamples estimate uncertainty. Training cutpoints and weights are frozen for validation. Weights are

conditional mixture coefficients, not causal contributions; shared NHANES PSUs mean this is internal holdout evidence. Supplementary Tables S13–S16 report effects, weights, diagnostics and repeated-split variation.

Supplementary Files

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

- SupplementaryInformation.docx