Research Square

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Single-visit adiposity-kidney phenotypes and mortality among adults without known baseline cardiovascular disease: a survey-weighted analysis of NHANES 1999–2018

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Research Article

Keywords: Cardiovascular-kidney-metabolic syndrome, albuminuria, estimated glomerular filtration rate, obesity, mortality, NHANES

Posted Date: November 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10898584/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Albuminuria and a reduced estimated glomerular filtration rate (eGFR) reflect related but distinct forms of kidney injury. Epidemiologic studies nevertheless combine the two into a single chronic kidney disease indicator. We examined whether this simplification obscures mortality differences across eight mutually exclusive obesity–albuminuria–eGFR phenotypes within a cardiovascular-kidney-metabolic (CKM) framework.

Methods

We analyzed NHANES 1999–2018 examinations linked to the 2019 mortality files. The survey-weighted cohort comprised adults aged ≥ 20 years with complete phenotype, mortality linkage, and baseline CVD information. Eight phenotypes combined obesity (body-mass index ≥ 30 kg/m²), albuminuria (urine albumin-to-creatinine ratio ≥ 30 mg/g), and reduced kidney function (2021 CKD-EPI race-free eGFR < 60 mL/min/1.73 m²). Single-visit abnormalities did not by themselves establish clinical CKD. Survey-weighted Cox models assessed all-cause mortality as the primary outcome and mortality from heart disease or cerebrovascular disease (hereafter, heart/cerebrovascular mortality) as the key secondary outcome.

Results

The cohort included 42,496 adults and 4,792 all-cause deaths, including 1,293 deaths from heart disease or cerebrovascular disease. Fully adjusted models included 37,533 adults, 4,180 all-cause deaths, and 1,125 deaths from these causes. Phenotypes containing albuminuria generally had higher mortality, and the point estimates were largest when both kidney abnormalities were present. Compared with the reference phenotype, all-cause HRs were 1.28 (95% CI 1.12–1.46) for reduced-eGFR-only and 1.86 (1.63–2.13) for albuminuria-only. The HR was 2.28 (1.89–2.76) for both abnormalities without obesity and 2.79 (2.15–3.61) for all three features. Corresponding heart/cerebrovascular HRs were 1.69, 2.13, 2.21, and 3.57. Albuminuria-only versus reduced-eGFR-only HRs were 1.46 (1.23–1.73) without obesity and 1.71 (1.32–2.21) with obesity; their ratio was 1.17 (0.87–1.58). A five-year internal split showed no clinically important gain in discrimination.

Conclusions

Among adults without known baseline CVD participating in NHANES, separating albuminuria from reduced eGFR across eight obesity–kidney phenotypes revealed meaningful heterogeneity in mortality associations that a composite kidney indicator can obscure. Albuminuria-only was more strongly associated with all-cause mortality than reduced-eGFR-only in both obesity strata, whereas coexisting abnormalities identified the phenotypes with the highest mortality associations. These findings support retaining UACR and eGFR as separate descriptors in population-level CKM research.

Research Insights

Question	Response
What is currently known about this topic?	UACR and eGFR capture complementary kidney abnormalities. KDIGO recommends interpreting them together rather than as a single binary marker. Their prognostic differences across adiposity strata in adults without recognized CVD remain incompletely quantified.
What is the key research question?	How do eight single-visit adiposity-kidney phenotypes associate with mortality, and do U-only and E-only associations differ across adiposity strata?
What is new?	The eight phenotypes showed heterogeneous adjusted mortality associations. U-only associations were stronger than E-only associations in both adiposity strata, although estimates became less precise after restriction to ages 55–79 years. Age top-code sensitivity analyses yielded similar contrasts. Separating the markers did not improve prediction.
How might this study influence CKM research?	CKM epidemiologic analyses should retain UACR and eGFR as separate markers without assigning CKD status from a single examination.

Background

Cardiovascular, kidney, and metabolic disorders tend to co-occur across the life course, and this multimorbidity carries a substantial mortality burden[1]. Earlier cardiorenal syndrome frameworks emphasized a bidirectional heart–kidney interaction [2]. The American Heart Association CKM framework extends that view and identifies adiposity and kidney abnormalities as features that appear before overt cardiovascular disease (CVD) develops [3]. Kidney involvement is commonly identified by albuminuria, a reduced eGFR, or both [4]. Epidemiologic studies, however, frequently collapse these markers into a single CKD indicator.

That composite is clinically convenient but physiologically imprecise. Albuminuria reflects glomerular barrier injury as well as systemic endothelial and microvascular dysfunction. A reduced eGFR reflects diminished filtration capacity. Large collaborative studies have shown that UACR and eGFR contribute complementary prognostic information across their continuous ranges[5]. A binary composite cannot separate a participant with albuminuria and preserved filtration from one with reduced filtration and no albuminuria. It also conceals the prognosis associated with the coexistence of the two abnormalities.

This distinction is especially relevant to CKM research. Zhao and colleagues used NHANES 1999–2018 to compare eight combinations of type 2 diabetes, established CVD, and composite CKD[6]. That study quantified the mortality burden of clinical multimorbidity but could not resolve discordant kidney-marker states, and established CVD was itself part of the phenotype definition. A prevention-oriented CKM analysis instead requires attention to adults before CVD is recognized.

We therefore evaluated eight mutually exclusive phenotypes defined by obesity, albuminuria, and reduced eGFR among adults without known baseline CVD. The primary outcome was all-cause mortality. Heart/cerebrovascular mortality, direct marker contrasts, and marker coexistence were key secondary outcomes. We also examined effect heterogeneity, continuous-marker associations, subgroup patterns, and fixed-horizon prediction. We used obesity as an early CKM axis, whereas we treated diabetes and other metabolic factors as covariates. This design differs from multimorbidity phenotypes centered on established diabetes and CVD.

Methods

Study design and population

NHANES uses a stratified, multistage probability sample to represent the non-institutionalized US population. We pooled ten two-year cycles (1999–2000 through 2017–2018) and linked examination records to the NCHS 2019 public-use mortality files by participant sequence number [7, 8]. Follow-up ended administratively on December 31, 2019, and the maximum observed follow-up was 20.75 years. Adults aged ≥ 20 years were eligible when BMI, UACR, serum creatinine, mortality linkage, and baseline CVD classification were available.

Self-reported physician diagnoses of congestive heart failure, coronary heart disease, angina, myocardial infarction, or stroke defined baseline CVD. Any positive response indicated baseline CVD; participants missing all five items were unclassifiable. The primary cohort excluded both groups. A sensitivity analysis required responses to all five items, and another retained all eligible adults and adjusted for baseline CVD. The sequential flow comprised 55,081 age-eligible adults, 47,515 with complete cohort-formation information, and 42,496 after 5,019 adults with known CVD were excluded. The fully adjusted Model 3 included 37,533 complete cases.

The NCHS Research Ethics Review Board approved the NHANES protocols, and participants provided written informed consent. This secondary analysis used de-identified public data and followed STROBE reporting principles [9].

Phenotype definitions

Obesity was defined as BMI ≥ 30 kg/m², and albuminuria as UACR ≥ 30 mg/g. Reduced kidney function was defined as eGFR < 60 mL/min/1.73 m², calculated with the 2021 CKD-EPI race-free creatinine equation [10]. We used the serum creatinine values

in the public-release cycle files, including NCHS corrections, without further recalibration. Separate sensitivity analyses adjusted for survey cycle or excluded the 1999–2000 and 2005–2006 cycles to assess possible assay differences.

Participants were assigned to eight mutually exclusive, study-specific adiposity-kidney phenotypes defined by obesity (A0/A1), albuminuria (U0/U1), and reduced eGFR (E0/E1): A0_U0_E0, A0_U0_E1, A0_U1_E0, A0_U1_E1, A1_U0_E0, A1_U0_E1, A1_U1_E0, and A1_U1_E1. These phenotypes were motivated by the CKM framework but were not AHA CKM stages. A0_U0_E0 served as the reference. Albuminuria and reduced eGFR were measured at one examination. Although compatible with CKD, these abnormalities do not demonstrate persistence for ≥ 3 months and therefore cannot establish a clinical CKD diagnosis [4]. A severity analysis divided albuminuria into UACR 30–299 and ≥ 300 mg/g, yielding 12 adiposity-UACR-eGFR phenotypes.

Mortality outcomes

All-cause mortality was the primary outcome. The key secondary outcome comprised deaths whose leading underlying cause was classified by the linked file as heart disease or cerebrovascular disease (UCOD_LEADING codes 1 or 5). We refer to this combined endpoint as heart/cerebrovascular mortality. We also examined the two causes separately. Follow-up ran from the NHANES examination to death or the administrative end date, measured in months. Cause-specific Cox models censored deaths from other causes at the observed death time. Their HRs describe covariate-adjusted rate associations, not cumulative incidence.

Covariates

Models adjusted for age, sex, race and ethnicity, education, poverty-income ratio, ever smoking, diabetes, mean systolic blood pressure, total cholesterol, and HDL cholesterol. These prognostic factors were consistently available across cycles. Physical activity, diet, inflammatory markers, and fasting biomarkers were omitted because their availability was inconsistent or they required different subsample weights. Ever smoking was the most consistently harmonized smoking measure across the ten cycles and minimized missingness; a sensitivity analysis used never/former/current categories instead. Race and ethnicity came from RIDRETH1 (1999–2010) and RIDRETH3 (2011–2018). Mexican American, other Hispanic, non-Hispanic White, and non-Hispanic Black categories were mapped consistently. Non-Hispanic Asian participants were identified separately only in later cycles; in earlier cycles, they fell into the other or multiracial category. Diabetes was defined by self-report, insulin or glucose-lowering pill use, or HbA1c ≥ 6.5%. Mean systolic blood pressure used up to four available BPX readings. Age entered the primary model as a natural spline with 3 degrees of freedom. Internal knots were at 37 and 55 years, with boundary knots at 20 and 85 years. The phenotype-defining components were not re-entered as continuous covariates in the primary phenotype models.

Statistical analysis

All analyses incorporated examination weights, strata, and primary sampling units. The pooled 20-year weight was WTMEC4YR/5 in 1999–2002 and WTMEC2YR/10 in 2003–2018. Analyses with complete 5-year follow-up used WTMEC4YR × 2/7 and WTMEC2YR/7. Analyses with complete 10-year follow-up used WTMEC4YR × 2/5 and WTMEC2YR/5 [7, 11]. The pooled weighting formulas and survey-design audit are detailed in Supplementary Table S1. We retained the horizon-specific weights in the temporal subsets because rescaling within a subset would only multiply every weight by a constant. We declared the survey design before any subpopulation restriction. Baseline characteristics were summarized as weighted means or proportions with design-based standard errors. UACR was summarized as a weighted median and interquartile range, and counts were unweighted.

Survey-weighted Cox models estimated HRs with design-robust 95% CIs. Model 1 adjusted for spline-modeled age, sex, and race and ethnicity. Model 2 added education, poverty-income ratio, and smoking. Model 3 further added diabetes, systolic blood pressure, total cholesterol, and HDL cholesterol. Model 3 was the primary fully adjusted prognostic model. Several covariates may follow from adiposity. We therefore interpreted its estimates as conditional associations rather than total

causal effects. Models 1 and 2 showed how the estimates changed with sequential adjustment. The global eight-phenotype association with all-cause mortality was the primary analysis. Heart/cerebrovascular mortality and within-model kidney-marker contrasts were key secondary analyses. Interaction, subgroup, continuous-marker, UACR-severity, and prediction analyses were exploratory. No multiplicity adjustment was applied to non-primary analyses, which were interpreted according to effect size, precision, and consistency rather than isolated P values. Global phenotype associations used design-based Wald tests.

We assessed the proportional-hazards assumption descriptively. Because cox.zph is not design-valid for survey models, Schoenfeld residuals came from normalized MEC-weighted and unweighted working Cox models. Survey-weighted survival curves were truncated at 15 years and used for display only. To check robustness, one model used attained age as the time scale. It stratified baseline hazards by sex, diabetes, and systolic blood pressure category (< 120, 120–129, 130–139, ≥ 140 mmHg). It also stratified by HDL cholesterol category (< 40, 40–49, 50–59, ≥ 60 mg/dL). A complementary model kept time since examination as the time scale. It stratified baseline hazards by age group (< 65 or ≥ 65 years) and the same non-proportional covariates and modeled age with a 5-degree-of-freedom spline.

All direct HR contrasts came from a single fully adjusted eight-phenotype model, so they shared its sample, covariate effects, and covariance matrix. These included two obesity-stratum U-only versus E-only contrasts, four both-versus-single-marker contrasts, and the cross-obesity ratio. We varied age specification in several ways. We used a 5-degree-of-freedom age spline, attained age, and formal stratification at 65 years. The spline had internal knots at 30, 40, 51, and 64 years and boundary knots at 20 and 85 years. We also used a common 55–79-year window to reduce the age imbalance between U-only and E-only groups while retaining adequate observations and events. This window was not the mathematical intersection of the groups' 5th–95th percentile ranges. Public-use age was top-coded at 85 years in 1999–2010 and at 80 years in 2011–2018. One analysis excluded cycle-specific top-coded ages. Another capped age at 80 years and recomputed eGFR and phenotypes before refitting Model 3. A design-based Wald test jointly assessed seven age-group-by-phenotype terms in the full Model 3 cohort. A separate age-interaction model among U-only and E-only participants included adiposity as a main effect, a 5-degree-of-freedom age spline, and the other Model 3 covariates. It estimated a common age-by-marker contrast across obesity strata.

Multiplicative models tested all pairwise and three-way interactions among obesity, albuminuria, and reduced eGFR. RERI, AP, and SI based on HRs were interpreted descriptively [12]. Additive interaction was assessed as risk-scale difference-in-differences at 5 and 10 years with 500 full-refit Rao-Wu survey-bootstrap replicates. These analyses were treated as association and heterogeneity analyses, not as evidence for biological mechanisms.

Continuous markers were modeled with separate 4-degree-of-freedom natural splines for $\log_2$(UACR) and eGFR without an interaction term, with internal knots at unweighted empirical quantiles. UACR was lower-bounded at 0.1 mg/g before transformation; eGFR was not truncated. Contrasts were interpreted only within the dense observed support.

Model-standardized 5- and 10-year absolute risks were estimated in cycles with complete follow-up at each horizon. For all-cause mortality, 95% CIs used 500 full-refit Rao-Wu survey-bootstrap replicates (seeds 20260813 and 20260818 for 5 and 10 years) [13, 14]. We refitted the Cox model and repeated standardization in every replicate; all 500 yielded finite estimates. Intervals used the bootstrap standard error on the logit scale for risks and the identity scale for risk differences. For heart/cerebrovascular mortality, we used a product integral to combine the cause-specific baseline-hazard increments for the target outcome and other deaths [13]. We refitted both cause-specific models and repeated standardization in 200 survey-bootstrap replicates (seeds 20260833 and 20260838). All replicates were finite, and we used the same scale-specific normal approximation. The lower replicate count reflected the two model fits required per replicate. Design-based HRs and CIs remained the primary inference.

Prediction analyses were secondary to the association questions. Model A combined obesity with a composite single-visit kidney abnormality; Model B entered obesity, albuminuria, and reduced eGFR separately; Model C used the eight phenotypes. Identical covariates and samples were compared at 5 years (1999–2012) and 10 years (1999–2008), when outcome status was fully observed. The supplement reports survey-weighted fixed-horizon AUC, Brier score, calibration, and an internal temporal split. Five hundred evaluation-sample replicates quantified uncertainty conditional on each fitted model and omitted

parameter-estimation uncertainty. The AUCs were not survey-valid Uno C-statistics [15], and the Brier scores were horizon-specific rather than integrated. The temporal split was an internal, not external, validation. We did not calculate NRI or IDI.

We tested the sensitivity of the primary associations to a range of specification choices. Adiposity was redefined as BMI ≥ 25 kg/m², standard BMI categories (18.5–24.9 kg/m² reference), continuous BMI, or waist circumference. Other analyses retained adults with baseline CVD and adjusted for it, restricted the cohort to never smokers, added current antihypertensive use, or separated heart from cerebrovascular deaths. Additional analyses varied age modeling and divided albuminuria into 30–299 and ≥ 300 mg/g. We also adjusted for cycle, excluded BMI < 18.5 kg/m², applied a 2-year landmark, required complete baseline CVD items, and excluded known pregnancies. Sex- and diabetes-stratified analyses were also conducted. RAAS-inhibitor- and SGLT2-inhibitor-specific analyses were omitted because medication coding, availability, and indications changed substantially over two decades, and SGLT2 inhibitors were absent from early cycles.

Missing covariates were addressed primarily by complete-case analysis. A sensitivity analysis used chained equations with 20 imputed datasets and 10 iterations per chain. Predictors included event indicators, Nelson-Aalen cumulative hazards, exposures, follow-up, survey weights, strata, PSUs, and cycle. Continuous variables were imputed with predictive mean matching, binary variables with logistic regression, and education with proportional-odds regression. Predictive mean matching preserved the poverty-income ratio's upper point mass at 5. Imputation diagnostics indicated no material convergence problems. Survey-weighted Cox estimates from each completed dataset were combined with Rubin's rules[16]. Analyses used R 4.6.0 with survey 4.5, survival 3.8.6, and mice 3.19.0.

Results

Participant selection and baseline characteristics

Of 101,316 NHANES participants, 55,081 were aged ≥ 20 years. Sequential exclusions for unavailable BMI (n = 3,751), UACR (n = 1,065), eGFR (n = 2,666), or mortality linkage (n = 84) left 47,515 adults. These adults had complete phenotype and mortality information and classifiable baseline CVD. Excluding 5,019 adults with known baseline CVD left 42,496 in the primary cohort (Fig. 1). Among these participants, 4,963 lacked at least one Model 3 covariate, yielding 37,533 complete cases. The primary cohort had 4,792 all-cause deaths, including 1,293 deaths from heart disease or cerebrovascular disease. The fully adjusted models included 4,180 all-cause deaths, including 1,125 deaths from these causes.

These were successive stages, and individual reasons for missingness could overlap, so the exclusion counts should not be summed. For example, three adults had unclassifiable baseline CVD after another required domain was already missing. Supplementary Table S15 presents the complete flow and selection audit.

Results are presented according to the analytical hierarchy described in Methods and Supplementary Table S17. This hierarchy was specified after the analysis was completed and was not prospectively registered.

The two phenotypes without kidney abnormalities predominated. A0_U0_E0 accounted for 59.3% of the weighted population, and obesity without either kidney abnormality accounted for 29.9%. Albuminuria-only without obesity accounted for 3.9%, reduced-eGFR-only without obesity for 1.6%, both kidney abnormalities without obesity for 0.6%, and all three features for 0.4% (Table 2). E-only participants were substantially older than U-only participants (mean ages 70.5 versus 50.4 years without obesity and 68.1 versus 49.4 years with obesity). Median UACR ranged from 5.7 mg/g in A0_U0_E0 to 107.9 mg/g in A1_U1_E1. The all-three group comprised 291 participants and 127 all-cause deaths. Table 1 presents weighted demographic, socioeconomic, metabolic, and kidney characteristics, and Supplementary Table S3 gives variable-specific missing counts. Supplementary Tables S2 and S4 provide the corresponding phenotype-specific baseline summaries, follow-up data, and weighted mortality rates.

Table 1
Weighted baseline characteristics by CKM phenotype.

Characteristic	A0_U0_E0	A0_U0_E1	A0_U1_E0	A0_U1_E1	A1_U0_E0	A1_U0_E1	A1_U1_E0	A1_U1_E1
Unweighted n	23913	903	2084	439	12622	609	1635	291
Age, years	43.5 (0.2)	70.5 (0.6)	50.4 (0.6)	71.3 (0.8)	44.9 (0.2)	68.1 (0.5)	49.4 (0.5)	63.3 (1.3)
Sex: Male, %	49.9 (0.4)	36.3 (2.4)	38.2 (1.5)	50.2 (3.2)	46.0 (0.6)	32.9 (2.5)	46.4 (1.7)	39.5 (3.7)
Sex: Female, %	50.1 (0.4)	63.7 (2.4)	61.8 (1.5)	49.8 (3.2)	54.0 (0.6)	67.1 (2.5)	53.6 (1.7)	60.5 (3.7)
Race/ethnicity: Mexican American, %	7.9 (0.5)	1.5 (0.3)	9.5 (0.8)	4.4 (0.9)	10.3 (0.8)	3.2 (0.6)	12.5 (1.0)	7.3 (1.6)
Race/ethnicity: Other Hispanic, %	5.9 (0.5)	2.4 (0.5)	6.3 (0.8)	4.0 (1.3)	5.7 (0.5)	2.2 (0.4)	8.4 (1.0)	3.6 (1.1)
Race/ethnicity: Non-Hispanic White, %	69.5 (1.0)	80.6 (1.6)	61.9 (1.7)	65.5 (2.7)	66.2 (1.3)	70.8 (2.4)	58.2 (2.0)	57.9 (3.9)
Race/ethnicity: Non-Hispanic Black, %	8.5 (0.4)	12.2 (1.2)	11.2 (0.8)	18.2 (2.1)	13.3 (0.8)	21.3 (2.0)	15.3 (1.2)	23.9 (2.9)
Race/ethnicity: Non-Hispanic Asian, %	3.2 (0.3)	1.4 (0.3)	4.3 (0.5)	3.9 (1.1)	0.9 (0.1)	0.2 (0.2)	1.2 (0.2)	0.7 (0.7)
Race/ethnicity: Other race, %	5.0 (0.3)	1.9 (0.6)	6.7 (0.8)	4.1 (1.4)	3.5 (0.3)	2.3 (0.7)	4.4 (0.8)	6.6 (2.4)
Education: Less than grade 9, %	5.0 (0.2)	9.1 (1.1)	10.2 (0.7)	13.1 (1.8)	4.9 (0.3)	8.3 (1.1)	8.8 (0.7)	11.5 (2.0)
Education: Grades 9–11, %	10.2 (0.4)	11.1 (1.2)	12.1 (0.9)	15.8 (2.0)	11.1 (0.4)	12.8 (1.6)	14.9 (1.0)	14.7 (2.3)
Education: High school graduate, %	22.2 (0.5)	27.1 (1.8)	25.3 (1.4)	27.1 (2.7)	25.3 (0.6)	30.6 (2.3)	25.7 (1.7)	27.9 (3.8)
Education: Some college, %	29.7 (0.5)	27.9 (2.1)	28.4 (1.5)	23.8 (3.1)	34.8 (0.6)	30.3 (2.4)	33.4 (1.7)	30.9 (3.9)
Education: College graduate or above, %	32.9 (0.9)	24.8 (2.2)	23.9 (1.6)	20.2 (3.0)	23.9 (0.7)	18.0 (1.8)	17.2 (1.6)	14.9 (2.4)
BMI, kg/m²	24.9 (0.0)	25.4 (0.1)	24.4 (0.1)	25.1 (0.2)	35.7 (0.1)	35.2 (0.2)	37.0 (0.2)	36.5 (0.4)
Waist circumference, cm	89.2 (0.1)	93.7 (0.4)	88.8 (0.4)	94.3 (0.5)	113.4 (0.2)	114.0 (0.6)	117.5 (0.6)	117.4 (1.1)
UACR, median (IQR), mg/g	5.7 (4.0-8.8)	7.8 (4.9–13.2)	53.2 (38.7-114.7)	86.2 (45.8-302.8)	6.0 (4.1–9.6)	7.3 (4.3–11.7)	63.1 (40.4–132.0)	107.9 (48.4–825.0)

Values are weighted mean (SE), weighted percentage (SE), or weighted median (IQR), unless stated otherwise. A0/A1: BMI < 30/≥30 kg/m²; U0/U1: UACR < 30/≥30 mg/g; E0/E1: eGFR ≥ 60/<60 mL/min/1.73 m². Single-visit kidney abnormalities are not clinical CKD diagnoses.

Characteristic	A0_U0_E0	A0_U0_E1	A0_U1_E0	A0_U1_E1	A1_U0_E0	A1_U0_E1	A1_U1_E0	A1_U1_E1
eGFR, mL/min/1.73 m²	101.2 (0.2)	51.3 (0.3)	98.8 (0.5)	43.8 (0.9)	100.1 (0.3)	50.6 (0.4)	98.8 (0.6)	42.4 (1.0)
Mean SBP, mmHg	118.8 (0.2)	134.2 (1.1)	128.2 (0.6)	145.5 (1.9)	123.6 (0.2)	130.4 (1.1)	134.0 (0.7)	142.2 (1.9)
Mean DBP, mmHg	70.4 (0.2)	65.9 (0.8)	71.0 (0.4)	67.0 (1.4)	73.1 (0.2)	65.2 (0.8)	76.5 (0.4)	71.1 (1.4)
Total cholesterol, mg/dL	196.3 (0.4)	202.0 (2.0)	200.6 (1.5)	194.4 (3.7)	198.6 (0.6)	194.8 (2.3)	202.7 (1.5)	195.4 (4.0)
HDL cholesterol, mg/dL	56.4 (0.2)	57.6 (0.7)	58.2 (0.7)	56.0 (1.4)	47.8 (0.2)	52.6 (1.0)	46.3 (0.4)	47.7 (0.9)
Poverty-income ratio	3.1 (0.0)	3.0 (0.1)	2.6 (0.1)	2.6 (0.1)	3.0 (0.0)	2.9 (0.1)	2.7 (0.1)	2.3 (0.1)
Diabetes, %	4.1 (0.2)	13.3 (1.4)	16.1 (1.0)	33.3 (3.3)	12.6 (0.4)	31.4 (2.5)	37.1 (1.7)	52.6 (3.7)
Ever smoking, %	45.2 (0.6)	44.3 (2.0)	48.8 (1.5)	49.2 (3.2)	43.2 (0.6)	43.0 (3.2)	48.9 (1.7)	47.4 (3.9)

Values are weighted mean (SE), weighted percentage (SE), or weighted median (IQR), unless stated otherwise. A0/A1: BMI < 30/≥30 kg/m²; U0/U1: UACR < 30/≥30 mg/g; E0/E1: eGFR ≥ 60/<60 mL/min/1.73 m². Single-visit kidney abnormalities are not clinical CKD diagnoses.

Table 2
Weighted phenotype prevalence, event counts, and mortality rates.

Phenotype	Weighted prevalence, % (95% CI)	n	All-cause deaths	All-cause rate	H/C deaths	H/C rate	Median follow-up, y
A0_U0_E0	59.3 (58.4–60.1)	23913	2115	0.61 (0.58–0.65)	504	0.13 (0.12–0.14)	10.1
A0_U0_E1	1.6 (1.5–1.8)	903	365	3.99 (3.50–4.48)	114	1.29 (1.00-1.58)	7.2
A0_U1_E0	3.9 (3.7–4.2)	2084	539	2.17 (1.92–2.43)	164	0.65 (0.52–0.77)	8.2
A0_U1_E1	0.6 (0.5–0.7)	439	259	8.51 (7.26–9.77)	73	2.31 (1.75–2.87)	5.7
A1_U0_E0	29.9 (29.1–30.7)	12622	923	0.62 (0.56–0.67)	239	0.16 (0.13–0.19)	9.4
A1_U0_E1	1.0 (0.9–1.2)	609	177	3.09 (2.61–3.57)	63	1.11 (0.82–1.40)	7.8
A1_U1_E0	3.2 (3.0-3.4)	1635	287	1.80 (1.56–2.04)	93	0.58 (0.43–0.74)	8.8
A1_U1_E1	0.4 (0.4–0.5)	291	127	6.29 (4.81–7.77)	43	2.17 (1.30–3.04)	5.3

Counts are unweighted; prevalence and rates are survey weighted. Rates are events per 100 person-years (95% CI). H/C denotes heart or cerebrovascular mortality. Four participants with zero follow-up contributed to prevalence and event summaries but not rate calculations.

Phenotypes and all-cause mortality

The fully adjusted estimates showed a graded pattern. Phenotypes containing albuminuria had higher point estimates than those with reduced eGFR alone, and phenotypes with both abnormalities had the highest estimates. Compared with A0_U0_E0, HRs were 1.28 (95% CI 1.12–1.46) for A0_U0_E1, 1.86 (1.63–2.13) for A0_U1_E0, and 2.28 (1.89–2.76) for A0_U1_E1. Among obese phenotypes, HRs were 1.04 (0.94–1.15) for A1_U0_E0 and 1.12 (0.93–1.35) for A1_U0_E1. They were 1.92 (1.60–2.30) for A1_U1_E0 and 2.79 (2.15–3.61) for A1_U1_E1 (global $P < 0.001$; Table 3, Fig. 3). Five-year standardized all-cause risks ranged from 2.29% (95% CI 2.10%–2.49%) in A0_U0_E0 to 5.36% (4.22%–6.79%) in A1_U1_E1 (Fig. 2). Intermediate risks were 2.69% (2.35%–3.09%), 3.91% (3.45%–4.44%), and 4.52% (3.79%–5.38%). The U-only minus E-only risk difference was 1.22 percentage points (0.69–1.75) without obesity and 1.61 points (0.78–2.44) with obesity. The direction and ordering of the associations remained consistent across sequential adjustment models (Supplementary Table S5).

Table 3
Fully adjusted mortality associations and direct kidney-marker contrasts.

Comparison	All-cause HR (95% CI)	H/C HR (95% CI)
A0_U0_E1	1.28 (1.12–1.46)	1.69 (1.30–2.20)
A0_U1_E0	1.86 (1.63–2.13)	2.13 (1.68–2.69)
A0_U1_E1	2.28 (1.89–2.76)	2.21 (1.62–3.01)
A1_U0_E0	1.04 (0.94–1.15)	1.27 (1.02–1.59)
A1_U0_E1	1.12 (0.93–1.35)	1.59 (1.16–2.18)
A1_U1_E0	1.92 (1.60–2.30)	2.82 (2.05–3.87)
A1_U1_E1	2.79 (2.15–3.61)	3.57 (2.17–5.89)
U-only vs E-only; no obesity	1.46 (1.23–1.73)	1.26 (0.91–1.73)
U-only vs E-only; obesity	1.71 (1.32–2.21)	1.77 (1.18–2.67)
Both vs E-only; no obesity	1.78 (1.44–2.21)	1.31 (0.88–1.94)
Both vs U-only; no obesity	1.23 (0.99–1.52)	1.04 (0.74–1.46)
Both vs E-only; obesity	2.49 (1.83–3.39)	2.25 (1.31–3.87)
Both vs U-only; obesity	1.45 (1.08–1.97)	1.27 (0.73–2.21)
Ratio of HRs; obesity/no obesity	1.17 (0.87–1.58)	1.41 (0.83–2.39)

Phenotype rows use A0_U0_E0 as reference. The shared complete-case cohort included 37,533 participants with 4,180 all-cause and 1,125 heart or cerebrovascular deaths. Every direct contrast and ratio derives from the same fully adjusted eight-phenotype model and covariance matrix. Models adjust for age spline, sex, race/ethnicity, education, poverty-income ratio, ever smoking, diabetes, systolic blood pressure, total cholesterol, and HDL cholesterol.

The primary cohort excluded participants with known or unclassifiable baseline cardiovascular disease. Complete-case sample sizes were outcome and model specific.

Risks were standardized to the covariate distribution of eligible cycles with complete follow-up. Error bars are 95% confidence intervals from full-refit Rao-Wu survey bootstrap: 500 replicates for all-cause mortality and 200 for heart or cerebrovascular cumulative incidence; all replicates were finite. Values are population averages, not patient-specific predictions.

Hazard ratios compare each phenotype with A0_U0_E0. Error bars show 95% confidence intervals. Heart or cerebrovascular deaths were analyzed with cause-specific Cox models.

The two obesity-stratum U-only versus E-only HRs and their cross-stratum ratio derive from the same fully adjusted eight-phenotype model and covariance matrix.

Phenotypes and heart/cerebrovascular mortality

Heart/cerebrovascular mortality followed a similar ordering, with wider CIs. Fully adjusted HRs were 1.69 (95% CI 1.30–2.20) for A0_U0_E1, 2.13 (1.68–2.69) for A0_U1_E0, and 2.21 (1.62–3.01) for A0_U1_E1. Among obese phenotypes, HRs were 1.27 (1.02–1.59) for A1_U0_E0 and 1.59 (1.16–2.18) for A1_U0_E1. They were 2.82 (2.05–3.87) for A1_U1_E0 and 3.57 (2.17–5.89) for A1_U1_E1 (global $P < 0.001$; Table 3, Fig. 3). Five-year standardized risks were 0.49% (0.40%–0.59%) for A0_U0_E0, 0.68% (0.47%–0.98%) for A0_U0_E1, 0.95% (0.74%–1.22%) for A0_U1_E0, and 1.22% (0.73%–2.04%) for A1_U1_E1 (Fig. 2). Separate analyses included only 201 cerebrovascular deaths and were too imprecise to support subtype-specific conclusions (Supplementary Table S9).

Discordant phenotypes and interaction

The direct contrasts distinguished the two kidney-marker states. U-only versus E-only all-cause HRs were 1.46 (95% CI 1.23–1.73) without obesity and 1.71 (1.32–2.21) with obesity. Their ratio was 1.17 (0.87–1.58; $P = 0.289$), leaving meaningful obesity

modification uncertain. Compared with E-only phenotypes, phenotypes with both abnormalities had HRs of 1.78 (1.44–2.21) without obesity and 2.49 (1.83–3.39) with obesity. Compared with U-only phenotypes, the corresponding HRs were 1.23 (0.99–1.52) and 1.45 (1.08–1.97). For heart/cerebrovascular mortality, U-only versus E-only HRs were 1.26 (0.91–1.73) without obesity and 1.77 (1.18–2.67) with obesity. The ratio was 1.41 (0.83–2.39; P = 0.201; Fig. 4). A 5-degree-of-freedom age spline gave nearly identical all-cause contrasts; attained-age analyses yielded HRs of 1.53 and 1.81 and a ratio of 1.19 (0.88–1.60). Complete estimates, confidence intervals, and P values for all direct kidney-marker contrasts are reported in Supplementary Table S6.

Two-way multiplicative interactions for all-cause mortality had P ≥ 0.51, and the three-way global interaction had P = 0.411. Descriptive HR-scale RERI, AP, and SI estimates did not establish departure from additivity. On the standardized-risk scale, the 5-year albuminuria-by-reduced-eGFR difference-in-differences was 0.20 percentage points without obesity (95% CI − 0.75 to 1.15; P = 0.683). It was 1.08 points with obesity (− 0.41 to 2.58; P = 0.156). The difference between obesity strata was 0.88 points (− 0.74 to 2.50; P = 0.285). At 10 years, these estimates were − 0.49 (− 2.67 to 1.69), 2.27 (− 1.17 to 5.70), and 2.76 (− 1.10 to 6.61) percentage points. These intervals were likewise compatible with no interaction (Supplementary Table S7).

Prediction and calibration analysis

The 5-year internal temporal split included 17,688 participants in model development and 8,183 in validation. The validation set had 297 all-cause deaths and 73 heart/cerebrovascular deaths. All-cause AUCs were 0.825, 0.827, and 0.827 for Models A, B, and C. Differences from Model A were 0.0012 (95% interval from 500 evaluation-sample replicates, − 0.0006 to 0.0031) for Model B and 0.0012 (− 0.0006 to 0.0032) for Model C. The heart/cerebrovascular evaluation had too few target deaths for comparative claims. Supplementary Table S18 and Supplementary Figure S2 summarize fixed-horizon performance and calibration. Disaggregation produced no clinically important or stable gain in discrimination.

Sensitivity and subgroup analyses

In descriptive proportional-hazards diagnostics, the normalized MEC-weighted all-cause model had global P < 0.001 and phenotype-term P = 0.461; unweighted, these values were P < 0.001 and P = 0.039. For heart/cerebrovascular mortality, weighted values were P = 0.113 and P = 0.888, and unweighted values were P = 0.066 and P = 0.480. Most evidence of non-proportionality involved age, sex, diabetes, systolic blood pressure, and HDL cholesterol (Supplementary Table S10).

Robustness models produced similar direct contrasts. An attained-age model with baseline hazards stratified by the covariates above yielded U-only versus E-only HRs of 1.57 without obesity and 1.91 with obesity. The ratio was 1.22 (0.89–1.66). In the complementary time-on-study model, baseline hazards were also stratified by age group and age was modeled with a 5-df spline. The corresponding HRs were 1.55 (1.29–1.87) and 1.69 (1.29–2.20), with a ratio of 1.08 (0.79–1.49; n = 37,529; 4,176 deaths). The main contrast was similar in both checks. These models do not demonstrate a constant HR over follow-up, so the primary estimates represent average relative-hazard associations (Supplementary Table S10).

The global age-group-by-eight-phenotype interaction was supported for all-cause mortality (design-based Wald F(7,120) = 5.10, P = 4.25×10^{-5}). It was also supported for heart/cerebrovascular mortality (F(7,120) = 3.48, P = 0.00198). Thus, at least one phenotype contrast varied by age group. This global test does not address the specific U-only versus E-only contrast. Among adults aged < 65 years, U-only versus E-only HRs were 1.35 (0.68–2.70) without obesity and 2.04 (1.10–3.79) with obesity. Among adults aged ≥ 65 years, the corresponding HRs were 1.54 (1.29–1.83) and 1.33 (0.99–1.80). A discordant-marker-only model estimated a ratio of HRs of 0.77 (0.50–1.17; P = 0.217; n = 4,586; 1,207 all-cause deaths). Sparse younger E-only cells limited precision (Supplementary Table S13).

In the common 55–79-year window, U-only versus E-only HRs were 1.66 (1.27–2.17) without obesity and 1.32 (0.96–1.82) with obesity. The analysis included 11,282 participants and 2,350 all-cause deaths. The estimate among participants with obesity was attenuated and imprecise but remained directionally compatible with the primary comparison. Supplementary Figure S3 shows the age distributions, and Supplementary Table S13 reports the estimates.

Flexible age adjustment yielded all-cause HRs of 1.27 for E-only, 1.85 for U-only, 2.26 for both abnormalities without obesity, and 2.77 for all three features. With attained age as the time scale, these estimates were approximately 1.16, 1.79, 2.12, and 2.65. The E-only estimate thus attenuated with age adjustment, whereas the overall gradient persisted. Excluding cycle-specific top-coded ages reduced the Model 3 sample from 37,533 to 36,659 and all-cause deaths from 4,180 to 3,747. U-only versus E-only HRs were 1.63 (1.33–2.00) without obesity and 1.68 (1.28–2.20) with obesity. Recomputing eGFR after capping age at 80 years retained 37,533 participants and yielded HRs of 1.48 (1.24–1.75) and 1.68 (1.30–2.17). Nineteen participants changed phenotype under the common age cap (Supplementary Table S19).

Cycle adjustment, exclusion of BMI < 18.5 kg/m², and the 2-year landmark all gave directionally consistent estimates. The same held after requiring complete baseline CVD items, excluding known pregnancy, or excluding the two cycles with possible creatinine assay concerns. These results are reported in Supplementary Tables S9, S13, S15, and S19. The strict-item CVD check reproduced the primary Model 3 cohort because complete baseline CVD classification was required for cohort entry.

Defining adiposity as BMI ≥ 25 kg/m² did not materially change the kidney-marker associations (Supplementary Table S12; Supplementary Figure S1). Each 5-kg/m² higher BMI corresponded to HRs of 0.99 for all-cause mortality and 1.12 for heart/cerebrovascular mortality. Each 10-cm higher waist circumference corresponded to HRs of 1.02 and 1.13, respectively. Standard BMI categories used 18.5–24.9 kg/m² as the reference and did not support a simple protective interpretation (Supplementary Table S12).

Replacing ever smoking with never/former/current categories yielded U-only versus E-only HRs of 1.38 (1.17–1.64) without obesity and 1.73 (1.33–2.25) with obesity. Estimates were directionally consistent among never smokers, after retaining and adjusting for baseline CVD, and after additional adjustment for current antihypertensive use (n = 35,497). In all adults adjusted for baseline CVD (n = 41,945), all-cause HRs were 1.23 for A0_U0_E1, 1.83 for A0_U1_E0, 2.22 for A0_U1_E1, and 2.55 for A1_U1_E1 (Supplementary Tables S9 and S14). The 20-imputation analysis, which included all 42,496 participants, yielded HRs of 1.26, 1.82, 2.33, and 2.63 (Supplementary Table S14).

Continuous-marker splines supported graded, threshold-sensitive associations (Supplementary Table S11). At an eGFR of 90 mL/min/1.73 m², a UACR of 30 versus 10 mg/g corresponded to an all-cause HR of 1.34 (95% CI 1.24–1.44). A UACR of 300 versus 10 mg/g corresponded to an HR of 2.19 (1.92–2.50). At a UACR of 10 mg/g, an eGFR of 60 versus 90 was not associated with mortality (HR 1.00, 0.91–1.11). An eGFR of 45 versus 90 was associated with mortality (HR 1.21, 1.06–1.39). The binary E-only estimate therefore reflects the range below 60 and the joint phenotype's age and covariate distributions. It does not imply risk at every value near the threshold.

With preserved eGFR, all-cause HRs for moderate and severe albuminuria were 1.83 and 2.44 without obesity and 1.80 and 3.12 with obesity. Estimates were higher when reduced eGFR accompanied albuminuria (Supplementary Table S11). Severe versus moderate albuminuria was associated with higher mortality among non-obese adults with reduced eGFR (HR 1.66, 1.12–2.46). The corresponding HR among obese adults with preserved eGFR was 1.73 (1.03–2.91). These secondary contrasts are consistent with a graded UACR association but cannot establish persistence.

Sex did not materially modify the associations (Supplementary Table S14), and diabetes did not modify the all-cause associations. A diabetes interaction was observed for heart/cerebrovascular mortality (global P = 0.025; Supplementary Table S14). Because this was one of several unadjusted tests with sparse cells, it is hypothesis-generating rather than definitive.

The age top-code audit identified 1,048 top-coded participants in the primary cohort; excluding them reduced heart/cerebrovascular events from 1,125 to 983. The common 80-year cap changed 19 binary phenotype assignments (Supplementary Table S19).

Discussion

Principal findings

In this survey-weighted NHANES sample, the eight single-visit phenotypes resolved kidney-marker patterns that a composite indicator would conceal. Albuminuria-only was more strongly associated with all-cause mortality than reduced-eGFR-only in both obesity strata, although the cross-stratum ratio left obesity modification uncertain. Coexisting abnormalities had the highest point estimates. Phenotypes with both abnormalities were associated with higher all-cause mortality than E-only phenotypes in both obesity strata. They were also associated with higher mortality than U-only phenotypes among participants with obesity, whereas the non-obesity both-versus-U-only interval included the null (Table 3; Fig. 4). Interaction estimates were compatible with no synergy. The findings provide a more granular epidemiologic description of a heterogeneous kidney-marker construct. They do not define a new biological mechanism or clinical staging system.

The internal temporal split showed little change in discrimination after UACR and eGFR were separated. Model C should not be used as a clinical score (Supplementary Table S18; Supplementary Figure S2).

Albuminuria, reduced eGFR, and age

Albuminuria reflects glomerular permeability and systemic vascular injury, whereas a reduced eGFR reflects loss of filtration. Their partially independent mortality associations agree with the collaborative meta-analysis by Matsushita and colleagues, in which both markers contributed complementary risk across continuous ranges[5]. Our mutually exclusive framework extends that evidence by comparing discordant binary states within obesity-defined CKM phenotypes.

Age requires particular attention because E-only participants were much older than U-only participants (70.5 versus 50.4 years without obesity and 68.1 versus 49.4 years with obesity). This age gap likely explains why crude mortality rates were higher in E-only, whereas standardized risks and HRs were higher in U-only. Flexible age adjustment and attained-age models attenuated the E-only HR from 1.28 to approximately 1.16, while the U-only estimate remained near 1.8 and the direct contrast remained elevated. Formal < 65 and ≥ 65 analyses were directionally compatible but imprecise in younger E-only cells, and the specific age-by-contrast interaction was likewise imprecise. In the common 55–79-year window, both contrasts retained their direction. The obesity-stratum estimate attenuated to 1.32, and its 95% CI included 1 (Supplementary Table S13; Supplementary Figure S3). This attenuation may reflect reduced precision; the available data cannot distinguish that explanation from a true change in association. We also examined the inconsistent high-age coding across cycles. Excluding cycle-specific top-coded ages yielded HRs of 1.63 without obesity and 1.68 with obesity, and recomputing eGFR after a common 80-year cap yielded 1.48 and 1.68. Nineteen participants changed phenotype after the cap. These checks reduce concern that age top-coding alone drove the main contrast. They do not, however, remove age noncomparability or the possibility of age-related filtration decline. An eGFR just below 60 in older adults may not reflect the same disease process that produces albuminuria. The two states therefore remain measured phenotypes, not clinical CKD. Residual age confounding, survivor selection, and creatinine physiology remain possible.

Adiposity, reverse causation, and the obesity paradox

Obesity alone was not associated with all-cause mortality after full adjustment, whereas its heart/cerebrovascular HR was modestly elevated. This finding does not imply that obesity is benign or protective. BMI cannot distinguish fat from lean mass or capture fat distribution, and illness-related weight loss can produce reverse causation [17, 18]. Neither continuous BMI nor waist circumference was associated with all-cause mortality; both were positively associated with heart/cerebrovascular mortality. Kidney-marker associations persisted among never smokers, after excluding underweight participants, after a 2-year landmark, and with standard BMI categories. These checks reduce, but cannot eliminate, concern about reverse causation.

The E-only all-cause estimate was 1.12 (95% CI 0.94–1.35; n = 609) with obesity and 1.28 (1.13–1.46; n = 903) without obesity. The E-only groups had similar mean ages, but the obese group was smaller. The intervals overlapped, and the obesity-by-reduced-eGFR interaction was null (P = 0.612). These features argue against interpreting the asymmetry as established effect modification. Precision, covariate composition, or selection may explain it. The U-only versus E-only ratio-of-HRs CI of 0.87–1.58 still includes potentially meaningful modification, so an obesity effect cannot be excluded.

Comparison with previous CKM research

Zhao et al. analyzed 42,697 NHANES participants across eight combinations of type 2 diabetes, established CVD, and composite CKD[6]. They reported 6,521 all-cause deaths, 2,046 CVD deaths, and an all-cause HR of 3.50 for participants with all three conditions. Their study addressed cumulative clinical multimorbidity and showed a graded burden as conditions accumulated. The samples overlap because both studies use NHANES 1999–2018. The size difference reflects our requirements for BMI, both kidney markers, mortality linkage, and baseline CVD classification. Our study excluded known CVD, used obesity as an early CKM axis, and separated the kidney markers that Zhao et al. combined. This allowed direct discordant-marker and joint-marker contrasts.

Other studies addressed different CKM questions. Li and Wei used formal AHA stages in NHANES and reported a mortality gradient across stages 0–4. However, that staging construct combines kidney and metabolic information and cannot estimate the discordant UACR/eGFR contrasts examined here [19]. Tan et al. studied the stress hyperglycemia ratio across CKM stages 0–3 and used CHARLS as a complementary replication cohort. Ji et al. described sex-specific CKM prevalence and mortality gradients over 30 years[20, 21]. All single-examination studies share the potential for within-person variability in kidney markers [22].

Recent studies have similarly distinguished broad CKM risk stratification from marker-specific assessment. Li et al. evaluated the triglyceride-glucose-body mass index across CKM stages 0–3, whereas Siverio-Morales et al. reported that UACR retained prognostic information among people with type 2 diabetes and normoalbuminuria [23, 24]. These studies support the value of marker-specific assessment, but neither examined mortality associations across joint UACR/eGFR phenotypes.

Separating UACR and eGFR provided greater resolution of kidney-marker heterogeneity but relied on single-visit measurements, produced smaller joint-phenotype groups, and lacked external validation. Disaggregation did not materially improve prediction over a composite kidney indicator (Supplementary Table S16; Supplementary Table S18; Supplementary Figure S2); its main contribution was explanatory. Individuals meeting the same composite kidney definition could have different adjusted prognoses. Treating this composite as homogeneous may understate average risk in U-only adults and overstate it in E-only adults, particularly given their different age distributions. The standardized risk was 1.22 percentage points higher for U-only than E-only without obesity and 1.61 points higher with obesity, with both bootstrap CIs excluding zero (Fig. 2; Supplementary Table S8). This distinction informs population-level interpretation rather than clinical CKD classification and is consistent with KDIGO recommendations to report UACR and eGFR separately.

Clinical and research implications

For epidemiologic CKM characterization, UACR and eGFR should remain separate descriptors. A composite single-visit kidney abnormality can conceal meaningful prognostic differences. Five-year standardized all-cause risks were 2.29% in the reference phenotype, 2.69% with E-only, 3.91% with U-only, and 4.52%–5.36% in selected phenotypes with both abnormalities. U-only minus E-only risk differences were 1.22 percentage points without obesity and 1.61 points with obesity, and both bootstrap CIs excluded zero. These are population-standardized contrasts, not patient-specific predictions, and the study did not test whether changing clinical reporting improves outcomes.

Future studies should replicate the complete phenotype in cohorts with repeated UACR and creatinine measurements, adjudicated cardiovascular outcomes, harmonized medication data, and enough events for external validation. Repeated measurements would distinguish persistent abnormalities from transient albuminuria or creatinine variation. Validation studies should define the prediction horizon in advance, harmonize outcome definitions, and assess calibration and net benefit alongside discrimination.

Strengths and limitations

Strengths include national probability sampling with design-weighted analysis, two decades of mortality linkage, race-free eGFR estimation, and direct kidney-marker contrasts from a single model. Additional strengths were the extensive design-aware sensitivity analyses and the uncertainty assessments through sequential adjustment, full-refit bootstrap intervals, multiple imputation, and temporal evaluation.

Several limitations remain. First, UACR and creatinine were each measured once. UACR varies substantially within individuals, generally more than creatinine-based eGFR, so the two threshold states may be misclassified differently [22], and the direction of that bias is uncertain. Transient albuminuria may carry prognostic information, repeat-test misclassification may vary with diabetes and treatment, and errors in UACR and eGFR may be correlated. A quantitative bias model would require age-, diabetes-, treatment-, and marker-specific transition parameters that were unavailable; we therefore avoided imposing an arbitrary reclassification rate. Continuous-marker splines, UACR severity categories, and threshold-limited conclusions assess robustness without claiming persistent CKD.

Second, laboratory methods changed across cycles. Public-release corrections and cycle sensitivity analyses lessen, but cannot eliminate, comparability concerns. Baseline CVD and several covariates were self-reported, and complete-case analysis and multiple imputation rely on different unverifiable assumptions. The 7,566 adults excluded before cohort formation differed from the primary cohort. Among those with an available marker, weighted albuminuria prevalence was 15.5% and reduced-eGFR prevalence was 18.7%, compared with 8.2% and 3.7% in the primary cohort. However, only 3,499 and 1,500 excluded adults had the corresponding measurements. Missing domains overlapped, and the joint phenotype was unobservable by definition. Therefore, the magnitude and direction of selection bias in the U-only versus E-only contrast cannot be determined (Supplementary Table S15). The target population is limited to NHANES adults with complete phenotype, mortality linkage, and baseline CVD information. Fully adjusted estimates are additionally conditional on measured covariates.

BMI is an imperfect measure of adiposity, pregnancy status was not uniformly observed, and residual confounding and reverse causation remain possible. An Asian-specific BMI threshold of 27.5 kg/m² could not be applied consistently because early cycles lacked harmonized ethnicity detail; BMI ≥ 30 kg/m² was therefore retained for temporal comparability. eGFR is indexed to body-surface area, and body composition may influence both creatinine-based eGFR and UACR through serum and urinary creatinine. Greater lean mass could shift the two classifications in opposite directions, and BMI cannot determine the direction or magnitude of this bias.

Third, several joint phenotypes and the cerebrovascular endpoint were sparse. Null interaction tests cannot exclude clinically important heterogeneity, and the RERI interval includes a meaningful positive departure from additivity. Available Firth Cox implementations do not preserve NHANES strata, PSU clustering, and design-based variance, so sparse cerebrovascular estimates were interpreted cautiously. Fourth, death-certificate categories are not adjudicated incident events, and cause-specific HRs differ from cumulative incidence. Fifth, the working-model proportional-hazards tests were descriptive rather than design-valid, although stratified attained-age models preserved the phenotype contrast.

Finally, the prediction analyses had several limitations. The fixed-horizon AUC was not a survey-valid Uno statistic, and Brier scores were horizon-specific rather than integrated. These intervals were conditional on the fitted model and did not account for parameter-estimation uncertainty. The heart/cerebrovascular temporal split included only 73 target deaths, and this within-NHANES evaluation is not external validation. Non-primary analyses were not multiplicity-adjusted, so nominal P values should not be interpreted as independent confirmatory evidence. Four participants with zero follow-up contributed to descriptive counts but not to person-time or risk estimates (Supplementary Table S15). Generalizability is limited to non-institutionalized US adults represented by NHANES who had complete phenotype, mortality linkage, and baseline CVD information.

Conclusions

Among adults without known baseline cardiovascular disease participating in NHANES, this survey-weighted study addresses an important gap in CKM research by disentangling albuminuria and reduced eGFR within eight mutually exclusive obesity-kidney phenotypes, rather than treating kidney involvement as a single composite abnormality. Albuminuria-only was associated with higher adjusted all-cause mortality than reduced-eGFR-only in both obesity strata, while coexisting albuminuria and reduced eGFR identified the groups with the highest mortality associations. The 5-year standardized all-cause risk was 1.22 percentage points higher for albuminuria-only than reduced-eGFR-only without obesity and 1.61 percentage points higher with obesity. These findings show that composite single-visit kidney indicators can conceal prognostically meaningful heterogeneity before overt cardiovascular disease and provide a more granular framework for epidemiologic CKM risk

characterization and future validation. UACR and eGFR should therefore be retained as complementary but separate descriptors in CKM research. Because both markers were measured at a single examination, these findings represent population-level associations and should not be used to assign a new CKM stage or a clinical CKD diagnosis.

Abbreviations

AHA, American Heart Association;

AP, attributable proportion due to interaction;

AUC, area under the curve;

BMI, body mass index;

BPX, NHANES blood pressure examination component;

CI, confidence interval;

CKD, chronic kidney disease;

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration;

CKM, cardiovascular-kidney-metabolic;

CVD, cardiovascular disease;

DBP, diastolic blood pressure;

eGFR, estimated glomerular filtration rate;

H/C, heart or cerebrovascular mortality;

HbA1c, glycated hemoglobin;

HDL, high-density lipoprotein cholesterol;

Declarations

Ethics StatementThe National Center for Health Statistics Research Ethics Review Board approved the NHANES protocols, and all participants provided informed consent. This analysis used de-identified public data and involved no new participant contact.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Availability of data and materials

NHANES public-use files and NCHS linked mortality files are publicly available [7,8].

Conflict of InterestThe authors declare that they have no competing interests

Funding

This study was supported by The Natural Science Foundation of Sichuan Province (NSFSC), China.(Grant No. 2026NSFSC0595)

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Qiang Lai and Xiaolong Li. The first draft of the manuscript was written by Qiang Lai, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

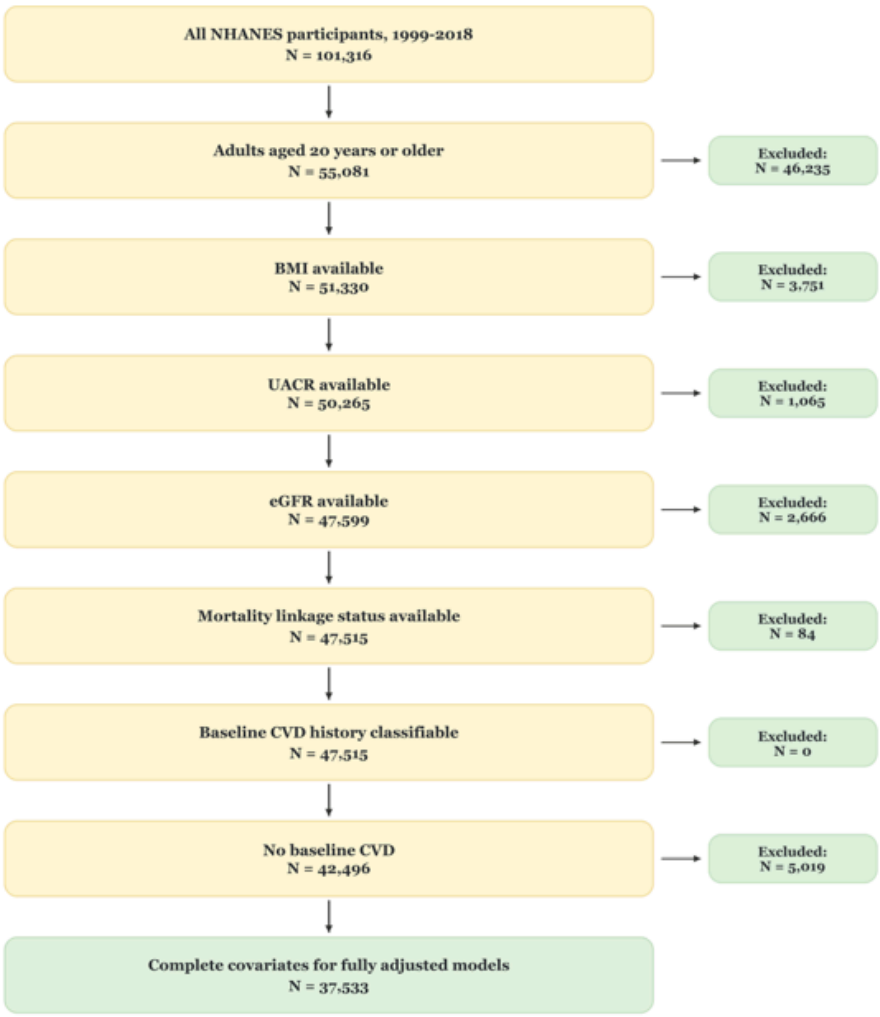


Figure 1

Selection of the primary analytic cohort.

The primary cohort excluded participants with known or unclassifiable baseline cardiovascular disease. Complete-case sample sizes were outcome and model specific.

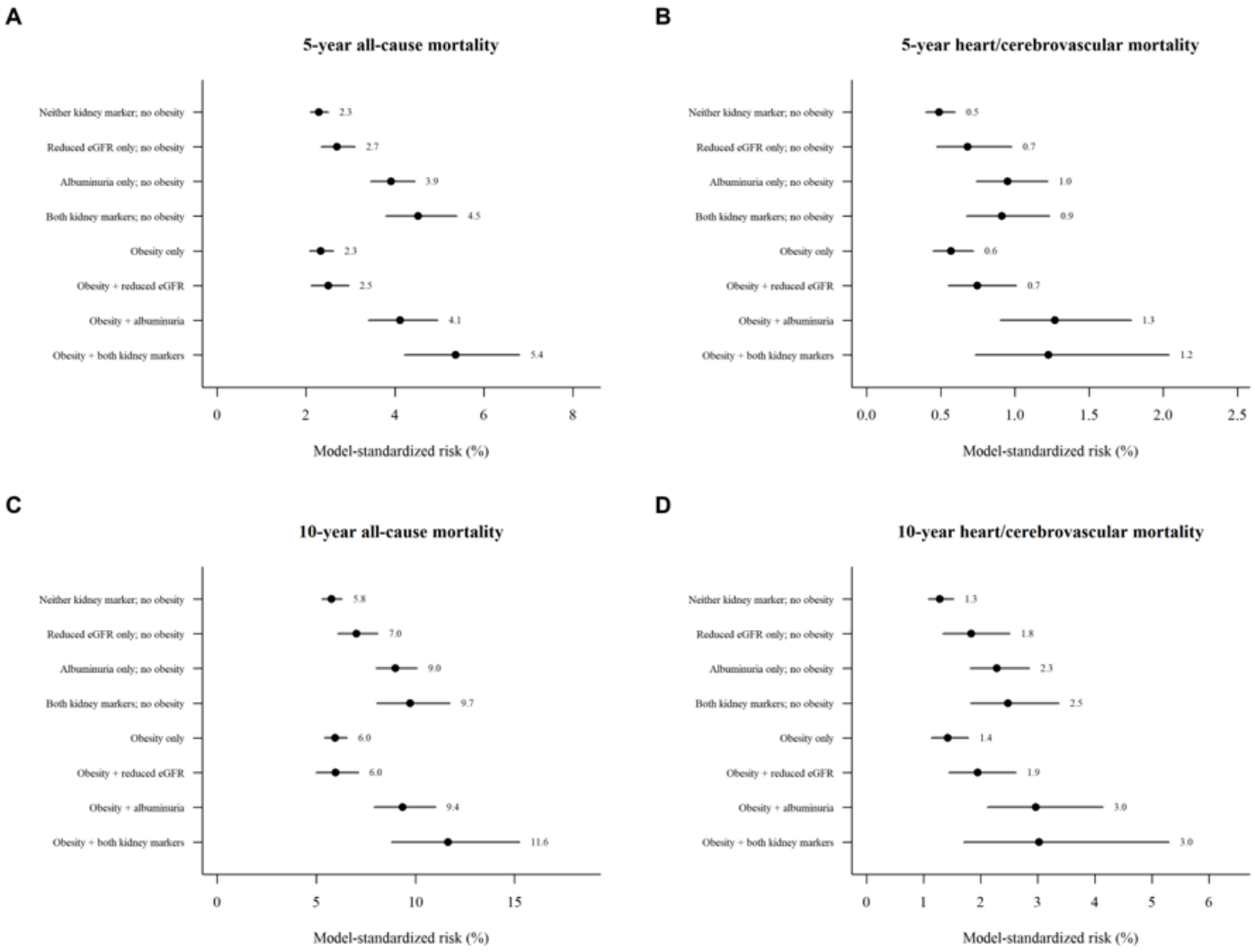


Figure 2

Model-standardized absolute mortality risks.

Risks were standardized to the covariate distribution of eligible cycles with complete follow-up. Error bars are 95% confidence intervals from full-refit Rao-Wu survey bootstrap: 500 replicates for all-cause mortality and 200 for heart or cerebrovascular cumulative incidence; all replicates were finite. Values are population averages, not patient-specific predictions.

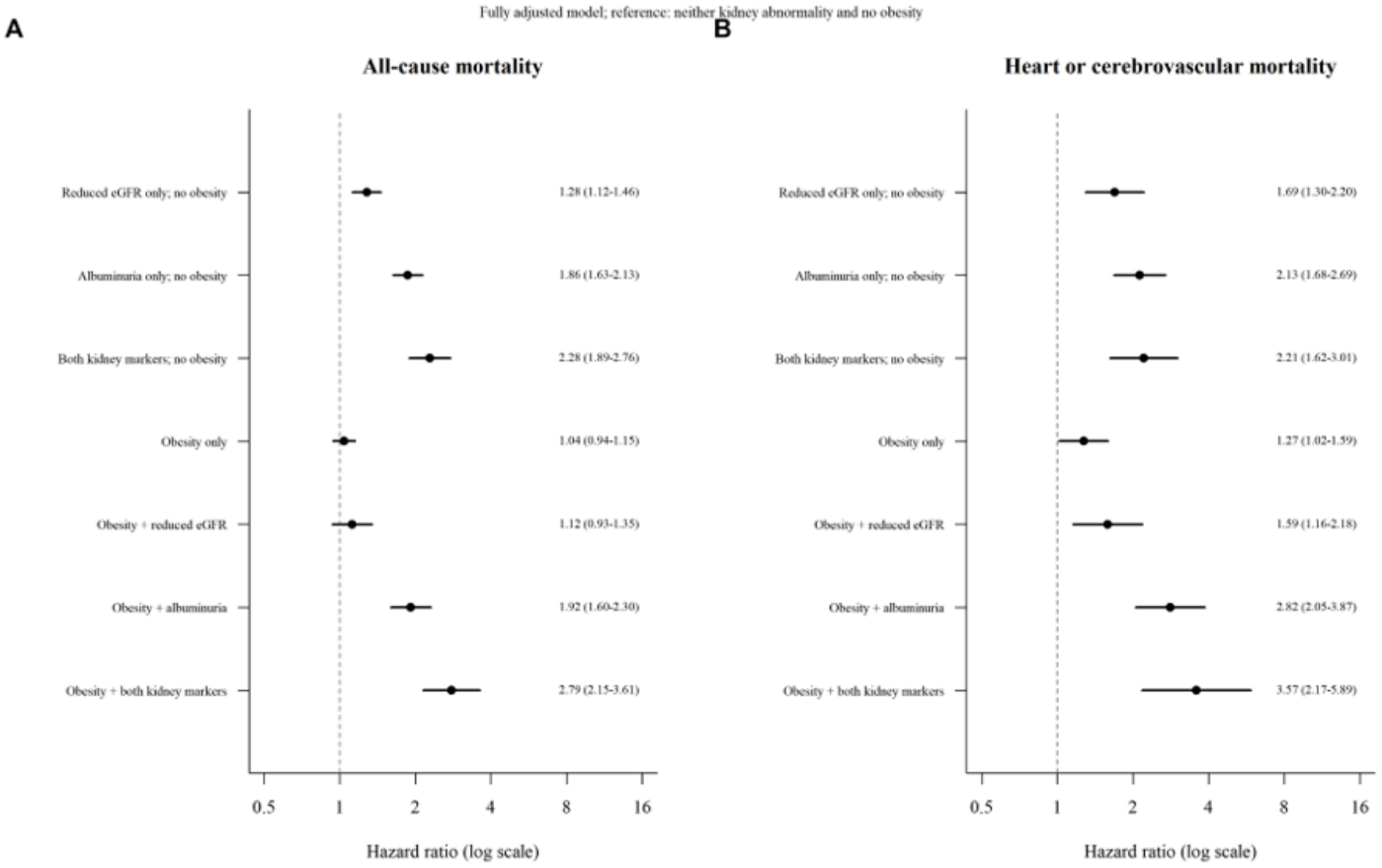


Figure 3

Fully adjusted mortality hazard ratios.

Hazard ratios compare each phenotype with A0_U0_E0. Error bars show 95% confidence intervals. Heart or cerebrovascular deaths were analyzed with cause-specific Cox models.

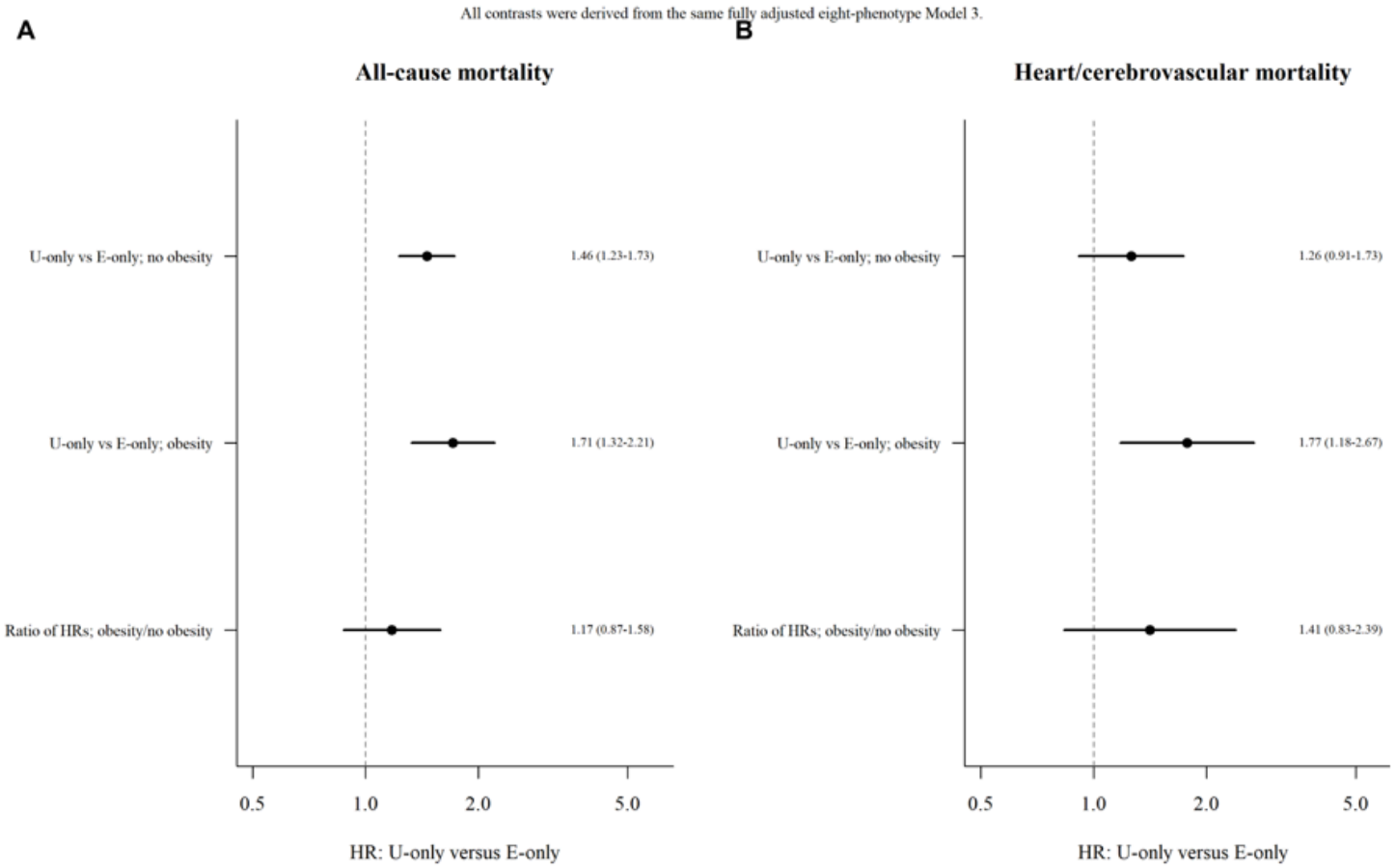


Figure 4

Unified direct discordant kidney-marker contrasts.

The two obesity-stratum U-only versus E-only HRs and their cross-stratum ratio derive from the same fully adjusted eight-phenotype model and covariance matrix.

Supplementary Files

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- 1.4supplementarymaterials.docx
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