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KIDNEY DYSFUNCTION, MODIFIABLE RISK-FACTOR BURDEN, AND LONG-TERM MORTALITY IN U.S. ADULTS: AN NHANES-NDI SURVIVAL ANALYSIS

By

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Abstract

Background: *Kidney dysfunction frequently coexists with modifiable cardiovascular risk factors, but the prognostic contribution of renal abnormalities remains clinically important even when common metabolic and behavioral exposures are considered. We evaluated a kidney dysfunction phenotype and cumulative modifiable risk-factor burden in relation to long-term all-cause and cardiovascular mortality in U.S. adults.* ***Methods:*** *Adults aged 20 years or older from NHANES 2007-2014 were linked to the National Death Index through December 31, 2019. Estimated glomerular filtration rate (eGFR) was calculated with the 2021 CKD-EPI creatinine equation. Kidney dysfunction was defined as eGFR <60 mL/min/1.73 m² and/or urinary albumin-to-creatinine ratio (UACR) >=30 mg/g. A four-component risk-factor burden score included hypertension, diabetes, obesity, and current smoking. Analyses incorporated NHANES examination weights, strata, and primary sampling units and used survey-weighted survival methods and Cox regression.* ***Results:*** *The primary cohort included 20,872 adults; 3,562 participants met the kidney dysfunction criteria, corresponding to a survey-weighted prevalence of 13.2%. During a median follow-up of 8.58 years, 2,450 all-cause deaths and 743 cardiovascular deaths occurred. Kidney dysfunction was associated with all-cause mortality after full adjustment (HR 1.96, 95% CI 1.75-2.19) and with cause-specific cardiovascular mortality (HR 2.21, 95% CI 1.80-2.71). Compared with eGFR >=90 mL/min/1.73 m², eGFR 45-59 was associated with HR 1.24 (95% CI 1.03-1.48), and eGFR <45 with HR 2.07 (95% CI 1.65-2.60). Mortality also increased across the exploratory risk-factor burden categories, reaching HR 2.40 (95% CI 2.03-2.83) for three or more factors versus none. The primary kidney association remained significant in age-stratified and attained-age sensitivity analyses.* ***Conclusions:*** *A single-visit kidney dysfunction phenotype based on reduced eGFR and/or albuminuria independently identified adults at substantially higher long-term all-cause and cardiovascular mortality risk. Risk increased with more severe eGFR reduction and greater modifiable risk-factor burden, and the association remained robust under alternative age specifications. These findings support integrating kidney markers with conventional risk profiling while recognizing that single-visit NHANES measurements cannot establish chronic CKD.*

Keywords: *kidney dysfunction; albuminuria; eGFR; mortality; cardiovascular mortality; NHANES*

1. Introduction

Chronic kidney disease (CKD) is defined by abnormalities of kidney structure or function that persist for at least three months and have implications for health [1]. Estimated glomerular filtration rate (eGFR) and albuminuria are central to contemporary CKD classification and prognosis. Large individual-participant meta-analyses have demonstrated that lower eGFR and higher urinary albumin excretion are independently associated with all-cause and cardiovascular mortality, with risk increasing as renal abnormalities become more severe [2,3]. These associations are clinically important because cardiovascular events and death often precede kidney failure.

The excess risk associated with kidney dysfunction is not explained solely by conventional cardiovascular risk factors. Progressive nephron loss can disturb sodium and volume regulation, activate neurohormonal pathways, promote endothelial dysfunction, and increase inflammation, oxidative stress, uremic toxin exposure, and mineral-metabolism abnormalities. These mechanisms contribute to arterial stiffness, vascular calcification, myocardial remodeling, and atherosclerotic injury [4,5]. Albuminuria adds complementary prognostic information because urinary albumin excretion reflects glomerular barrier injury and is also linked to systemic endothelial and vascular dysfunction [6].

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U.S. population data have long supported the prognostic value of kidney markers. In NHANES III, lower eGFR and higher albuminuria independently predicted cardiovascular and all-cause mortality [7]. More recent NHANES analyses have also shown strong gradients in mortality across global cardiovascular-health profiles that incorporate metabolic and behavioral factors [8]. However, contemporary analyses that combine a race-free eGFR equation, albuminuria-based kidney phenotyping, eGFR severity categories, a simple modifiable risk-factor burden, and explicit age-related sensitivity analyses can provide a clinically interpretable update using the 2019 public-use mortality linkage.

Accordingly, this study evaluated the association of a single-visit kidney dysfunction phenotype with long-term all-cause and cardiovascular mortality in U.S. adults. Secondary objectives were to characterize mortality across eGFR categories, examine whether increasing modifiable risk-factor burden was associated with progressively poorer survival, and assess the robustness of the kidney dysfunction association under alternative approaches to age adjustment.

2. Materials and Methods

2.1 Study design and population

This observational, population-based analysis used four consecutive National Health and Nutrition Examination Survey (NHANES) cycles: 2007-2008, 2009-2010, 2011-2012, and 2013-2014. Reporting was structured according to the STROBE recommendations for observational studies [9]. NHANES is conducted by the National Center for Health Statistics (NCHS) using a complex, multistage probability sampling design intended to represent the civilian, noninstitutionalized U.S. population [10,11]. Participants complete household interviews and standardized mobile examination center assessments that include anthropometry and collection of blood and urine specimens.

All eligible observations in the selected survey cycles were considered; no a priori sample-size calculation was performed. The pooled dataset contained 40,617 participants. Sequential eligibility criteria retained 23,482 adults aged >=20 years, 23,430 individuals eligible for mortality linkage with known vital status, 21,184 with serum creatinine measurements, and 20,874 with complete eGFR and UACR information. Two participants were excluded because follow-up time was invalid or non-positive, yielding 20,872 individuals in the primary survival cohort. Complete-case multivariable models included 20,147 participants.

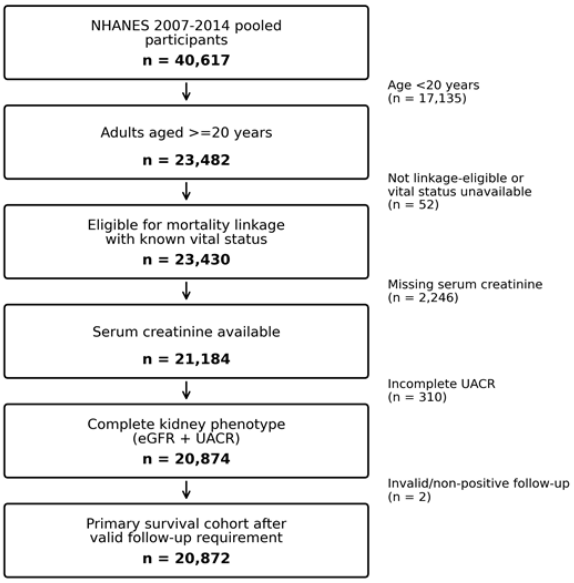


Figure 1. Participant flow from the pooled NHANES 2007-2014 sample to the primary survival cohort. eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

2.2 Mortality linkage and outcomes

Mortality status and follow-up time were obtained from the NCHS 2019 Public-Use Linked Mortality Files, which link eligible NHANES participants with the National Death Index and provide follow-up through December 31, 2019 [12]. Follow-up time was measured from the mobile examination center examination to death or administrative censoring.

The primary outcome was all-cause mortality. The secondary outcome was cardiovascular mortality, operationalized from the public-use underlying cause-of-death categories as diseases of the heart or cerebrovascular diseases. For cardiovascular analyses, deaths from other causes were treated as censoring events; the resulting Cox estimates therefore represent cause-specific hazards rather than competing-risk cumulative incidence. NCHS notes that selected follow-up-time or underlying cause-of-death values were replaced with synthetic values in the public-use files for disclosure protection, whereas vital status was not perturbed [12].

2.3 Kidney function and albuminuria

Serum creatinine was obtained from the standardized NHANES biochemistry profile. eGFR was calculated using the 2021 CKD-EPI creatinine equation, which does not include a race coefficient [13]. UACR was calculated from urinary albumin and urinary creatinine concentrations and expressed as mg/g (UACR = 100 × urinary albumin [µg/mL] / urinary creatinine [mg/dL]).

The primary kidney dysfunction phenotype was defined as eGFR <60 mL/min/1.73 m² and/or UACR >=30 mg/g, corresponding to clinically relevant GFR and albuminuria thresholds used in CKD classification [1]. Because NHANES provides renal measurements at a single examination, persistence for at least three months could not be confirmed. The exposure is therefore described as a kidney dysfunction

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phenotype compatible with CKD rather than confirmed CKD. For secondary severity analyses, eGFR was categorized as >=90, 60-89, 45-59, and <45 mL/min/1.73 m².

2.4 Modifiable risk factors

Hypertension was operationally defined as current antihypertensive medication use and/or a mean measured systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg. When more than one blood pressure reading was available, the first reading was excluded and the remaining readings were averaged; if only one reading was available, that value was retained. This definition was used as an epidemiologic study variable and should not be interpreted as a complete contemporary clinical diagnosis of hypertension.

Diabetes was classified by self-reported physician diagnosis, use of insulin or glucose-lowering medication, and/or glycated hemoglobin (HbA1c) >=6.5% [14]. Because a single survey HbA1c value cannot provide confirmatory clinical testing in an asymptomatic participant, this definition is also an epidemiologic classification. Obesity was defined as body mass index (BMI) >=30 kg/m². Current smoking required a lifetime history of at least 100 cigarettes and current smoking every day or some days.

An exploratory cumulative modifiable risk-factor burden score assigned one point each for hypertension, diabetes, obesity, and current smoking (range, 0-4). Participants were grouped as 0, 1, 2, or >=3 factors for survival analyses. Kidney dysfunction was not part of this score because it was the primary exposure. The score was designed as a simple count for this analysis and was not intended to reproduce a validated cardiovascular-health instrument such as Life's Essential 8.

2.5 Statistical analysis

All population-level analyses incorporated NHANES mobile examination center weights, masked variance strata, and primary sampling units in accordance with NCHS analytic recommendations [11]. Four 2-year cycles were pooled using an 8-year examination weight equal to one-fourth of the 2-year mobile examination center weight. Unweighted participant counts and survey-weighted estimates were reported where appropriate.

Continuous baseline variables were summarized using survey-weighted means and standard deviations, except UACR, which was summarized with a weighted median and interquartile range because of its skewed distribution. Categorical variables were reported as unweighted counts with survey-weighted percentages. Absolute standardized mean differences (SMDs) described baseline imbalance without relying on significance testing.

Survey-weighted Kaplan-Meier curves characterized all-cause survival, and survey-adjusted log-rank tests compared groups. For cardiovascular mortality, non-cardiovascular deaths were censored, providing a cause-specific survival representation. Associations with mortality were estimated using survey-weighted Cox proportional hazards models and are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). For all-cause mortality, Model 1 was unadjusted; Model 2 adjusted for age and sex; and Model 3 additionally adjusted for hypertension, diabetes, BMI, current smoking, and total cholesterol. The eGFR-category model used the same covariate set. The exploratory risk-factor-burden model adjusted for age, sex, and total cholesterol. The cardiovascular mortality model used the same covariates as Model 3.

No missing-data imputation was performed; multivariable models used complete cases. Secondary eGFR, risk-burden, and cardiovascular analyses were considered supportive and no multiplicity correction was applied. The proportional-hazards assumption was evaluated with Schoenfeld residuals from a parallel conventional Cox model used for diagnostics. Kidney dysfunction itself did not show evidence of non-proportionality, although the global test was significant and driven mainly by age. Two sensitivity analyses were therefore performed: a Cox model stratified by age category (20-39, 40-59, 60-79, and >=80 years) and a model using attained age as the survival time scale. Statistical significance was defined as two-sided $p<0.05$. Analyses were performed in R version 4.6.1 using the survey and survival packages.

2.6 Ethics

NHANES protocols for the included cycles were reviewed and approved by the NCHS Ethics Review Board, and participants provided informed consent [15]. The present study used publicly available, de-identified public-use data and involved no participant contact or intervention.

3. Results

3.1 Study population and baseline characteristics

The primary survival cohort comprised 20,872 adults: 17,310 without kidney dysfunction and 3,562 meeting the kidney dysfunction criteria. The survey-weighted prevalence of the kidney dysfunction phenotype was 13.2%. Median observed follow-up was 8.58 years (interquartile range, 6.50-10.67 years). Participants with kidney dysfunction were older and had higher weighted prevalences of hypertension and diabetes, lower mean eGFR, and markedly higher UACR (Table 1).

Table 1. Baseline characteristics according to kidney dysfunction phenotype

Characteristic	Overall	No kidney dysfunction	Kidney dysfunction	Absolute SMD
Unweighted sample size	20,872	17,310	3,562	-
Age, years	47.1 (16.7)	45.2 (15.7)	59.7 (17.7)	0.86
Female sex, n (weighted %)	10,690 (51.6%)	8,805 (50.7%)	1,885 (57.5%)	0.14

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Body mass index, kg/m²	28.8 (6.7)	28.6 (6.5)	29.9 (7.4)	0.18
Hypertension, n (weighted %)	7,432 (31.6%)	5,041 (26.8%)	2,391 (63.0%)	0.78
Diabetes, n (weighted %)	3,243 (11.3%)	1,937 (8.3%)	1,306 (31.0%)	0.59
Obesity, n (weighted %)	7,665 (35.6%)	6,131 (34.3%)	1,534 (43.7%)	0.19
Current smoking, n (weighted %)	4,396 (20.5%)	3,746 (20.8%)	650 (18.3%)	0.06
Total cholesterol, mg/dL	194.7 (41.4)	195.0 (40.7)	192.3 (45.8)	0.06
eGFR, mL/min/1.73 m²	96.3 (21.0)	99.5 (17.4)	75.4 (29.3)	1.00
UACR, mg/g	6.6 (4.3-11.7)	6.0 (4.1-9.3)	44.1 (20.5-97.7)	-

Values are unweighted n with survey-weighted percentages for categorical variables and survey-weighted mean (SD) for continuous variables, except UACR, shown as weighted median (IQR). SMD, standardized mean difference; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

3.2 Kidney dysfunction phenotype and all-cause mortality

During follow-up, 2,450 all-cause deaths occurred. The crude survey-weighted mortality rate was 6.58 per 1,000 person-years among participants without kidney dysfunction and 38.42 per 1,000 person-years among those with kidney dysfunction. Survey-weighted Kaplan-Meier curves separated early and remained distinct throughout follow-up (log-rank p<0.001; Figure 2).

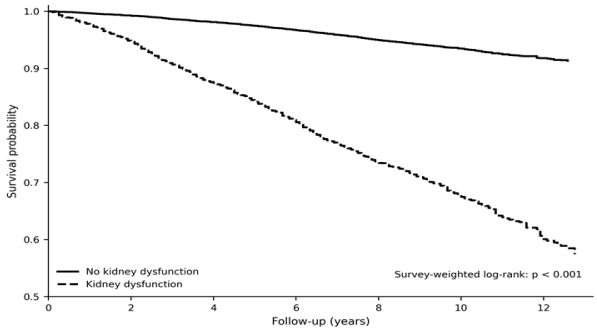


Figure 2. Survey-weighted Kaplan-Meier curves for all-cause survival according to kidney dysfunction phenotype. Numbers at risk are unweighted participant counts.

In the unadjusted Cox model, kidney dysfunction was associated with an approximately six-fold higher mortality hazard (HR 5.99, 95% CI 5.45-6.58). Adjustment for age and sex attenuated the estimate (HR 2.24, 95% CI 2.02-2.50). In the fully adjusted model, kidney dysfunction remained associated with a 96% higher hazard of all-cause mortality (HR 1.96, 95% CI 1.75-2.19; p<0.001) after adjustment for age, sex, hypertension, diabetes, BMI, current smoking, and total cholesterol (Table 2).

Table 2. Association of kidney dysfunction phenotype with all-cause mortality

Analysis	N	Deaths	HR	95% CI	p value
Model 1: unadjusted	20,872	2,450	5.99	5.45-6.58	<0.001
Model 2: age + sex	20,872	2,450	2.24	2.02-2.50	<0.001
Model 3: fully adjusted	20,147	2,344	1.96	1.75-2.19	<0.001
Sensitivity: age-stratified baseline hazards	20,147	2,344	2.04	1.82-2.29	<0.001
Sensitivity: attained age as time scale	20,147	2,344	1.77	1.58-1.98	<0.001

Model 3 adjusted for age, sex, hypertension, diabetes, body mass index, current smoking, and total cholesterol. HR, hazard ratio; CI, confidence interval.

Within the fully adjusted model, current smoking showed one of the largest associations among modifiable factors (HR 2.32, 95% CI 2.07-2.61), while diabetes (HR 1.31, 95% CI 1.16-1.47) and hypertension (HR 1.19, 95% CI 1.05-1.34) were also associated with mortality. Female sex was associated with lower mortality (HR 0.71, 95% CI 0.66-0.78), whereas BMI was not independently associated. For interpretability, Figure 3 displays age per 10 years, BMI per 5 kg/m², and total cholesterol per 10 mg/dL.

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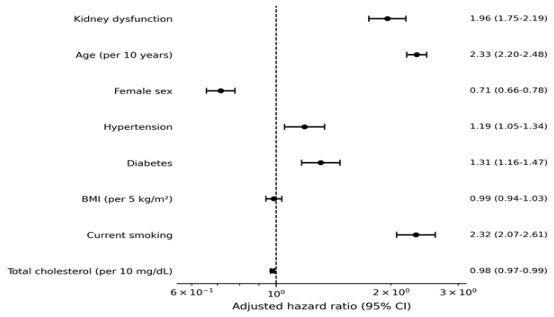


Figure 3. Forest plot of the fully adjusted survey-weighted Cox model for all-cause mortality. Continuous covariates are rescaled for visual interpretability as indicated. The vertical reference line denotes HR=1.0.

3.3 Mortality across eGFR categories

All-cause survival differed across eGFR categories (survey-weighted log-rank p<0.001; Figure 4). After multivariable adjustment and using eGFR >=90 mL/min/1.73 m² as the reference, eGFR 60-89 was not associated with higher mortality (HR 0.91, 95% CI 0.79-1.03; p=0.142). In contrast, eGFR 45-59 was associated with higher mortality (HR 1.24, 95% CI 1.03-1.48; p=0.022), and eGFR <45 with an approximately two-fold mortality hazard (HR 2.07, 95% CI 1.65-2.60; p<0.001). These secondary estimates were not additionally adjusted for UACR and therefore should not be interpreted as eGFR effects independent of albuminuria.

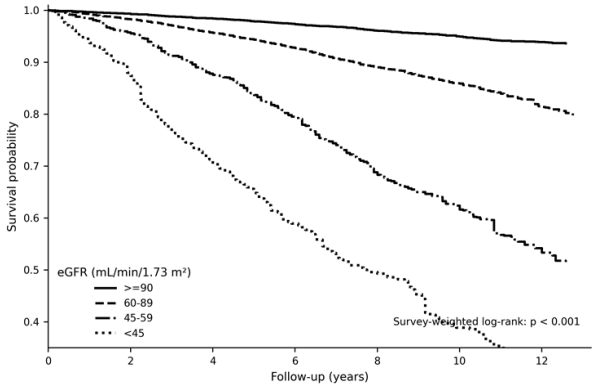


Figure 4. Survey-weighted Kaplan-Meier curves for all-cause survival according to eGFR category. Numbers at risk are unweighted participant counts.

3.4 Modifiable risk-factor burden and mortality

Survival declined progressively as the number of modifiable risk factors increased (survey-weighted log-rank p<0.001; Figure 5). Relative to participants with none of the four factors, the age-, sex-, and total-cholesterol-adjusted mortality hazard was HR 1.38 (95% CI 1.16-1.63) for one factor, HR 1.73 (95% CI 1.51-1.99) for two factors, and HR 2.40 (95% CI 2.03-2.83) for three or more factors. Because this secondary model did not additionally adjust for kidney dysfunction or other social and clinical confounders, the estimates are interpreted as graded prognostic associations rather than independent causal effects.

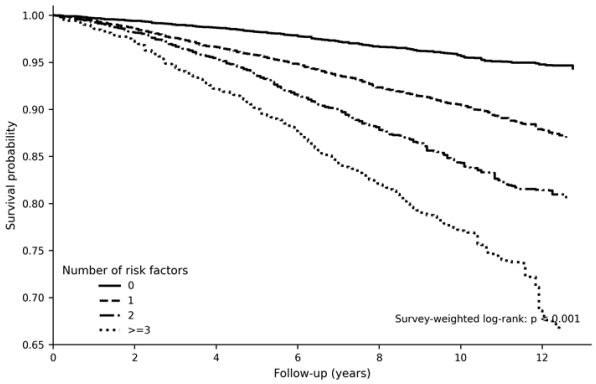


Figure 5. Survey-weighted Kaplan-Meier curves for all-cause survival according to cumulative modifiable risk-factor burden. The score comprised hypertension, diabetes, obesity, and current smoking. Numbers at risk are unweighted participant counts.

Adjusted estimates for the eGFR-category and risk-factor-burden analyses are summarized in Table 3.

Table 3. Secondary adjusted mortality associations across eGFR and risk-factor categories.

Exposure	N	Deaths	Adjusted HR	95% CI	*p value*
eGFR 60-89 vs >=90 mL/min/1.73 m²	20,147	2,344	0.91	0.79-1.03	0.142
eGFR 45-59 vs >=90 mL/min/1.73 m²	20,147	2,344	1.24	1.03-1.48	0.022
eGFR <45 vs >=90 mL/min/1.73 m²	20,147	2,344	2.07	1.65-2.60	<0.001
1 risk factor vs 0	20,147	2,344	1.38	1.16-1.63	<0.001
2 risk factors vs 0	20,147	2,344	1.73	1.51-1.99	<0.001
>=3 risk factors vs 0	20,147	2,344	2.40	2.03-2.83	<0.001

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The eGFR model adjusted for age, sex, hypertension, diabetes, body mass index, current smoking, and total cholesterol. The exploratory risk-factor-burden model adjusted for age, sex, and total cholesterol. HR, hazard ratio; CI, confidence interval.

3.5 Cardiovascular mortality

A total of 743 cardiovascular deaths occurred in the primary cohort. The crude survey-weighted cardiovascular mortality rate was 1.59 per 1,000 person-years among participants without kidney dysfunction and 13.41 per 1,000 person-years among those with kidney dysfunction. Cause-specific survival was lower in the kidney dysfunction group (survey-weighted log-rank p<0.001; Figure 6), with non-cardiovascular deaths treated as censoring events.

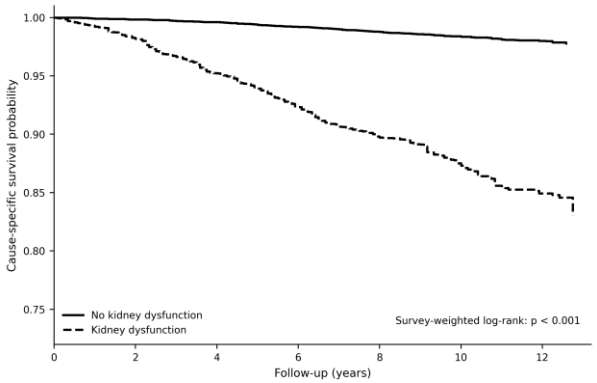


Figure 6. Survey-weighted cause-specific survival curves for cardiovascular mortality according to kidney dysfunction phenotype. Non-cardiovascular deaths were treated as censoring events; the curves therefore do not represent competing-risk cumulative incidence. Numbers at risk are unweighted participant counts.

In the fully adjusted cause-specific Cox model, which included 20,147 participants and 708 cardiovascular deaths after complete-case restriction, kidney dysfunction was associated with more than twice the hazard of cardiovascular death (HR 2.21, 95% CI 1.80-2.71; p<0.001). Hypertension (HR 1.39, 95% CI 1.08-1.80), diabetes (HR 1.36, 95% CI 1.11-1.67), and current smoking (HR 2.14, 95% CI 1.65-2.78) were also associated with cardiovascular mortality. BMI and total cholesterol were not statistically significant (Table 4).

Table 4. Fully adjusted survey-weighted cause-specific Cox model for cardiovascular mortality

Variable	Adjusted HR	95% CI	*p value*
Kidney dysfunction phenotype	2.21	1.80-2.71	<0.001
Age, per 10 years	2.91	2.59-3.27	<0.001
Female sex	0.64	0.52-0.78	<0.001
Hypertension	1.39	1.08-1.80	0.011
Diabetes	1.36	1.11-1.67	0.003
Body mass index, per 5 kg/m²	1.08	0.99-1.17	0.098
Current smoking	2.14	1.65-2.78	<0.001
Total cholesterol, per 10 mg/dL	0.98	0.96-1.01	0.156

N=20,147; cardiovascular deaths=708. Model adjusted simultaneously for all variables shown. Non-cardiovascular deaths were censored. HR, hazard ratio; CI, confidence interval.

3.6 Sensitivity analyses

The Schoenfeld-residual diagnostic showed no evidence of non-proportional hazards for the kidney dysfunction exposure (p=0.144), although the global test was significant (p=0.00049), driven primarily by age. The primary kidney association remained significant when the baseline hazard was stratified by age category (HR 2.04, 95% CI 1.82-2.29; p<0.001) and when attained age was used as the analysis time scale (HR 1.77, 95% CI 1.58-1.98; p<0.001). These estimates were directionally consistent with the primary model (Table 2).

4. Discussion

In this nationally representative analysis of U.S. adults, a single-visit kidney dysfunction phenotype defined by reduced eGFR and/or albuminuria was associated with substantially higher long-term all-cause and cardiovascular mortality. The primary all-cause association remained after adjustment for major demographic and modifiable risk factors and was robust

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to two alternative treatments of age. Lower eGFR categories below 60 mL/min/1.73 m² identified progressively higher-risk groups, while a simple count of modifiable cardiovascular risk factors showed a parallel graded association with mortality.

The renal findings are consistent with extensive prior evidence. The CKD Prognosis Consortium showed that eGFR and albuminuria provide complementary information for all-cause and cardiovascular mortality in general populations [2] and that these kidney measures improve cardiovascular risk prediction beyond traditional risk factors [3]. Earlier NHANES III work similarly found that reduced eGFR and albuminuria independently predicted cardiovascular and all-cause mortality in U.S. adults [7]. The present analysis does not overturn that established relationship; rather, it provides a contemporary replication using NHANES 2007-2014, the 2019 mortality linkage, and the 2021 race-free CKD-EPI creatinine equation, with explicit survey design and age-sensitivity analyses.

The eGFR analysis also followed the expected risk pattern. eGFR 60-89 mL/min/1.73 m² was not associated with excess mortality relative to >=90 after adjustment, whereas risk became significant at 45-59 and was greatest below 45. This pattern is compatible with pooled evidence showing relatively stable mortality risk at higher filtration levels and progressively increasing risk at lower eGFR [2]. Biologically, more substantial loss of filtration capacity is accompanied by increasing disturbance of sodium and volume handling, neurohormonal activation, uremic solute accumulation, anemia, inflammation, oxidative stress, and mineral-metabolism abnormalities; these processes promote endothelial dysfunction, arterial stiffness, cardiac remodeling, and vascular calcification [4,5]. Because UACR was not included as a covariate in the secondary eGFR-category model, the category-specific estimates should be viewed as prognostic rather than as effects isolated from albuminuria.

Albuminuria likely contributes materially to the prognostic signal of the combined kidney phenotype. UACR is not simply a surrogate for eGFR: increased urinary albumin excretion reflects glomerular barrier injury and is associated with broader endothelial and vascular dysfunction [6]. This complementarity is one reason contemporary CKD staging incorporates both filtration and albuminuria [1]. In the present cohort, the marked separation in UACR between groups supports the biological plausibility of the combined phenotype, while the single-visit design prevents clinical confirmation of persistent CKD.

The cardiovascular mortality findings are also biologically plausible. Kidney dysfunction promotes vascular vulnerability through pathways not fully captured by conventional atherosclerotic risk factors, including chronic inflammation, oxidative stress, uremic toxin exposure, disordered mineral metabolism, and vascular smooth-muscle-cell calcification [4,5]. The adjusted cause-specific cardiovascular HR remained above 2, supporting a strong prognostic relationship. Nevertheless, non-cardiovascular deaths were treated as censoring events, so these estimates address cause-specific hazard rather than absolute cardiovascular-death probability in a competing-risk framework.

The graded association observed for the four-component modifiable risk-factor burden is directionally consistent with contemporary NHANES analyses of broader cardiovascular-health constructs. For example, higher Life's Essential 8 scores have been associated with lower all-cause and cardiovascular mortality in U.S. adults [8]. Our simplified score was intentionally different: it counted hypertension, diabetes, obesity, and current smoking and did not include diet, physical activity, sleep, or a full lipid metric. It should therefore be interpreted as an exploratory, clinically intuitive burden indicator rather than a validated cardiovascular-health score. The model was adjusted for age, sex, and total cholesterol but not for kidney dysfunction, so it does not establish an effect independent of renal status.

Current smoking showed one of the largest associations among modifiable variables in both the all-cause and cardiovascular models. This agrees with cohort evidence demonstrating higher all-cause and cardiovascular mortality among smokers with kidney disease [16] and with NHANES-based evidence linking cigarette smoking to excess mortality in the broader U.S. population [17]. Mechanistically, smoking promotes endothelial injury, oxidative stress, inflammation, sympathetic activation, thrombosis, and atherosclerosis; these pathways may compound the vascular and metabolic abnormalities that accompany kidney dysfunction.

The age sensitivity analyses strengthen confidence in the primary kidney association. Although age contributed to a significant global proportional-hazards diagnostic, the kidney dysfunction exposure itself did not show evidence of non-proportionality. Stratifying the baseline hazard by age category and using attained age as the time scale both preserved a substantial association, indicating that the main finding was not solely an artifact of a single age specification.

4.1 Strengths and limitations

Important strengths include the large nationally representative sample, standardized NHANES examination and laboratory procedures, explicit incorporation of survey weights and design variables, combined use of eGFR and albuminuria, evaluation of both all-cause and cardiovascular mortality, transparent reporting of complete-case sample sizes, and sensitivity analyses addressing the principal proportional-hazards concern. The study also used the 2021 CKD-EPI creatinine equation without a race coefficient, aligning renal estimation with contemporary practice [13].

Several limitations should temper interpretation. First, eGFR and UACR were measured once, whereas CKD requires persistence for at least three months [1]; the exposure therefore represents a CKD-compatible kidney dysfunction phenotype, not confirmed CKD. Second, this observational study cannot establish causality, and residual confounding remains possible. The prespecified primary model did not include self-reported race/ethnicity, socioeconomic indicators, or prevalent cardiovascular disease, all of which may influence both kidney status and mortality. Third,

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hypertension and diabetes were operational epidemiologic classifications based partly on single-visit measurements, and the selected >=140/90 mmHg blood-pressure threshold is more conservative than some contemporary definitions. Fourth, the exploratory risk-factor burden was a simple count rather than a validated cardiovascular-health score, and its model did not adjust for kidney dysfunction. Fifth, the eGFR-category model did not additionally adjust for UACR. Sixth, baseline exposures may have changed over follow-up, and no time-updated covariates were available. Seventh, complete-case analysis can introduce selection bias when missingness is informative. Eighth, public-use mortality files include synthetic follow-up-time or cause-of-death values for selected records [12]. Finally, the cardiovascular analyses used cause-specific censoring of non-cardiovascular deaths; a competing-risk cumulative-incidence analysis could yield different absolute-risk estimates. These considerations support a prognostic, rather than causal, interpretation of the findings.

5. Conclusion

In this nationally representative sample of U.S. adults, a single-visit kidney dysfunction phenotype defined by reduced eGFR and/or albuminuria identified a population with markedly poorer long-term survival. After adjustment for demographic and cardiometabolic covariates, kidney dysfunction remained associated with a 96% higher hazard of all-cause mortality and more than a twofold higher hazard of cardiovascular mortality. The persistence of this association in both age-stratified and attained-age sensitivity analyses indicates that the excess risk was not explained solely by the older age distribution of participants with renal abnormalities.

The risk pattern was also graded rather than simply binary: mortality increased once eGFR declined below 60 mL/min/1.73 m², was greatest at eGFR <45 mL/min/1.73 m², and rose progressively as modifiable risk factors accumulated. Taken together, these findings indicate that eGFR, albuminuria, and modifiable risk-factor burden capture complementary dimensions of long-term prognosis and may improve identification of adults at elevated renal and cardiovascular risk. Because kidney status was assessed at a single visit, the study cannot confirm chronic kidney disease or establish causality; nevertheless, the consistency of the associations across all-cause and cardiovascular mortality and across sensitivity analyses supports the prognostic relevance of integrating kidney markers with conventional risk assessment. Future prospective studies with repeated renal measurements should determine whether integrated risk stratification improves early identification of high-risk individuals and helps guide interventions capable of reducing cardiovascular and premature mortality.

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