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# Association of chronic kidney disease and cardiovascular disease risk with all-cause mortality: an interaction, joint and mediation analysis in Chinese adults

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## Abstract

**Background** Chronic kidney disease (CKD) is a global public health problem. This study aimed to evaluate the complex relationship of CKD and cardiovascular disease (CVD) risk with mortality in different age groups and the mediation effect of CVD risk among Chinese adults.

**Methods** A total of 7533 participants from the 2009 wave of China Health and Nutrition Survey (CHNS) cohort were included in this study and followed up to 2015. CKD was defined as the estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m$^2$. Framingham risk score (FRS) was used to assess CVD risk. The interaction, joint association of CVD risk and CKD on mortality, and subsequent mediation effect were evaluated using multivariable Cox regression.

**Results** CHNS cohort recorded 266 deaths over a mean follow-up time of 5.04 years. The all-mortality rates among adults with CKD and high CVD risk were significantly higher than healthy controls (22.48 and 21.30 per 1000 person-years). After adjusting for covariates of age, gender, BMI, hypertension, diabetes, hyperuricemia, smoking status, and alcohol consumption, the adjusted hazard ratios (aHR) of CKD and high CVD risk were 1.70 (95% CI 1.27–2.28) and 1.62 (95%CI 1.26–2.09), respectively. Joint effect analysis revealed that mortality hazard was highest in CKD patients with high CVD risk (aHR = 3.15, 95% CI 1.92–5.16). Mediation analysis showed that significant partial mediation by SBP and fasting glucose, accounting for 19.2% ($p < 0.001$) and 3.52% ($p = 0.012$) of the total effect of CKD on mortality.

**Conclusions** Comprehensive strategies including lifestyle modifications, diet restrictions, and cardio-nephrology multidisciplinary treatment for mitigating CVD risk in CKD patients should focus on middle-aged people and early disease detection.

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**Keywords** Chronic kidney disease, Cardiovascular disease, Mortality, Mediation analysis, China health and nutrition survey

## Introduction

Chronic kidney disease (CKD) is a global public health problem, affecting over 10% of adults with ominous outcomes [1]. About 1.2 million people died from CKD in 2017 globally, according to the Global Burden of Disease (GBD). Moreover, the global all-age mortality rate of CKD has increased by 41.5% in the last three decades [2]. In 2017, the estimated loss of life (YLLs) due to CKD was 28.5 million (ranked 16th), an increase of 21.0% from 2007. In 2040, it is projected to reach 52.6 million (ranked 5th ), an increase of 100.3% from 2016 [3, 4]. Cardiovascular disease (CVD) is common among the general population and a critical prognostic complication in CKD patients. The Mendelian randomization analyses found that mild-to-moderate kidney dysfunction is causally related to the risk of coronary heart disease [5]. United States Renal Data System (USRDS) reported that the presence of CVD was much greater among CKD patients (64.7%) [6]. Shared risk factors, including diabetes, hypertension, dyslipidemia, and smoking, result in both cardiac and renal dysfunction [7]. Although CKD patients have a high risk of developing CVD, CKD has not been included in the CVD risk prediction models [8, 9].

CKD patients with CVD have an increased financial burden with a high risk of hospitalization and death [10]. A US study estimated that the annual average medical cost of patients with CKD and CVD was more than thrice that of patients with CKD only [11]. Systematic analysis showed that the risk of mortality was significantly higher in CKD patients compared with those without CKD [12], and even kept increasing in CKD patients who constituted coronary artery calcification [13]. GBD estimated that the number of CVD deaths caused by kidney dysfunction doubled from 1990 to 2019, reaching 1.73 million [14]. However, limited research has been performed on the interaction and joint associations of CKD and CVD with mortality. It was still unclear what proportion of CKD deaths was directly due to CKD itself and what proportion was indirectly caused by the increased risk of CVD. Moreover, CKD and CVD were regarded as aging-related diseases and their interaction might be mediated by age. To this end, we used the perspective cohort of the China Health and Nutrition Survey (CHNS) to evaluate the interaction and joint associations relationship of CKD and CVD risk with mortality among different age groups and analyze the mediation effect of CVD risk.

## Materials and methods

### Study population

The CHNS is an ongoing open cohort, designed to assess the health and nutrition status of the Chinese population. It covers fifteen provinces with wide geographical, economic, and cultural diversity. In CHNS, the participants surveyed in each province are sampled through a multistage, random cluster process. The first wave of the CHNS was begun in 1989, and nine additional panels were collected in 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011 and 2015. Written informed consent was obtained from all participants, and this cohort was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. Longitudinal data, including demographics, dietary intake, anthropometry, blood pressure, health history, and health-related behaviors, were collected in each wave. Fasting blood was collected for the first time in 2009, covering twenty-six measures. Survival status and time of death was obtained for the 2009, 2011 and 2015 cohorts. However, the cause of death was not collected. The CHNS data are updated to 2015, and publicly available on the website (https://www.cpc.unc.edu/projects/china/news). In the present study, a total of 9516 participants were selected from 2009 wave of CHNS as baseline subjects and followed up through the 2011 and 2015 wave. After excluding those who were under 18 years old ($n=787$) and pregnant ($n=62$), had implausible data ($n=12$), failed blood testing ($n=53$), and lost follow-up ($n=1330$), a total of 7533 participants constituted the study cohort (Supplementary Fig. S1).

### Definition of chronic kidney disease (CKD) and cardiovascular risk

Fasting blood samples were collected and processed by certified laboratory professionals in the CHNS cohort. Then they were immediately frozen for storage (-80 ℃) and transferred to the national central lab in Beijing under strict control [15]. Serum creatinine was measured by using the picric acid method. CKD was defined as eGFR < 60 mL/min/1.73 $m^2$ according to Kidney Disease: Improving Global Outcomes (KDIGO) guideline [16], Framingham risk score (FRS) was used to evaluate CVD risks: low (FRS < 10%), medium (FRS 10–20%), or high (FRS > 20%) [17]. FRS was designed to quantify the 10-year absolute CVD risk, including age, gender, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), smoking status, and diabetes [18].

### Measurement of covariates

A standardized structured questionnaire was used to collect data on demographics (age, gender, education, residence, and ethnicity), comorbidity (hypertension, diabetes, and myocardial infarction), and health-related behaviors (smoking, alcohol drinking, energy and protein intake, physical exercise). Residence was categorized as either urban or rural. Ethnicity was categorized as Han and ethnic minority. Education level was categorized as never (0 years of education), primary school (1–6 years of education), junior high school (7 ~ 9 years of education), senior high school (10 ~ 12 years of education) and post-secondary education (> 12 years of education). Smoking and drinking status were categorized as never, former and current. Physical exercise was categorized based on tertile distribution of metabolic equivalents: low (< 57.17 MET/week), medium (57.17–148.06 MET/week) and high (≥ 148.06 MET/per week). Anthropometric parameters, including weight, height and waist-hip ratio were evaluated using standard protocols. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). The waist-hip ratio (WHR) was calculated as waist circumference (cm) divided by the hip circumference (cm). Blood pressure (BP) was measured thrice using a mercury sphygmomanometer at a resting state. Moreover, the blood biomarkers included triglyceride (TG), TC, HDL-C, LDL-C, fasting glucose, hemoglobin A1c, hemoglobin, albumin, and uric acid.

### Statistical analysis

Less than 10% of the total data were missing, except for systolic and diastolic BP (13.6% in Supplementary Fig. S2). The pattern of missing data met the criteria for missing at random (MAR). Continuous variables with normal distributions were expressed as mean and standard deviation (SD), while continuous variables with skewed distributions were expressed as median and quartiles. Also, categorical variables were expressed as frequency and percentage. Student's t test, Wilcoxon test, Pearson chi-square test, and Cochran-Mantel-Haenszel (CMH) test were used to compare demographics, comorbidity, health-related behaviors, and biomarkers among CKD and non-CKD adults where appropriate. Correlation analysis between CKD and CVD risk was performed among different age groups (18–45, 45–64, and 65- years old). Person-year was calculated from baseline until the date of death or end of follow-up. Survival analysis of mortality associated with CKD and CVD risk was conducted using the Kaplan–Meier (KM) method with Log-rank test. Hazard ratio (HR) and 95% confidence intervals (CI) in different age groups were estimated using the Cox proportional hazard regression models. Crude model included CKD or CVD risk only. Adjusted model further incorporated covariates of age, gender, BMI, hypertension, diabetes, hyperuricemia, smoking status, and alcohol consumption. Moreover, we additionally included a product term of age, (low-medium, high) CVD risk, and CKD status to quantify the multiplicative interactions. Subgroup analyses were performed of stratifying age and CKD (or CVD risk) depending on which association was examined. To assess the joint effect, we further classified participants into four groups (non-CKD + low-medium CVD risk, non-CKD + high CVD risk, CKD + low-medium CVD risk, and CKD + high CVD risk). The mortality rate and HR were calculated in each classification group. Mediation analysis was used to investigate the mediating effects of modifiable CVD risks (TC, HDL-C, SBP and fasting glucose) on CKD in terms of all-cause mortality. The hypothesis of mediation analysis is to divide the total effect into direct and indirect effects, and the indirect effect on the outcome is mediated via a mediator. It produces an average causal mediation effect (ACME), average direct effect (ADE), and total effect. The mediation effect was defined as the proportion of ADE in the total effect. Moreover, sensitivity analyses were performed to test the robustness of findings. We compared the basic characteristic in follow-up samples and lost to follow-up samples. Multiple imputations (random forest method) were used to impute the missing values. Then we assessed the consistency of the results in the Cox models and joint models among the original dataset and imputation dataset. All statistical tests were two-tailed, and differences were considered statistically significant at $p < 0.05$. All statistical analyses were conducted in R software (version 4.2.1, R core team) by using the "ggplot2", "ggpubr", "magrittr" and "cowplot" packages for graph production, "epiR" packages for interaction analysis, "gmodels" packages for cross-tabulation tests for factor independence, "survival" and "survminer" packages for survival analysis, "mediation" packages for causal mediation analysis, "mice" and "VIM" for multivariate imputation.

## Results

### Baseline characteristics of the study population

The baseline characteristics of the study population were shown in Table 1. Among 7533 adults from the CHNS cohort (mean age 52.51 ± 14.57, 47.2% men), 947 (12.6%) had CKD with eGFR < 60 mL/min/1.73 $m^2$. CKD was more common in the elderly (68.71 ± 10.90), women (60.7%), urban residents (37.3%), the less educated (67.8% for < 6 years of education), former smokers and drinkers (18.7% and 29.0%), patients with hypertension (53.6%) and diabetes (11.2%), or patients who have less physical exercise (55.6%). CVD risk factors, including higher levels of BP, TC, TG, LDL-C, fasting glucose, hemoglobin A1c, and uric acid, were more prevalent among CKD patients. As a result, CKD patients shared a higher FRS value (13.7

**Table 1** Baseline characteristics of participants with and without CKD in CHNS ($n=7533$)

| Variables | Total | CKD | Non-CKD | Statistics | *p*-value[#] |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 52.51 ± 14.57 | 68.71 ± 10.90 | 50.18 ± 13.51 | 40.375 | < 0.001 |
| Female (%) | 3977(52.8) | 575(60.7) | 3402(51.7) | 27.288 | < 0.001 |
| Urban (%) | 2379(31.6) | 353(37.3) | 2026(30.8) | 16.256 | < 0.001 |
| Ethnicity (Han)* | 6674(88.8) | 812(86.0) | 5862(89.3) | 8.710 | 0.003 |
| Education (years of education)* | | | | 357.181 | < 0.001 |
| Never (0 years) | 988(13.1) | 268(28.4) | 720(11.0) | | |
| Primary school (1 ~ 6 years) | 2230(29.7) | 372(39.4) | 1858(28.3) | | |
| Junior high school (7 ~ 9 years) | 2559(34.0) | 155(16.4) | 2404(36.6) | | |
| Senior high school (10 ~ 12 years) | 844(11.2) | 53(5.6) | 791(12.0) | | |
| Post-secondary education (> 12 years) | 898(11.9) | 96(10.2) | 802(12.2) | | |
| ***Comorbidity*** | | | | | |
| Hypertension* | 2174(28.9) | 508(53.6) | 1666(25.3) | 323.571 | < 0.001 |
| Diabetes* | 388(5.2) | 106(11.2) | 282(4.3) | 80.551 | < 0.001 |
| Myocardial infarction* | 127(1.7) | 43(4.6) | 84(1.3) | 53.072 | < 0.001 |
| ***Health-related behaviors*** | | | | | |
| Smoking status | | | | 39.535 | < 0.001 |
| Never smoker | 4399(58.4) | 573(60.5) | 3826(58.1) | | |
| Former smoker | 1035(13.7) | 177(18.7) | 858(13.0) | | |
| Current smoker | 2099(27.9) | 197(20.8) | 1902(28.9) | | |
| Alcohol drinking | | | | 96.024 | < 0.001 |
| Never drinker | 3558(47.2) | 480(50.7) | 3078(46.7) | | |
| Former drinker | 1517(20.1) | 275(29.0) | 1242(18.9) | | |
| Current drinker | 2458(32.6) | 192(20.3) | 2266(34.4) | | |
| Energy intake (kcal/day)* | 2144 ± 675 | 1927 ± 610 | 2175 ± 679 | -10.560 | < 0.001 |
| Protein intake (g/day)* | 65.86 ± 22.99 | 58.61 ± 20.48 | 66.91 ± 23.15 | -10.394 | < 0.001 |
| Physical exercise level (%)* | | | | 254.066 | < 0.001 |
| Low | 2311(33.3) | 449(55.6) | 1862(30.4) | | |
| Medium | 2313(33.4) | 257(31.8) | 2056(33.6) | | |
| High | 2311(33.3) | 102(12.6) | 2209(36.1) | | |
| ***Anthropometry and Blood biomarkers*** | | | | | |
| WHR* | 0.88 ± 0.08 | 0.89 ± 0.08 | 0.87 ± 0.08 | 5.703 | < 0.001 |
| BMI (kg/m$^2$)* | 23.40 ± 3.48 | 23.39 ± 3.81 | 23.40 ± 3.43 | -0.111 | 0.911 |
| Systolic BP (mm Hg)* | 125.49 ± 19.12 | 136.65 ± 21.66 | 123.75 ± 18.09 | 19.113 | < 0.00 |
| Diastolic BP (mm Hg)* | 80.59 ± 11.19 | 82.38 ± 11.83 | 80.31 ± 11.06 | 5.098 | < 0.001 |
| Triglyceride (mmol/L) | 1.69 ± 1.50 | 1.74 ± 1.25 | 1.68 ± 1.53 | 1.210 | 0.226 |
| Total cholesterol (mmol/L) | 4.88 ± 1.00 | 5.23 ± 1.07 | 4.82 ± 0.98 | 11.660 | < 0.001 |
| HDL-C (mmol/L) | 1.44 ± 0.51 | 1.45 ± 0.39 | 1.43 ± 0.52 | 1.140 | 0.255 |
| LDL-C (mmol/L)* | 2.99 ± 0.98 | 3.28 ± 1.02 | 2.95 ± 0.97 | 9.882 | < 0.001 |
| Blood glucose (mmol/L) | 5.42 ± 1.49 | 5.80 ± 1.81 | 5.36 ± 1.43 | 8.465 | < 0.001 |
| HbA1c (%)* | 5.63 ± 0.93 | 5.79 ± 1.00 | 5.61 ± 0.92 | 5.488 | < 0.001 |
| Hemoglobin (g/L)* | 141.28 ± 20.57 | 135.24 ± 20.96 | 142.15 ± 20.37 | -9.711 | < 0.001 |
| Albumin (g/L) | 47.38 ± 3.41 | 46.83 ± 4.04 | 47.46 ± 3.30 | -5.349 | < 0.001 |
| Uric acid (umol/L) | 308.76 ± 105.76 | 357.90 ± 97.74 | 301.70 ± 105.00 | 15.531 | < 0.001 |
| Framingham score* | 6.7[3.3,13.7] | 13.7[8.6,25.3] | 6.3[2.8,13.2] | —— | < 0.001 |
| CVD risk grade* | | | | 481.638 | < 0.001 |
| Low (0 ~ 10%) | 4674(62.4) | 298(32.2) | 4376(66.6) | | |

**Table 1** (continued)

| Variables | Total | CKD | Non-CKD | Statistics | *p*-value[#] |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Medium (10 ~ 20%) | 1621(21.6) | 287(31.0) | 1334(20.3) | | |
| High (20 ~ 30%) | 1198(15.9) | 340(36.8) | 858(13.1) | | |

Abbreviation: BMI body mass index, BP blood pressure, CHNS China Health and Nutrition Survey, CKD chronic kidney disease, CVD cardiovascular disease, eGFR estimated glomerular filtration rate, HbA1c Glycosylated Hemoglobin, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, WHR waist to hip circumference ratio. Data are presented as No. (%), mean ± SD or median [IQR]

[#] P value was calculated by using Student's t test and Wilcoxon test for continuous variables and Pearson chi-square test and Cochran-Mantel-Haenszel test for categorical variables

* 14 participants were not available for education level; 21 participants were not available for ethnicity; 4 participants were not available for hypertension; 15 participants were not available for diabetes; 37 participants were not available for myocardial infarction; 100 participants were not available for energy and protein intake; 598 participants were not available for physical exercise level; 212 participants were not available for WHR; 137 participants were not available for BMI; 1027 participants were not available for SBP/DBP; 2 participants were not available for LDL-C; 53 participants were not available for HbA1c; 32 participants were not available for Hemoglobin; 40 participants were not available for Framingham score and CV D risk

vs. 6.3, $p < 0.001$) and a greater proportion of high CVD risk (36.8% vs. 13.1%, $p < 0.001$) than those without CKD. In the subgroup analysis by age, the significant association between CVD risk and CKD was only found among patients aged 45–64 years ($p < 0.001$), while no significant association was found in the 18–44 and 65- age groups ($p = 0.276$ and 0.296, Supplementary Fig. S3).

### Association between CKD and CVD risks with all-cause mortality

A total of 266 deaths were recorded during a mean follow-up of 5.04 years (all-cause mortality: 7.01 per 1000 person-years). The hazards of death were significantly higher among CKD patients (22.48 vs. 4.93 per 1000 person-years, $p < 0.001$) and those with high CVD risk (21.30 vs. 8.53 vs. 2.65 per 1000 person-years, $p < 0.001$). After adjusting the covariates of demographics, comorbidities, smoking and drinking status, the HRs for all-cause mortality were 1.70 (95% CI 1.27 to 2.28) in CKD patients, and 1.62 (95% CI 1.26 to 2.09) for each additional level of CVD risk. Mortality was associated with CKD in 45–64 age group (adjusted hazard ratios (aHR) = 3.13, 95% CI: 1.73–5.69, $p < 0.001$) and 65- years age group (aHR = 1.41, 95% CI: 1.01–1.96, $p < 0.001$). No statistical analyses were performed due to the very small number of mortality events in the 18 ~ 44 age group (Fig. 1).

### Interaction and joint analysis

Initial univariate analysis demonstrated a negative interaction between CKD and CVD risk on all-cause mortality ($p < 0.001$), which was attenuated to non-significance following multivariable adjustment ($p = 0.734$). The subgroup analyses revealed that CKD was significantly associated with death in adults with low + medium CVD risk (aHR = 1.87, 95% CI 1.20–2.91). Among those with high CVD risk, the adjusted HR was 1.52 (95% CI 1.03–2.24). Notably, the significant effect of CVD risk on death was only observed in the CKD group (aHR = 2.91, 95% CI 1.56–5.46) rather than the non-CKD group (aHR = 1.47, 95% CI 0.93–2.31 in Fig. 2). Age-stratified analysis identified the 45–64 year group as having the strongest mortality associations across risk categories. The joint effect of CKD and CVD risks on death across ages was shown in Fig. 3. In total, the mortality rate in non-CKD adults with low-medium CVD risk was 1.98 per 1000 person-years, which increased to 27.01 per 1000 person-years in CKD patients with high CVD risk (aHR = 3.15, 95% CI 1.92–5.16). In the subgroup analysis by age, this increasing trend was more obvious in the 45–64 age group (aHR = 2.29→7.51).

### Mediation analysis

We further applied mediation analysis to investigate the mediating effects of modifiable CVD risk (TC, HDL-C, SBP and fasting glucose) on CKD in terms of all-cause mortality. The analysis revealed significant partial mediation by SBP and fasting glucose, accounting for 19.2% ($p < 0.001$) and 3.52% ($p = 0.012$) of the total effect of CKD on mortality in two distinct models (Fig. 4C-D). In contrast, neither TC nor HDL-C demonstrated statistically significant mediating effects (ACME $p = 0.084/0.410$, Fig. 4A-B).

### Sensitivity analysis

Participants lost to follow-up were more likely to have a good education, urban resident, and were less likely to have comorbidities, or a smoking/drinking history. These participants also had lower levels of BMI, BP, and FRS (Supplementary Table S1). This was mainly due to the younger age of participants lost to follow-up (39.18 vs. 52.51 years old). Furthermore, the association between CKD and CVD risks on all-cause mortality across all age groups was analyzed using the original and imputed datasets, and similar results were found (Supplementary Table S2). The joint effect analysis also found similar results based on imputation data (Supplementary Table S3).

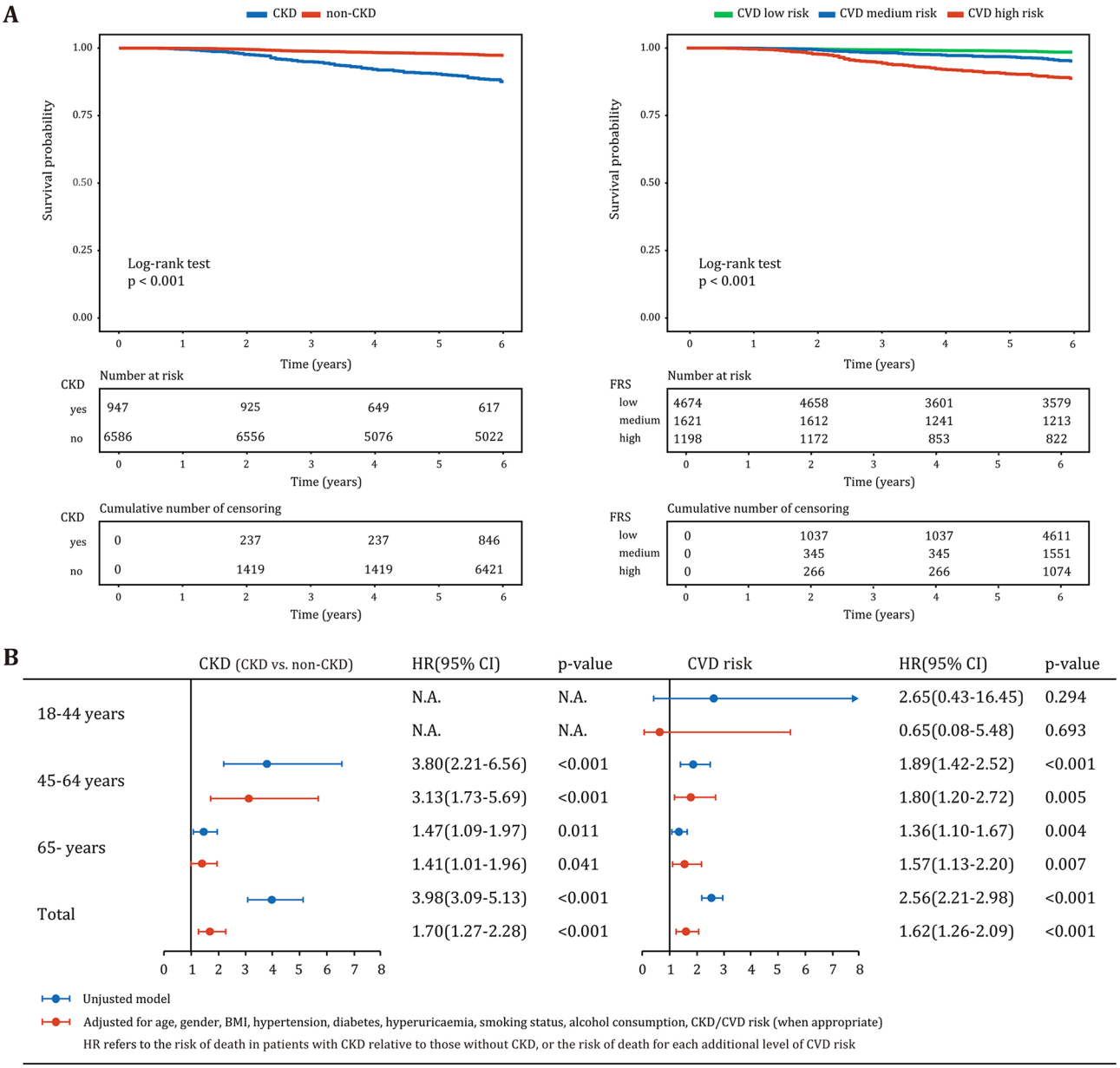



**Fig. 1** Survival analysis of CKD and CVD risk for all-cause mortality. (**A**. K-M curves, **B**. Cox regression models overall and across age groups)

## Discussion

In this study, CKD was associated with a higher hazard of all-cause mortality. The mediation analysis revealed significant partial mediation by SBP and fasting glucose, accounting for 19.2% and 3.52% of the total effect of CKD on mortality. Joint effect analysis also suggested that CKD patients with high CVD risk had the highest hazard of mortality. Although previous studies have assessed the effect of CKD and CVD risks on mortality [19–22], this study was innovative and unique in several ways. First, the CHNS cohort recruited representative participants from fifteen provinces in China. The large sample size enabled the interaction analysis in different statuses of CVD risk, CKD, and age groups. In addition, interaction, joint and mediation analyses were conducted to comprehensively evaluate the complex relationship between CKD and CVD risks on mortality. A series of sensitivity analyses were also performed using the imputed dataset to show the robustness of the findings.

CKD is associated with several CVD outcomes, including coronary heart disease, stroke, peripheral artery disease, arrhythmias, heart failure and venous thrombosis [23]. The kidneys and heart interact in a complex bidirectional manner, indicating that abnormalities in one organ are correlated with abnormalities in the other organ [7, 24]. Mendelian-randomization analyses have

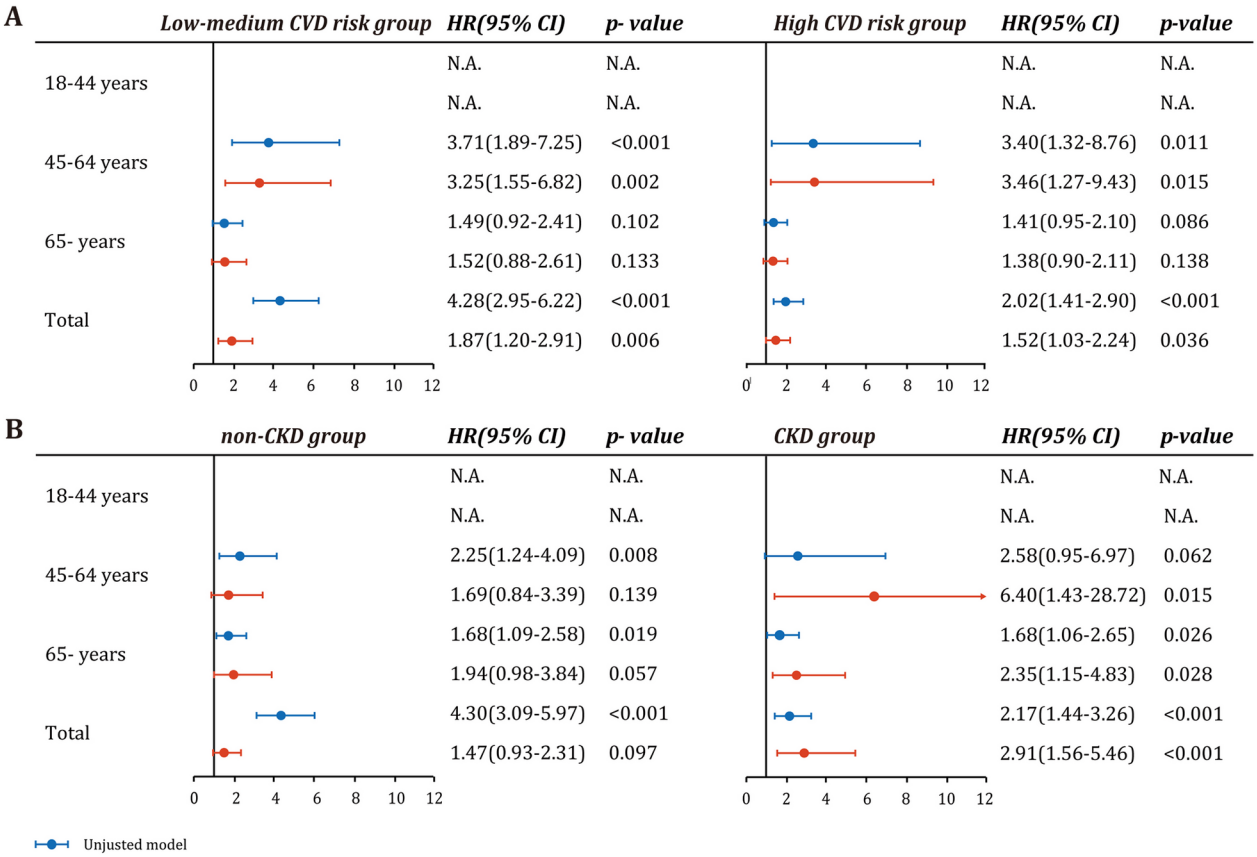
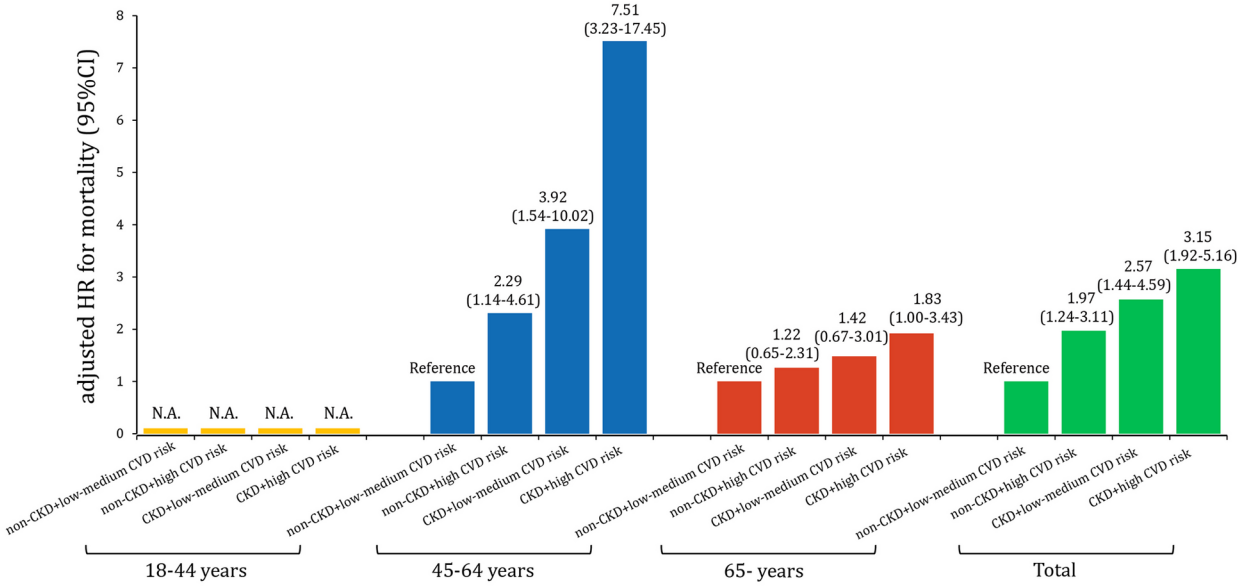



**Fig. 2** Cox regression models examining the effects of CKD and CVD risk on all-cause mortality overall and across age groups (**A**. stratified by CVD risk grade, **B**. stratified by CKD)

revealed that cardiometabolic factors affect CKD [25], and CKD patients, in turn, were causally related to the risk of CVD [5]. In this study, more CKD patients had a high risk of CVD than those without CKD, and 19.2% and 3.2% of CKD-related mortality was due to SBP and fasting glucose This broad impact of CKD on the cardiovascular system probably reflects the involvement of several pathophysiological mechanisms that link CKD to CVD development — shared risk factors (diabetes and hypertension), changes in bone mineral metabolism, anemia, volume overload, inflammation and the presence of uremic toxins [23, 26]. Both hypertension and CKD are intrinsically related, as hypertension is a strong determinant of worse renal and cardiovascular outcomes and renal function decline aggravates hypertension [27]. Kidney dysfunction reduces sodium and water excretion, increasing blood volume and leading to high blood pressure. Additionally, it results in overactivation of the renin-angiotensin-aldosterone (RAAS) system, causing vasoconstriction and further elevating blood pressure [28]. This bidirectional relationship is also overserved in diabetes and CKD. About 23.1% of CKD patients without diabetes were detected as insulin resistance (IR) [29]. IR can reduce insulin sensitivity and increase blood sugar, leading to diabetes [30]. Kidney dysfunction also impairs the metabolism and clearance of insulin, making it difficult to maintain stable blood glucose levels. Diabetes increases the risk of macrovascular disease (coronary heart disease) and microangiopathy of the kidneys [31]. Moreover, CKD patients often exhibit abnormalities in apolipoprotein synthesis and metabolism, leading to increased levels of LDL-C. These increased risk factors make CKD patients vulnerable to several CVD outcomes, including coronary heart disease, stroke, peripheral artery disease, arrhythmias, heart failure and venous thrombosis. USRDS reported that the presence of hypertension and diabetes was 90.0% and 51.1% [6]. In this study, data on CKD and CVD risk factors were collected in the same wave of CHNS, and the relationship between them should be associative rather than causal. Another CKD cohort in Japan found that CKD patients with hypertension and diabetes shared a higher risk of composite outcomes of CVD and all-cause death than those with glomerulonephritis




| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of participants | 2159 | 63 | 21 | 0 | 1996 | 1397 | 149 | 142 | 221 | 732 | 128 | 485 | 4376 | 2192 | 298 | 627 |
| Person years | 10740 | 322 | 106 | 0 | 10386 | 7251 | 773 | 702 | 1114 | 3567 | 624 | 2186 | 22239 | 11140 | 1503 | 2888 |
| No of events | 10 | 1 | 0 | 0 | 19 | 40 | 6 | 11 | 15 | 75 | 13 | 67 | 44 | 116 | 19 | 78 |
| Mortality rates (%) | 0.46 | 1.59 | 0.00 | 0.00 | 0.95 | 2.86 | 4.03 | 7.75 | 6.79 | 10.25 | 10.16 | 13.81 | 1.01 | 5.29 | 6.38 | 12.44 |
| Mortality rates (1000 person-years) | 0.93 | 3.11 | 0.00 | 0.00 | 1.83 | 5.52 | 7.76 | 15.67 | 13.47 | 21.02 | 20.83 | 30.65 | 1.98 | 10.41 | 12.64 | 27.01 |

HR was adjusted for age, gender, BMI, hypertension, diabetes, hyperuricaemia, smoking status, alcohol consumption.

**Fig. 3** Joint effect of CKD and CVD risks for all-cause mortality (overall and across age groups)

[32]. Besides, patients with advanced CKD experience electrolyte disorders. Calcium and phosphorus abnormality can accelerate vascular calcification and arterial stiffness, thus increasing CVD risk [33, 34]. Dyskalemia is associated with an increased risk of sudden cardiac death [35]. Impaired kidneys produce low erythropoietin levels, thus decreasing hemoglobin as CKD progresses [36]. Anemia can increase cardiac workload, inducing left ventricular hypertrophy (LVH) and heart failure [37]. Excessive sodium loading due to reduced glomerular filtration causes volume overload, LVH, and left ventricular dilatation [38]. CKD is a chronic proinflammatory disease, caused by defective kidney clearance, uremia, oxidative stress, insulin resistance, post-translational modification of lipoproteins and infection [39]. CKD inflammation facilitates malignant myocardial fibrosis and cardiac remodeling. Reduced clearance of kidneys leads to uremic solute retention, causing endothelial damage, cardiovascular and renal dysfunction [40]. In terms of genetic factors, we found that the prevalence of CKD was higher in participants with ethnic minority than in Han participants. However, the interactive effects of CKD×ethnicity and CVD risk×ethnicity on mortality were not significant ($\beta_{CKD\times ethnicity}$ =-0.1679, $p=0.642$ and $\beta_{CVD\ risk\times ethnicity}=0.02987$, $p=0.887$).

The initial univariate analysis demonstrated a negative interaction between CKD and CVD risk on all-cause mortality ($p<0.001$), which was attenuated to non-significance following multivariable adjustment ($p=0.734$). Its negative interaction to non-significance following covariate adjustment suggests potential residual confounding factors influencing the initial association. Beyond the measured covariates, there are many unknown biological and socioeconomic factors that may alter the CKD-CVD risk relationship. In high CVD risk subgroup, many drugs for hypertension and diabetes also have renal protective effects, which may underestimate the effect of CKD on mortality. Age-stratified analysis identified the 45–64-year group as having the strongest mortality associations across risk categories. Comorbidities become complex with age, and thus they can overshadow the effects of CKD on mortality. Therefore, multifactorial intervention strategies, focusing on middle-aged people and the early stage of disease, were of importance to reduce the risk of CVD associated with CKD. Lifestyle modifications, diet restrictions, and medication adherence can also control CVD risks. J-DOIT3 trial in Japan demonstrated that intensified intervention can significantly reduce the onset and progression of diabetic kidney disease compared with current recommended care [41]. The individual

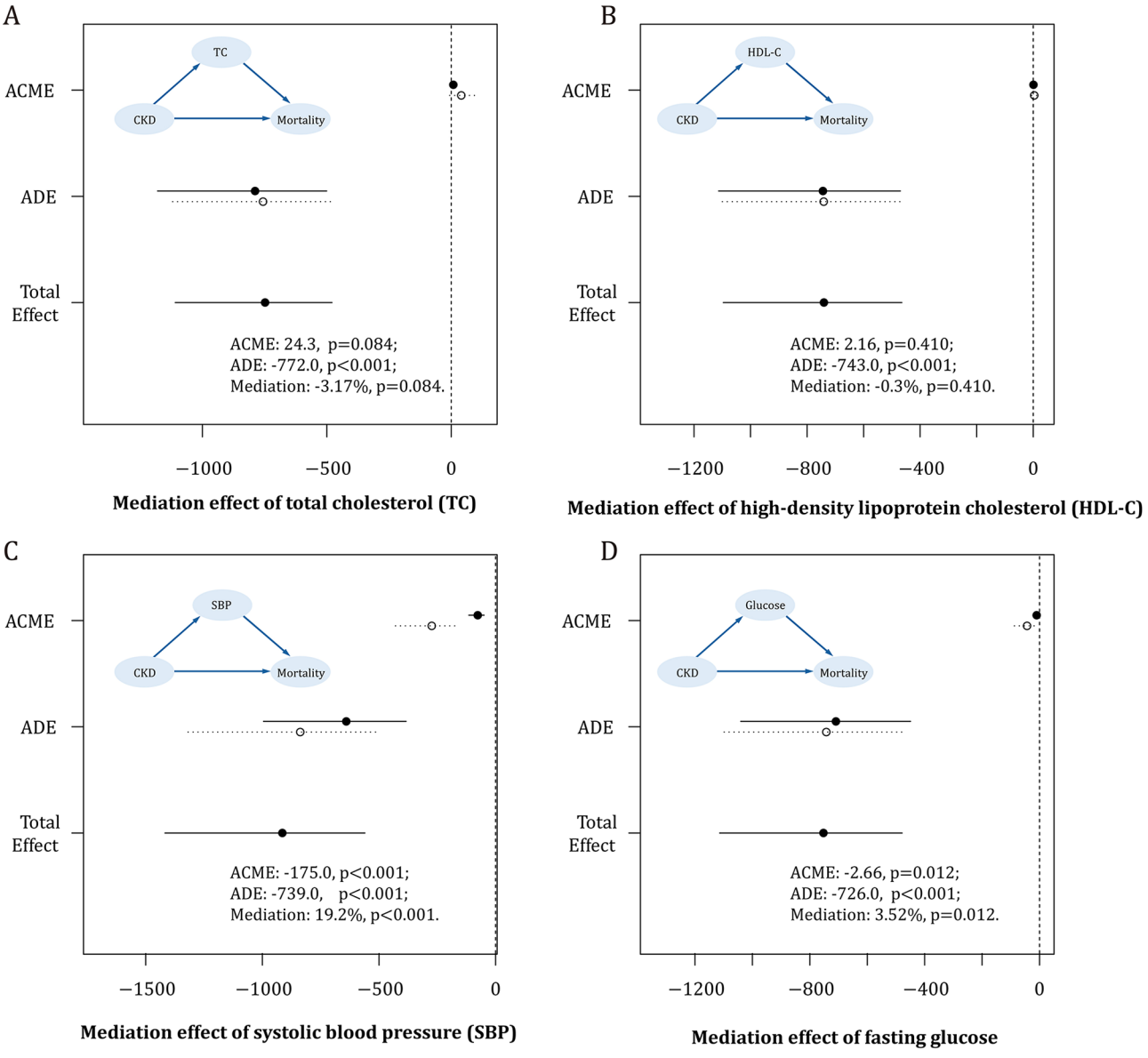



**Fig. 4** Mediation analysis for all-cause mortality (**A**. total cholesterol (TC), **B**. high-density lipoprotein cholesterol (HDL-C), **C**. systolic blood pressure (SBP), **D**. fasting glucose.unadjusted, **B-D**. moderated by age, the solid and dashed lines represent CKD group and non-CKD group)

target of systolic BP and HbA1c are <120 mmHg and 6.5-8.0% in CKD patients according to KIDGO guidelines [42, 43]. However, CVD risk factors are not well controlled. Kitamura et al. found that the rates of uncontrolled hypertension and diabetes were 52.9% and 25.1% in CKD patients [44], suggesting that the therapy of CKD-related CVD factors should be improved. SGLT2 inhibitors can increase glucose excretion by preventing glucose reabsorption in the proximal convoluted tubule [45]. SGLT2 can also reduce body weight and blood pressure by inducing diuresis [45]. A meta-analysis suggested that SGLT2 inhibitors can reduce the risk of cardiovascular and renal outcomes in participants with CKD, without clear evidence of additional safety concerns [46]. Moreover, the clinical management of CKD patients with CVD requires multidisciplinary diagnosis and treatment, with the collaboration of nephrologists, cardiologists, nurses, pharmacists, and dietitians [47]. cTNT and NT-proBNP were proved to be useful and noninvasive biomarkers of CVD risk in CKD patients [48]. Therefore, early and dynamic monitoring of these biomarkers can facilitate the management of high CVD risk group.

Our study has some limitations. First, CKD diagnosis was based on serum creatinine, ignoring albuminuria. It may lead to misclassification of CKD. Besides, eGFR and albuminuria can reflect different pathological mechanisms. Second, CVD risk was measured based on traditional factors, ignoring putative nontraditional factors of depression, frailty, socioeconomic status, and polypharmacy. It may underestimate the indirect effect of CVD risk on mortality. Third, the mean follow-up duration was only 5.04 years. Those who died during the study period might have had unknown diseases at baseline. Although the analysis after adjusting for comorbidities at baseline generated robust results, the possibility of reverse causation and residual confounding cannot be fully eliminated. Forth, most participants lost to follow-up were younger, and this could result in a low number of deaths and poor statistical power in the 18–44 age group. Fifth, although we controlled for potential covariates, confounding was still possible and causal inference cannot be confirmed because of the nature of observational studies. Sixth, the survival data did not meet the hypothesis of proportional hazards. Hazards are usually not proportional in medical studies because disease susceptibility varies between individuals. Although Stensrud et al. suggested that hazard ratio will vary over the follow-up period, tests of proportional hazards yielding high P-values are probably underpowered [49], the potential bias existed in HR estimates. Seventh, the multi-dimensional grouping in the joint analysis shortened the sample size, resulting in large confidence intervals for some groups to estimate HR.

## Conclusion

CKD was significantly associated with a higher hazard of mortality, and the association is modestly mediated by modified CVD risks. Comprehensive strategies, including lifestyle modifications, diet restrictions, and cardio-nephrology multidisciplinary diagnosis and treatment, should focus on middle-aged people and early disease detection.

## Supplementary Information

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Supplementary Material 1

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**Author contributions**

YL, YF and XD contributed to the conception or design of the work. YL, YS and BZ contributed to the acquisition, analysis, or interpretation of data for the work. YL and BZ drafted the manuscript. YL, YS and YC critically revised the manuscript. BS, SZ and NS contribute to analysis, or interpretation of the work. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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**Data availability**

The data were available online: https://www.cpc.unc.edu/projects/china.

## Declarations

**Ethical approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants. CHNS was approved by the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill and local IRB.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

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