Journal of Health, Population and Nutrition

RESEARCH

Open Access

# Associations between kidney function with all-cause and cause-specific mortality in type 2 diabetes mellitus patients: a prospective cohort study in China

Jialiu He[1†], Ya'nan Wan[2†], Xikang Fan[2], Hao Yu[2], Yu Qin[2], Jian Su[2,3], Yan Lu[4], Enchun Pan[5], Dong Hang[3], Chong Shen[3], Jinyi Zhou[2,3*] and Ming Wu[1,2*]

## Abstract

**Background** Abnormal kidney function is associated with adverse outcomes in patients with type 2 diabetes mellitus (T2DM). However, the evidence between kidney function and mortality among Chinese patients with T2DM were still limited.

**Methods** This cohort study included 19,919 participants with baseline T2DM from 2013 to 2014 in Jiangsu, China. Serum estimated glomerular filtration rate (eGFR), urea, and uric acid were measured at baseline, and Cox regression models were used to evaluate hazard ratios (HRs) and 95% confidential intervals (95%CIs) of all-cause and cause-specific mortality. Restricted cubic splines were used to analyze dose-response relationships, and we explored the best cut-off values by receiver operating characteristic (ROC) curves.

**Results** During a median follow-up of 9.77 years, 4,428 deaths occurred, including 1,542 (34.8%) due to cardiovascular disease (CVD), and 1,074 (24.3%) due to cancer. Compared to lowest quintile level (Q1), the highest quintile (Q5) of eGFR was negatively associated with all-cause (HR = 0.67, 95%CI: 0.58–0.77) and CVD mortality (HR = 0.57, 95%CI = 0.44–0.75). The higher levels of urea and uric acid were positively associated with all-cause mortality (Q5 vs. Q1: HR = 1.27, 95%CI: 1.16–1.39; HR = 1.21, 95%CI: 1.10–1.34), with an overall "U-shaped" dose-response relationships. Moreover, higher urea was negatively associated with cancer mortality (Q5 vs. Q1: HR = 0.79, 95%CI: 0.66–0.95). The best cut-off values with all-cause mortality were 88.50 ml/min/1.73m$^2$, 6.95 mmol/L and 342.50 μmol/L for eGFR, urea, and uric acid, respectively.

†Jialiu He and Ya'nan Wan contributed equally to this work.

*Correspondence:
Jinyi Zhou
zhoujinyi74@sina.com
Ming Wu
jswuming@vip.sina.com

Full list of author information is available at the end of the article

**Conclusion** We found abnormal kidney function was associated with mortality among people with T2DM. More clinical researches are needed to validate the effects and cut-off values of kidney function on mortality risk for T2DM prevention and management.

**Keywords** Type 2 diabetes mellitus, Mortality, Kidney function, Cardiovascular disease, Cancer

## Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide. According to the data of International Diabetes Federation (IDF) in 2021, there were 573 million people suffer from diabetes in the world, of which more than 90% were type 2 diabetes mellitus (T2DM) [1]. In 2019, the age-standardized mortality rate of T2DM was 18.49 per 100,000, and may increase to 19.1 by 2030–2034 [2]. Approximately 30% of T2DM cases were reported in China, as a leading cause of mortality among Chinese [3]. Consequently, T2DM imposes a serious burden of social healthcare.

However, the severe disease burden of diabetes predominantly arises from its complications or subsequent diseases [4]. Previous studies have found that cardiovascular disease (CVD) is the leading cause of death among patients with T2DM [5], nearly half of patients die from CVD, and the CVD mortality is twice as high as that in the general population [6]. In addition, other diseases, such as cancers (e.g., colorectal, pancreatic, breast) and respiratory diseases, are also associated with T2DM and are common causes of death globally [7, 8]. Given the complexity of mortality causes among people with T2DM, exploring modifiable risk factors is conducive to preventing premature death and promoting long-term health benefits [9].

For patients with T2DM, long-term exposure to hyperglycemia can cause structural and functional changes in the kidneys, leading to reduced urinary function, excretory dysfunction, metabolic retention, and other pathological alterations [10]. Diabetic kidney disease (DKD) is a common chronic complication of T2DM and a major cause of chronic kidney disease and renal failure. Clinically, DKD is typically characterized by a reduced glomerular filtration rate (GFR) and the presence of albuminuria [11]. The filtering capacity of the glomerulus is commonly assessed by the estimated glomerular filtration rate (eGFR), which is independently associated with an increased risk of all-cause mortality [12]. The relationship between eGFR and mortality due to T2DM has been explored in some previous studies, but the results were inconsistent because of different causes of death [13–15]. A Japanese cohort study showed when eGFR < 50 ml/min/1.73m$^2$, the risk of CVD mortality was significantly increased [16]. Another cohort study showed the similar results, but for other cause-specific mortality, current population studies provided insufficient evidence [17].

Kidney impairment is also manifested by abnormalities in metabolic capacity. Serum urea and uric acid are degradation products of protein and purine nucleotide metabolism. Increased levels of urea and uric acid are both important indicators of abnormal kidney function, which can reflect reduced kidney filtration or reabsorption capacity [18, 19]. Uric acid is widely recognized as a risk factor for macrovascular complications, and associated with risk of different cancers [20]. Of note, hyperuricemia is highly prevalent in people with diabetes, but the results of uric acid level with mortality for T2DM were still inconsistent.

In summary, the relationship between kidney function and mortality among people with T2DM has not been fully elucidated. To a certain extent, the etiology of diseases and the compositions of cause-specific mortality vary across regions and populations, and may lead to inconsistent results. With increasing incidence and mortality, CVD and cancer are the leading causes of death in China, which are major public health problems [21, 22]. However, few researches on kidney function and mortality for Chinese patients. Considering the severe situation of T2DM in China, we explored the associations of kidney function indexes (eGFR, serum urea and uric acid) with all-cause and cause-specific mortality for individuals with T2DM based on a prospective cohort.

## Materials and methods

### Study population

All participants were enrolled from the Comprehensive Research on the Prevention and Control of the Diabetes (CRPCD) project in Jiangsu province, China. This project is an ongoing prospective cohort study, and 20,340 patients were recruited at baseline [23]. T2DM was defined according to the criteria of American Diabetes Association (ADA), diagnosed by fasting blood glucose (FBG) ≥ 7.0mmol/L, or hemoglobin A1c (HbA1c) ≥ 6.5%, or 2-hour blood glucose of oral glucose tolerant test (OGTT) ≥ 11.1 mmol/L, or random glucose ≥ 11.1 mmol/L for patients with classic symptoms of hyperglycemia or hyperglycemic crisis [24].

Baseline survey was started in October 2013 and completed in July 2014. A face-to-face questionnaire was performed to collect personal information, including demographic characteristics, daily lifestyles, personal history and family history of diseases. Participants were also asked to complete physical medical examination (height, weight, waist circumstance and blood pressure) and

blood sample collection. We excluded 287 participants with missing baseline information, 134 with missing measurement data or biological samples. Finally, 19,919 participants were included (Supplementary Fig. 1).

#### Kidney function measurement

Fasting blood samples were collected at the same time of baseline survey, and then immediately coagulated to obtain serum. All participants were required to fast for at least 8 hours before blood collection. Serum samples were measured in the laboratory at KingMed Diagnostics (Nanjing, China). The eGFR level (ml/min/1.73m$^2$) was calculated according to serum creatinine (SCr) concentration by the MDRD formula [25].

Scr (μmol/L), urea (mmol/L), and uric acid (μmol/L) were measured by Jaffé assay, enzyme-linked immunosorbent assay (ELISA) and uricase-peroxidase assay, respectively. All indexes were measured by the automatic chemistry analyzer (Roche Cobas C701, Roche Diagnostics, Shanghai Ltd).

#### Death outcome ascertainment

All participants were followed-up from the date of baseline enrollment until September 30, 2023. Cause of death data were obtained from the death surveillance system of the Jiangsu Provincial Center for Disease Control and Prevention, which is operated by the Jiangsu National Health Commission [26]. This system provided medically validated information on mortality. In cases where the cause of death was complex, we used the underlying cause rather than the immediate cause for determination.

We used the underlying causes as the basis for participants. Death information was recorded according to International Classification of Diseases 10th reversion (ICD-10), mainly included all-cause mortality (A00-Z99), CVD mortality (I00-I79), cancer mortality (C00-C97), chronic respiratory disease mortality (J30-J98), and others. We focused on CVD-related mortality, which includes coronary heart disease (CHD, I20-25) and stroke (I60-I64), and classified them into subtypes: myocardial infarction (MI, I21), hemorrhagic stroke (HS, I61), and ischemic stroke (IS, I63). Cancer deaths were showed by common subtypes: esophageal cancer (C15), stomach cancer (C16), colorectal cancer (C18-C20), liver cancer (C22), and lung cancer (C34).

#### Covariates assessment

Covariates were defined by baseline questionnaire information. Smoker was defined as smoked more than 100 cigarettes during personal life, and smoking status was categorized as never, pervious and current smoking [27]. Alcohol consumption was defined as drank at least 1 time per month on average for more than 1 year. Physical activity was calculated through MET intensities, and converted to daily average MET (MET-h/d) [28]. Furthermore, body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m$^2$). The duration of T2DM was defined by the date of first diagnosed with T2DM until baseline survey.

#### Statistical analysis

We divided the participants into quintiles of eGFR to describe baseline characteristics. Baseline continuous variables were described as means ± standard deviation (SDs), and categorical variables were expressed as constituent ratios (n, %). Follow-up period was calculated as the period from baseline survey to death date or follow-up deadline. Continuous variables were analyzed using one-way ANOVA for normally distributed data or the Kruskal-Wallis test for non-normally distributed data, while categorical variables were analyzed using the $\chi^2$ test.

We used Cox regression models to evaluate the associations of kidney function indexes with all-cause mortality and cause-specific mortality. Hazard ratios (HRs) and 95% confidential intervals (CIs) were calculated according to the quintiles of three indexes. We applied three models to explore the associations by adjusting for different covariates. Model1 was only adjusted for age and sex. Model2 was additionally adjusted for education level, annual household income, smoking, alcohol consumption, BMI, waist circumstance, physical activity (MET-h/d), personal medical history (hypertension, stroke, CHD, cancer, dyslipidemia, and kidney diseases), and family history (stroke, CHD, diabetes, hypertension, and dyslipidemia). Moreover, Model3 was further adjusted for T2DM duration, oral antidiabetic medication and insulin injection.

We performed restricted cubic splines (RCS) to assess the dose-response relationships of kidney function indexes with mortality risk. We used 4 knots to fit the curve for each index and set the P20 of each indicator as the reference point with an HR of 1.00. Specifically, during the analysis of the dose-response relationship, we excluded data below the 1st percentile and above the 99th percentile for each indicator to minimize the impact of extreme values on the results. We also performed stratified analysis according to covariates (e.g. age, sex, smoking, alcohol consumption, T2DM duration, etc.). We evaluated the interactions between the levels of three indexes and stratified covariates by likelihood ratio test.

In addition, sensitivity analysis was then performed by excluding participants who died within first 2 years of follow-up, who died due to accident events, whose T2DM duration ≤ 1 year, and participants with cancer at baseline. Additionally, we also excluded individuals with diagnosed kidney disease prior to participating in the baseline survey. Considering the complexity of mortality,

we applied competing risk models to assess the competing effects of CVD and cancer mortality versus other cause-specific mortality [29]. We further explored their best cut-off values, aim to provide a reference for clinical precise prediction of mortality risk specific to patients with T2DM. The best cut-off values were explored by receiver operating characteristic (ROC) curves by Youden index [30]. Besides, we also analyzed the cut-off values on cause-specific mortality, including CVD, cancer, and chronic respiratory diseases.

All analysis were conducted by R software (version 4.4.0, R Foundation for Statistical Computing.). Overall, two-sided *P*-value < 0.05 was considered as statistically significant.

## Results

### Demographic characteristics of participants

Baseline characteristics of T2DM participants were showed in Table 1. The mean age was 62.9 years, and the proportion of females were higher than males. Participants with lower eGFR levels had longer T2DM durations, higher serum urea and lower urea acid levels (All $P < 0.05$). Most patients had oral antidiabetic medication history, and as eGFR levels decreased, the proportion of hypertension also increased.

During a median follow-up of 9.77 years (interquartile: 9.63–9.82 years), 4,428 participants died, of which 2,024 were males (45.7%) and 2,404 were females (54.3%). We listed cause-specific mortality, which included 1,542 CVD deaths (7.74%), 1,074 cancer deaths (5.39%), 278 due to chronic respiratory diseases (1.40%), and 1,534

**Table 1** Baseline characteristics of T2DM participants ($N = 19919$)

| Baseline characteristics | eGFR (ml/min/1.73m$^2$) | | | | | *P*-value |
|---|---|---|---|---|---|---|
| | Q1 (< 70.62) | Q2 (70.62~) | Q3 (84.67~) | Q4 (93.07~) | Q5 (≥ 100.34) | |
| No. of participants | 3985 | 3979 | 3979 | 3992 | 3984 | / |
| Age (years) | 69.5 (8.7) | 66.9 (8.2) | 65.5 (7.6) | 60.7 (5.9) | 51.8 (7.6) | < 0.001 |
| Female, *n* (%) | 2403 (60.3) | 2257 (56.7) | 2359 (59.3) | 2465 (61.8) | 2624 (65.9) | < 0.001 |
| BMI (kg/m$^2$) | 25.43 (3.53) | 25.41 (3.42) | 25.21 (3.53) | 25.20 (3.37) | 25.41 (3.48) | 0.001 |
| Waist circumstance (cm) | 87.39 (9.86) | 86.92 (9.52) | 86.32 (9.56) | 85.83 (9.26) | 85.51 (9.52) | < 0.001 |
| Diabetes duration (years) | 7.47 (6.76) | 6.51 (5.86) | 5.91 (5.61) | 5.66 (4.98) | 4.96 (4.54) | < 0.001 |
| Physical activity (MET-h/d) | 8.09 (11.75) | 10.17 (14.43) | 11.00 (15.38) | 12.69 (15.64) | 14.27 (18.06) | < 0.001 |
| Smoking, *n* (%) † | | | | | | < 0.001 |
| Never | 2884 (72.4) | 2787 (70.0) | 2813 (70.7) | 2818 (70.6) | 2985 (74.9) | |
| Quit | 777 (19.5) | 894 (22.5) | 877 (22.0) | 976 (24.5) | 832 (20.9) | |
| Current | 295 (7.4) | 270 (6.8) | 264 (6.6) | 170 (4.3) | 134 (3.4) | |
| Alcohol consumption, *n* (%) † | | | | | | < 0.001 |
| Never | 3235 (81.2) | 3050 (76.7) | 3074 (77.3) | 3050 (76.4) | 3103 (77.9) | |
| Quit | 489 (12.3) | 678 (17.0) | 703 (17.7) | 770 (19.3) | 730 (18.3) | |
| Current | 251 (6.3) | 240 (6.0) | 192 (4.83) | 157 (3.9) | 137 (3.4) | |
| Oral antidiabetic medication, *n* (%) | 2744 (68.9) | 2714 (68.2) | 2704 (68.0) | 2823 (70.7) | 2824 (70.9) | 0.006 |
| Insulin injection, *n* (%) | 839 (21.1) | 570 (14.3) | 499 (12.5) | 513 (12.9) | 594 (14.9) | 0.923 |
| Baseline self-reported diseases | | | | | | |
| Hypertension, *n* (%) | 2800 (70.3) | 2536 (63.7) | 2325 (58.4) | 2115 (53.0) | 1530 (38.4) | < 0.001 |
| Dyslipidemia, *n* (%) | 688 (17.3) | 677 (17.0) | 652 (16.4) | 759 (19.0) | 681 (17.1) | 0.002 |
| Cancer, *n* (%) | 112 (2.8) | 109 (2.7) | 119 (3.0) | 99 (2.5) | 73 (1.8) | 0.011 |
| Stroke, *n* (%) | 690 (17.3) | 568 (14.3) | 524 (13.2) | 393 (9.8) | 234 (5.9) | < 0.001 |
| CHD, *n* (%) | 580 (14.6) | 469 (11.8) | 399 (10.0) | 300 (7.5) | 180 (4.5) | < 0.001 |
| Kidney diseases, *n* (%) | 281 (7.1) | 140 (3.5) | 132 (3.3) | 123 (3.1) | 110 (2.8) | < 0.001 |
| Family history | | | | | | |
| Hypertension, *n* (%) | 1511 (37.9) | 1654 (41.6) | 1621 (40.7) | 1690 (42.3) | 1705 (42.8) | < 0.001 |
| Dyslipidemia, *n* (%) | 103 (2.6) | 121 (3.0) | 107 (2.7) | 120 (3.0) | 130 (3.3) | 0.261 |
| Diabetes, *n* (%) | 800 (20.1) | 874 (22.0) | 903 (22.7) | 1021 (25.6) | 1115 (28.0) | < 0.001 |
| Stroke, *n* (%) | 237 (6.0) | 295 (7.4) | 260 (6.5) | 269 (6.7) | 280 (7.0) | 0.007 |
| CHD, *n* (%) | 140 (3.5) | 191 (4.8) | 148 (3.7) | 182 (4.6) | 195 (4.9) | < 0.001 |
| Urea (mmol/L) | 7.79 (3.03) | 6.05 (1.43) | 5.77 (1.40) | 5.68 (1.37) | 5.45 (1.37) | < 0.001 |
| Uric acid (μmol/L) | 389.95 (115.43) | 324.17 (76.22) | 302.70 (71.51) | 289.70 (69.33) | 269.91 (69.38) | < 0.001 |

† The total proportion < 100% for participants who chose "unclear" in relatively small proportion

Continuous variables are presented as mean ± standard deviation, while categorical variables are expressed as frequency (%)

due to other diseases (7.70%). Each cause-specific mortality was showed in Supplementary Table 1.

### Associations between kidney function indexes and mortality

We defined the lowest quintiles (Q1) of eGFR, urea and uric acid as the reference groups. As showed in Table 2, compared to Q1, the higher level of eGFR was significantly negative association with all-cause mortality (HRs < 1.00). However, negative associations were found in the Q2 (HR = 0.87, 95%CI: 0.79–0.96) and Q3 (HR = 0.89, 95%CI: 0.81–0.98) of urea, but positive association was found in the highest quintile (Q5 vs. Q1: HR = 1.27, 95%CI: 1.16–1.39). Moreover, similar trend was also showed in uric acid (Q3 vs. Q1: HR = 0.88, 95%CI: 0.79–0.97; Q5 vs. Q1: HR = 1.21, 95%CI: 1.10–1.34, respectively).

Subsequently, we analyzed the associations of kidney function indexes and cause-specific mortality. Consistent with the results for all-cause mortality, increased eGFR level reduced CVD mortality risk. Positive associations were found in highest quintiles of urea (HR = 1.48, 95%CI: 1.27–1.73) and uric acid (HR = 1.39, 95%CI: 1.18–1.64). Specially, the negative association was found in increased urea level and cancer mortality. For chronic respiratory disease mortality, we observed negative associations for all indexes (Supplementary Table 2).

In addition, the negative associations were found for higher eGFR level with significant trend due to CVD mortality in subtypes. Whereas, we found increased urea and uric acid were negative associated with HS mortality and IS mortality, respectively (Supplementary Table 3). Specially, the highest level of eGFR increased the risk of stomach cancer mortality (HR = 2.00, 95%CI: 1.04–3.82), while increased uric acid decreased liver cancer mortality (Q3 vs. Q1: HR = 0.54, 95%CI: 0.33–0.90). Similarly, higher levels of uric acid appeared to decrease mortality risk due to colorectal and liver cancer (Supplementary Table 4).

### Dose-response relationships

As showed in Fig. 1A, when using Q1 as the reference, the overall risk of all-cause mortality decreased with increasing eGFR level (HR < 1.00). However, when eGFR > 100 ml/min/1.73m$^2$, the mortality risk slightly increased but remained < 1.00. In addition, the dose-response relationships between urea, uric acid, and all-cause mortality decreased initially and then increased; furthermore, significant positive association was observed when their concentrations continued to rise

**Table 2** Associations of baseline kidney function indexes with all-cause mortality among participants

| Serum indexes | No. of death/Person-years | HR (95% CI) † | | |
|---|---|---|---|---|
| | | Model 1 | Model 2 | Model 3 |
| eGFR (ml/min/1.73m$^2$) | | | | |
| Q1 (< 70.62) | 1733/31,420 | ref | ref | ref |
| Q2 (70.62~) | 1054/34,745 | 0.66 (0.61–0.71) | 0.67 (0.62–0.73) | 0.69 (0.64–0.75) |
| Q3 (84.67~) | 865/35,587 | 0.61 (0.56–0.67) | 0.62 (0.57–0.67) | 0.64 (0.59–0.70) |
| Q4 (93.07~) | 476/37,173 | 0.51 (0.46–0.57) | 0.52 (0.46–0.58) | 0.53 (0.47–0.59) |
| Q5 (≥ 100.34) | 300/37,660 | 0.65 (0.56–0.75) | 0.65 (0.56–0.75) | 0.67 (0.58–0.77) |
| *P*-trend | | < 0.001 | < 0.001 | < 0.001 |
| Urea (mmol/L) | | | | |
| Q1 (< 4.70) | 834/38,695 | ref | ref | ref |
| Q2 (4.70~) | 774/37,473 | 0.88 (0.80–0.98) | 0.89 (0.81–0.98) | 0.87 (0.79–0.96) |
| Q3 (5.50~) | 689/32,647 | 0.88 (0.80–0.98) | 0.89 (0.81–0.99) | 0.89 (0.81–0.98) |
| Q4 (6.20~) | 876/36,109 | 0.93 (0.84–1.02) | 0.95 (0.86–1.04) | 0.91 (0.83–1.01) |
| Q5 (≥ 7.30) | 1255/31,662 | 1.35 (1.24–1.48) | 1.36 (1.24–1.48) | 1.27 (1.16–1.39) |
| *P*-trend | | < 0.001 | < 0.001 | < 0.001 |
| Uric acid (μmol/L) | | | | |
| Q1 (< 242.00) | 739/36,151 | ref | ref | ref |
| Q2 (242.00~) | 727/36,694 | 0.81 (0.73–0.90) | 0.82 (0.74–0.91) | 0.83 (0.75–0.92) |
| Q3 (284.00~) | 786/35,427 | 0.83 (0.75–0.91) | 0.85 (0.77–0.95) | 0.88 (0.79–0.97) |
| Q4 (325.00~) | 923/35,049 | 0.88 (0.79–0.97) | 0.91 (0.83–1.01) | 0.93 (0.84–1.03) |
| Q5 (≥ 379.00) | 1253/33,264 | 1.11 (1.01–1.22) | 1.17 (1.07–1.29) | 1.21 (1.10–1.34) |
| *P*-trend | | < 0.001 | < 0.001 | < 0.001 |

Abbreviations: HR, hazard ratio; CI, confidential interval

† HRs (95% CIs) were calculated by adjusting covariates. Model 1: Adjusted for age and sex. Model 2: Additionally adjusted for education level, annual household income, smoking, alcohol consumption, BMI, WC, physical activity, hypertension, stroke, CHD, cancer, dyslipidemia, kidney diseases, family history of stroke, family history of CHD, family history of diabetes, family history of hypertension and family history of dyslipidemia. Model 3: Additionally adjusted for diabetes duration, oral antidiabetic medication and insulin injection

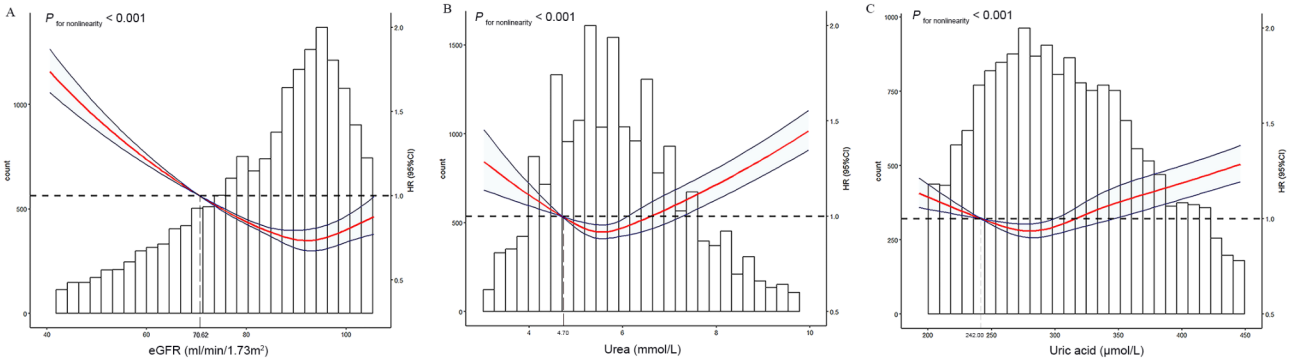


**Fig. 1** The RCS curves of non-linear dose-response relationships between kidney function indexes and all-cause mortality among T2DM patients. **(A)** The relationship of eGFR level with all-cause mortality risk. **(B)** The relationship of serum urea level with all-cause mortality risk. **(C)** The relationship of serum uric acid level with all-cause mortality risk. The red line represents the hazard ratio (HR), while the blue lines indicate the 95% confidence interval (CI).

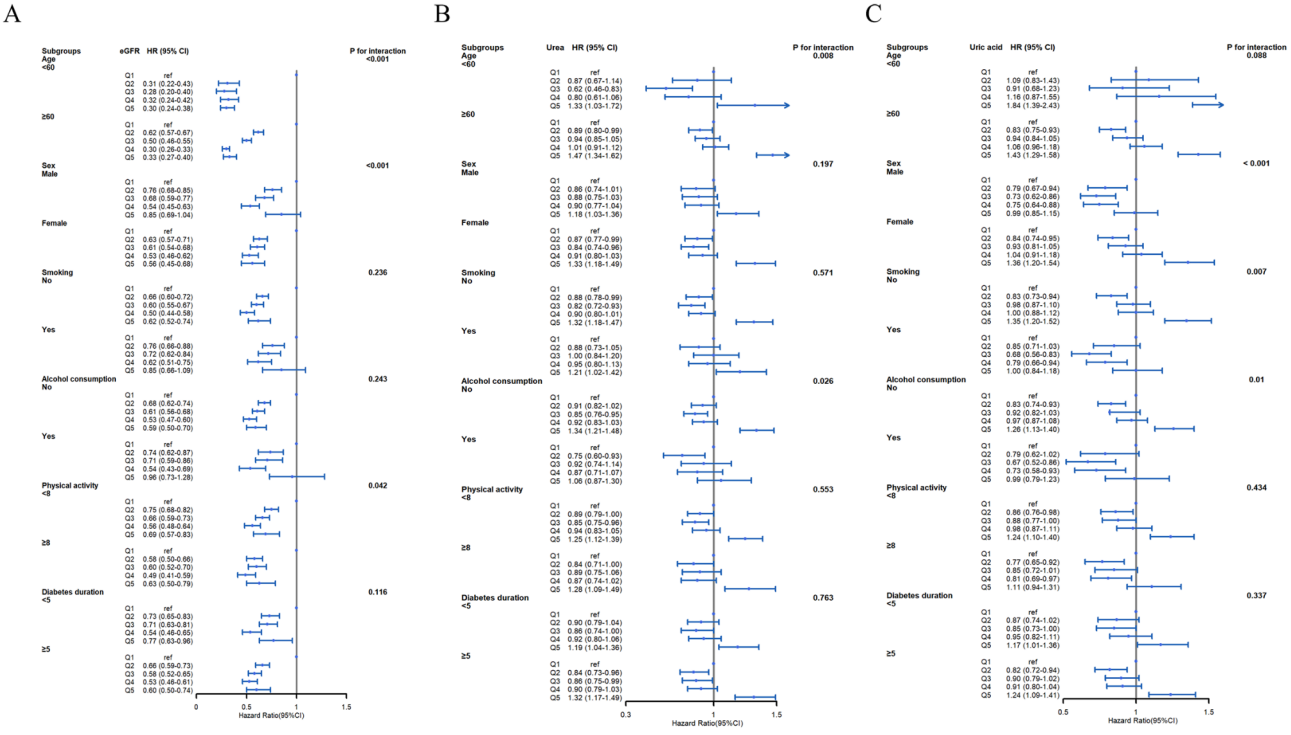


**Fig. 2** Forest plots for stratified analysis of all-cause mortality according to kidney function indexes among T2DM patients

(Fig. 1B and C). To specific-cause mortality (CVD, cancer and respiratory disease), we found the dose-response relationships were consistent with Cox regression for each index (Supplementary Fig. 2-Fig. 4).

### Stratified analysis

To further explore whether the association between kidney function indexes and mortality risk varies across different populations, we conducted a stratified analysis based on age, sex, smoking status, alcohol consumption, physical activity, and diabetes duration (Fig. 2). As compared to Q1, the risk for highest level of eGFR was not significant in males (HR = 0.85, 95%CI: 0.69–1.04), smokers (HR = 0.65, 95%CI: 0.37–1.01), and alcohol drinkers (HR = 0.73, 95%CI: 0.44–1.23). On the other hand, significant interactions were observed between eGFR and age, sex, and physical activity. For urea, significant interactions were observed after stratifying by age and alcohol consumption; while uric acid showed significant interactions with sex, smoking, and alcohol consumption ($P_{\text{for interaction}} < 0.05$).

Furthermore, negative associations between higher eGFR levels and CVD mortality were observed across subgroups stratified by age, sex, T2DM duration, smoking status, and alcohol consumption (Supplementary Table 5). Besides, the highest urea levels were positively

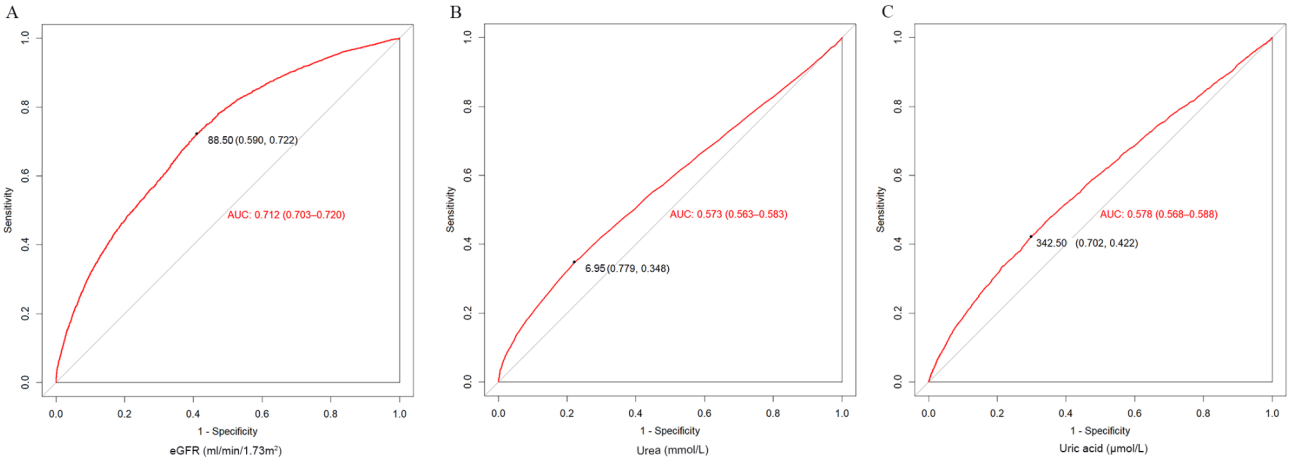


**Fig. 3** The best cut-off values of each kidney function index for all-cause mortality risk by using ROC curves

associated with the risk of CVD mortality. In addition, urea level showed negative associations with cancer mortality in people who were < 60 years, non-smokers, none of alcohol consumption, and with T2DM duration ≥ 5 years (Supplementary Table 6). We observed that eGFR was negatively associated with chronic respiratory disease mortality in those aged ≥ 60 years, while high urea levels were negatively associated in those aged < 60 years old (Supplementary Table 7).

### Sensitivity analysis

In the sensitivity analysis, we found that when excluding participants who died within the first 2 years of follow-up ($n = 570$) and those with a diabetes duration ≤ 1 year ($n = 4{,}251$), higher eGFR levels remained negatively associated with all-cause mortality when using Q1 as the reference group. Besides, we further excluded those with baseline kidney disease ($n = 786$), those with baseline cancer ($n = 512$), and who died in accidents ($n = 237$), similar associations were still found. We also found the significant associations between highest level of urea and mortality risk by sensitivity analysis. As compared to Q1, higher levels of uric acid showed negative associations with mortality risk (Supplementary Table 8).

Moreover, we used competing risk model to estimate the "competing" effect of cause-specific mortality. We found the similar associations of eGFR, urea and uric acid for CVD mortality, but there might be a positive association between eGFR and cancer mortality risk (Q3 vs. Q1: HR = 1.21, 95%CI: 1.01–1.45). After controlling other cause-specific deaths, higher levels of urea could reduce cancer mortality risk, while uric acid was not significantly associated with cancer mortality (Supplementary Table 9).

### Best cut-off values of kidney function indexes for mortality

We explored the best cut-off values of eGFR, urea and uric acid, to evaluate specific references for mortality among participants. We used ROC curves to find the best values according to Youden index. In Fig. 3, the best cut-off values for each index due to all-cause mortality were 88.50 ml/min/1.73m$^2$, 6.95 mmol/L, and 342.50 μmol/L, and we also reported the true positive rate, false positive rate and area under curve (AUC) for each index.

Furthermore, we also explored the cut-off values for cause-specific mortality. As listed in Supplementary Table 10, the eGFR cut-off values for CVD, cancer, and chronic respiratory diseases are 87.68, 91.27, and 92.89 ml/min/1.73m$^2$, respectively. In addition, the cut-off values of blood urea for these specific causes of death are 6.95, 6.05, and 6.55mmol/L, while those of uric acid are 322.50, 328.50, and 367.50μmol/L, respectively.

## Discussion

Serum biomarkers, i.e. creatinine, urea and uric acid, have been commonly used to indicate kidney function in clinical diagnosis [31]. In this cohort study, we found eGFR showed significant negative association with all-cause mortality and CVD mortality. Meanwhile, highest levels of urea and uric acid might increase the risk of all-cause mortality, but some negative associations were also existed for different cause-specific mortality.

Previous studies have demonstrated the association between eGFR and mortality risk due to different diseases. Another cohort study reported that eGFR < 60 ml/min/1.73m$^2$ was associated with higher stroke risk for individuals with T2DM (HR = 2.53, 95%CI = 1.27–5.03) [32]. Caplan et al. suggested that when eGFR decreased by nearly 40%, the mortality risk could increase about 98% among patients with T2DM (HR = 1.98, 95%CI = 1.87–2.10) [33]. The results from Kailuan cohort also reported an approximately 1.50-fold higher

risk of all-cause mortality among T2DM cases with eGFR < 45 ml/min/1.73m$^2$, but no significant effect on CVD mortality [34].

The close relationship between kidney function and heart or cerebral pathological conditions has been explored. Due to T2DM, hyperglycemia increases the levels of reactive oxygen species (ROS) and advanced glycosylation end-products (AGE) in human microenvironment, leading to vasoconstriction [35]. Oxidative stress increases the formation and accumulation of vascular plaques, which is thought to be one of the initial mechanisms that lead to atherosclerosis [36]. Bobot et al. also suggested that kidney severity was associated with worse prognosis and death in stroke, and this association persisted by adjusting T2DM [37]. Our results were generally consistent with previous studies, and further demonstrated the ability of eGFR as a biomarker for CVD mortality risk due to T2DM.

There seems to be a lack of strong evidence for the association between eGFR and cancer mortality risk. Kitchlu et al. analyzed eGFR among CKD patients for cancer incidence, and found increased risk of bladder cancer and kidney cancer risk [38]. A Swedish study measured baseline eGFR among a large population and reported "U-shaped" relationship for risk of skin cancer, prostate cancer, and urinary tract cancers [39]. T2DM was thought to be associated with risk of chronic respiratory diseases (e.g. asthma or COPD), and the data of China Health and Retirement Longitudinal Study (CHARLS) showed a strong relationship between lung function and eGFR [40, 41]. Zhang et al. concluded that chronic inflammation and oxidative stress caused by T2DM induces kidney disease and COPD [42]. Our results also reflected the protective effect of higher level of eGFR with respiratory disease mortality with the trend was not significant, which due to small number of deaths in our cohort.

In addition to eGFR, serum urea and uric acid can reflect changes for metabolic ability for kidney. The level of urea depends on the rate of protein decomposition, the amount of protein intake and the excretory capacity of kidney [43]. We also found the significant increase in all-cause mortality when serum urea level ≥ 7.30 mmol/L, but the trend was opposite when urea < 6.20 mmol/L. Elevated urea could lead to a reduction in the proliferation rate of human endothelial cells. Moreover, urea induced actin filament rearrangement, which were directly related to CVD [44]. However, the potential signaling pathways involved need to be explored in more researches.

When we distinguished types of diseases, increased urea showed negative association with cancer mortality risk. Gao et al. evaluated the negative effect between urea and colorectal cancer risk in T2DM participants (HR = 1.26, 95%CI: 1.13–1.41) [45]. Urea cycle is accomplished through urease, which can convert ingested nitrogen into urea for excretion. Animal experiment have showed ablation of glutamine synthetase (GS) in the liver exacerbated hyperammonemia and promoted nonessential amino acids, which subsequently stimulated the mechanistic target of rapamycin complex 1 ($mTORC_1$) to suppress liver cancer [46]. Among T2DM, related amino acids of urea cycle also showed higher expression, so the higher urea level may have an important role in inhibiting development of liver cancer.

We evaluated the relationship between elevated uric acid levels and mortality outcomes. A previous cohort study in the Chinese population also found a "U-shaped" relationship between uric acid levels and mortality [47]. However, this association has not been widely validated in individuals with T2DM. For example, used the data of the National Health and Nutrition Examination Survey (NHANES), it was observed that compared to the lowest concentration group, higher uric acid levels were associated with an increased mortality risk in the T2DM population [48]. When uric acid is in a hydrophobic environment, its prooxidizability are enhanced, promoting the involvement of oxidative stress in the pathology of CVD [49]. In a large Mendelian randomization study, it was found that higher uric acid concentration was indeed associated with an increased mortality rate from CHD [50]. The association of T2DM with hyperuricemia, chronic inflammation and cancer, suggest that uric acid may play an important role between T2DM and cancer development [51].

We further explored the cut-off values for uric acid to distinguish mortality risk due to T2DM. Honestly, there might be some differences between our analysis and previous studies. For instance, in the URic acid Right for heArt Health (URRAH) study, the cut-off value for uric acid in the T2DM population was reported as 261.11 μmol/L, which is slightly lower than our findings [52]. This discrepancy could be attribute to racial differences between the two studies. Moreover, the cut-off value in the URRAH study was not specifically set for T2DM individuals but was rather based on the general population [53].

We observed that the AUC values for blood urea and uric acid were low across different causes of death, suggesting limited predictive ability for cause-specific mortality. The significant nonlinear relationship between these indexes and mortality may explain the suboptimal predictive performance. Similar findings have been reported in previous studies, where blood urea also showed low AUC values for cause-specific mortality [53]. Additionally, this nonlinear trend has been documented in other studies, further highlighting the complexity of these biomarkers in mortality prediction [54, 55]. Furthermore, blood urea and uric acid are nonspecific

biomarkers of kidney function, influenced by various factors such as the stage of kidney impairment, age, sex, diet, and other clinical conditions. While the AUC values may be relatively low, these biomarkers still hold clinical utility in identifying feasible risk thresholds for mortality assessment.

Our study had some strengths. Firstly, the participants were derived from the community rather than hospitals, making it more representative. Community populations typically reflected the general population's health status, whereas hospital populations tended to be biased toward patients with severe conditions or specific diseases. Secondly, the mortality data was accurate, so we can clarify the cause of death for different diseases. Thirdly, all kidney function indexes were measured in the same platform, which effectively controlled the measurement bias. In addition, we used competing risk model to control other causes when analyzing cause-specific mortality, thus the results were stable and authentic. Meanwhile, we also explored the best cut-off values for each index, aiming to provide more accurate risk assessment criteria for clinical practice and help identify high-risk patients for timely intervention. However, several limitations were still existed. Firstly, we only used baseline measurement in this cohort study, however, kidney function tends to fluctuate over time due to factors such as disease progression, medication use, and acute illnesses. Future studies should incorporate repeated measurements to provide more robust evidence. Secondly, there are various formulas for calculating eGFR, and some studies suggest that the CKD-EPI formula provides a more accurate risk prediction factor. However, our study did not compare different eGFR calculation formulas nor explore the potential impact of these formulas on the study results [56]. In addition, the decline in kidney function is not only defined by low eGFR levels but also includes the presence of albuminuria. However, our study did not collect morning urine samples from the participants, therefore, data on albuminuria was not available. Furthermore, we excluded people with kidney disease at baseline in sensitivity analysis, but the sequence of kidney disease and T2DM was unclear. We were also unable to analyze some other causes of death, such as several types of cancer (including breast, cervical, bladder, and prostate cancer), due to the limited number of deaths. Additionally, this study was conducted in a province with advanced socioeconomic conditions in China, which may limit the generalizability of such findings to the entire Chinese population. Meanwhile, potential confounding cannot be completely eliminated. Finally, the deadline of follow-up was 2023, encompassing the period of Covid-19 pandemic, which might exacerbate mortality for participants.

## Conclusions

In conclusion, we found abnormal kidney function was associated with all-cause and cause-specific mortality among T2DM patients. More attention should be focused on lower eGFR, higher urea and uric acid to reduce the mortality. Future researches are needed to explore the mechanism with abnormal kidney function to cause-specific mortality.

### Abbreviations

| | |
|---|---|
| T2DM | Type 2 diabetes mellitus |
| eGFR | Estimated glomerular filtration rate |
| CVD | Cardiovascular disease |
| CKD | Chronic kidney disease |
| DKD | Diabetic kidney disease |
| FBG | Fasting blood glucose |
| HbA1c | Hemoglobin A1c |
| BMI | Body mass index |
| RCS | Restricted cubic splines |
| HR | Hazard ratio |
| ROC | Receiver operating characteristic |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41043-025-00809-2.

Supplementary Material 1

### Acknowledgements

Thanks to all participants and staffs for their contributions.

### Author contributions

Jialiu He and Ming Wu developed the concept and design of the study. Ya'nan Wan, Xikang Fan, Hao Yu, Yu Qin, Jian Su, Yan Lu, Enchun Pan, Chong Shen, and Jinyi Zhou were responsible for data acquisition. Ming Wu, Xikang Fan, Jian Su, and Yan Lu were responsible for funding acquisition. Jialiu He and Ya'nan Wan performed data analysis, and wrote the first draft. Dong Hang, Jian Su, and Ming Wu reviewed and edited the manuscript. All authors approved the final version of this manuscript.

### Funding

This study was supported by grants from Jiangsu Province Leading Talents and Innovation Team Program (No. K201105), Jiangsu Provincial Fifth "333 Project" (BRA2020090), Jiangsu Provincial Health Commission 2020 Medical Research Project Approval (M2020085), Jiangsu Provincial Health Commission 2023 Medical Research Project Approval (H2023022), and Suzhou Program of Science & Technology Development (SS202010).

### Data availability

The data in the study are available from the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

Ethics approval was granted by the Ethics board of Jiangsu Provincial Center for Disease Control (No. 2013026). All participants provided their informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

**Running title**
Kidney function and mortality among people with T2DM.

**Author details**
[1]Department of Epidemiology and Health Statistics, Southeast University, 87 Dingjiaqiao Road, Nanjing 210009, China
[2]Jiangsu Provincial Center for Disease Control and Prevention, Nanjing 210009, China
[3]School of Public Health, Nanjing Medical University, Nanjing 211166, China
[4]Department of Chronic Disease Prevention and Control, Suzhou City Center for Disease Control and Prevention, Suzhou 215004, China
[5]Department of Chronic Disease Prevention and Control, Huai'an City Center for Disease Control and Prevention, Huai'an 223021, China

Received: 23 September 2024 / Accepted: 25 February 2025
Published online: 13 March 2025

**References**

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
2. Ye J, Wu Y, Yang S, Zhu D, Chen F, et al. The global, regional and National burden of type 2 diabetes mellitus in the past, present and future: a systematic analysis of the global burden of disease study 2019. Front Endocrinol (Lausanne). 2023;14:1192629.
3. Deng W, Zhao L, Chen C, Ren Z, Jing Y, et al. National burden and risk factors of diabetes mellitus in China from 1990 to 2021: results from the global burden of disease study 2021. J Diabetes. 2024;16(10):e70012.
4. Ceriello A, Prattichizzo F. Variability of risk factors and diabetes complications. Cardiovasc Diabetol. 2021;20(1):101.
5. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. Nat Rev Cardiol. 2023;20(10):685–95.
6. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17(1):83.
7. Pearson-Stuttard J, Papadimitriou N, Markozannes G, Cividini S, Kakourou A, et al. Type 2 diabetes and cancer: an umbrella review of observational and Mendelian randomization studies. Cancer Epidemiol Biomarkers Prev. 2021;30(6):1218–28.
8. Yen FS, Wei JC, Yang YC, Hsu CC, Hwu CM. Respiratory outcomes of Metformin use in patients with type 2 diabetes and chronic obstructive pulmonary disease. Sci Rep. 2020;10(1):10298.
9. Eva JJ, Kassab YW, Neoh CF, Ming LC, Wong YY, et al. Self-Care and Self-Management among adolescent T2DM patients: A review. Front Endocrinol (Lausanne). 2018;9:489.
10. Lin L, Tan W, Pan X, Tian E, Wu Z, et al. Metabolic Syndrome-Related kidney injury: A review and update. Front Endocrinol (Lausanne). 2022;13:904001.
11. Mlynarska E, Bulawska D, Czarnik W, Hajdys J, Majchrowicz G et al. Novel insights into diabetic kidney disease. Int J Mol Sci 2024, 25(18).
12. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073–81.
13. Heerspink HJL, Oshima M, Zhang H, Li J, Agarwal R, et al. Canagliflozin and Kidney-Related adverse events in type 2 diabetes and CKD: findings from the randomized CREDENCE trial. Am J Kidney Dis. 2022;79(2):244–e256241.
14. Yamamoto Y, Hanai K, Mori T, Yokoyama Y, Yoshida N, et al. Kidney outcomes and all-cause mortality in people with type 2 diabetes exhibiting non-albuminuric kidney insufficiency. Diabetologia. 2022;65(1):234–45.
15. Jin Q, Kuen Lam CL, Fai Wan EY. Association of eGFR slope with all-cause mortality, macrovascular and microvascular outcomes in people with type 2 diabetes and early-stage chronic kidney disease. Diabetes Res Clin Pract. 2023;205:110924.
16. Nagai K, Sairenchi T, Irie F, Watanabe H, Ota H, et al. Relationship between estimated glomerular filtration rate and cardiovascular mortality in a Japanese cohort with Long-Term Follow-Up. PLoS ONE. 2016;11(6):e0156792.
17. Jung HH. Evaluation of serum glucose and kidney disease progression among patients with diabetes. JAMA Netw Open. 2021;4(9):e2127387.
18. Laville SM, Couturier A, Lambert O, Metzger M, Mansencal N, et al. Urea levels and cardiovascular disease in patients with chronic kidney disease. Nephrol Dial Transpl. 2022;38(1):184–92.
19. Tang X, Xu L, Meng RG, Du YQ, Liu SJ, et al. Association between serum uric acid and the early marker of kidney function decline among Chinese Middle-Aged and older population: evidence from the China health and retirement longitudinal study. Biomed Environ Sci. 2023;36(3):231–40.
20. Chang DY, Wang JW, Chen M, Zhang LX, Zhao MH. Association between serum uric acid level and mortality in China. Chin Med J (Engl). 2021;134(17):2073–80.
21. Li S, Liu Z, Joseph P, Hu B, Yin L, et al. Modifiable risk factors associated with cardiovascular disease and mortality in China: a PURE substudy. Eur Heart J. 2022;43(30):2852–63.
22. Wang Y, Yan Q, Fan C, Mo Y, Wang Y, et al. Overview and countermeasures of cancer burden in China. Sci China Life Sci. 2023;66(11):2515–26.
23. Su J, Fan X, Li M, Yu H, Geng H et al. Association of lifestyle with reduced stroke risk in 41 314 individuals with diabetes: two prospective cohort studies in China. Diabetes Obes Metab 2024.
24. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Suppl 1):S81–90.
25. Kuo CF, Yu KH, Shen YM, See LC. The Chinese version of the modification of diet in renal disease (MDRD) equation is a superior screening tool for chronic kidney disease among middle-aged Taiwanese than the original MDRD and Cockcroft-Gault equations. Biomed J. 2014;37(6):398–405.
26. Yan Y, Jiang Y, Liu R, Eddleston M, Tao C, et al. Impact of pesticide regulations on mortality from suicide by pesticide in China: an interrupted time series analysis. Front Psychiatry. 2023;14:1189923.
27. Park SK, Oh CM, Kim E, Ryoo JH, Jung JY. The longitudinal analysis for the association between smoking and the risk of depressive symptoms. BMC Psychiatry. 2024;24(1):364.
28. Ao L, Zhou J, Han M, Li H, Li Y, et al. The joint effects of physical activity and air pollution on type 2 diabetes in older adults. BMC Geriatr. 2022;22(1):472.
29. Yang M, Qing S, Xie G, Sheng G, Yang J. Oxidative stress mediates the association between triglyceride-glucose index and risk of cardiovascular and all-cause mortality in metabolic syndrome: evidence from a prospective cohort study. Front Endocrinol (Lausanne). 2024;15:1452896.
30. Zhang Y, Ding X, Hua B, Liu Q, Gao H, et al. Predictive effect of triglyceride–glucose index on clinical events in patients with type 2 diabetes mellitus and acute myocardial infarction: results from an observational cohort study in China. Cardiovasc Diabetol. 2021;20(1):43.
31. Ferguson MA, Waikar SS. Established and emerging markers of kidney function. Clin Chem. 2012;58(4):680–9.
32. Dal Canto E, Elders PJM, van der Heijden AA, van Ballegooijen AJ, Lissenberg-Witte BI, et al. Kidney function measures and cardiovascular outcomes in people with diabetes: the Hoorn diabetes care system cohort. Diabetologia. 2023;66(3):482–94.
33. Caplan EO, Sheer R, Schmedt N, Evers T, Cockrell M, et al. Glomerular filtration rate change and outcomes in type 2 diabetes. Am J Manag Care. 2021;27(8 Suppl):S160–7.
34. Wang A, Chen G, Cao Y, Liu X, Su Z, et al. Estimated glomerular filtration rate, proteinuria, and risk of cardiovascular diseases and All-cause mortality in diabetic population: a Community-based cohort study. Sci Rep. 2017;7(1):17948.
35. Matsushita K, Ballew SH, Wang AY, Kalyesubula R, Schaeffner E, et al. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. Nat Rev Nephrol. 2022;18(11):696–707.
36. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovasc Res. 2018;114(4):590–600.
37. Bobot M, Suissa L, Hak JF, Burtey S, Guillet B, et al. Kidney disease and stroke: epidemiology and potential mechanisms of susceptibility. Nephrol Dial Transpl. 2023;38(9):1940–51.
38. Kitchlu A, Reid J, Jeyakumar N, Dixon SN, Munoz AM, et al. Cancer risk and mortality in patients with kidney disease: A Population-Based cohort study. Am J Kidney Dis. 2022;80(4):436–e448431.
39. Xu H, Matsushita K, Su G, Trevisan M, Arnlov J, et al. Estimated glomerular filtration rate and the risk of Cancer. Clin J Am Soc Nephrol. 2019;14(4):530–9.
40. Su J, Li M, Wan X, Yu H, Wan Y, et al. Associations of diabetes, prediabetes and diabetes duration with the risk of chronic obstructive pulmonary disease: A prospective UK biobank study. Diabetes Obes Metab. 2023;25(9):2575–85.
41. Han S, Xu Y, Wang Y. Association between pulmonary function and rapid kidney function decline: a longitudinal cohort study from CHARLS. BMJ Open Respir Res 2024, 11(1).

42. Zhang H, Qi G, Wang K, Yang J, Shen Y, et al. Oxidative stress: roles in skeletal muscle atrophy. Biochem Pharmacol. 2023;214:115664.
43. Escribano J, Luque V, Ferre N, Zaragoza-Jordana M, Grote V, et al. Increased protein intake augments kidney volume and function in healthy infants. Kidney Int. 2011;79(7):783–90.
44. Colombo G, Altomare A, Astori E, Landoni L, Garavaglia ML et al. Effects of physiological and pathological Urea concentrations on human microvascular endothelial cells. Int J Mol Sci 2022, 24(1).
45. Gao P, Mei Z, Liu Z, Zhu D, Yuan H, et al. Association between serum Urea concentrations and the risk of colorectal cancer, particularly in individuals with type 2 diabetes: A cohort study. Int J Cancer. 2024;154(2):297–306.
46. Dai W, Shen J, Yan J, Bott AJ, Maimouni S et al. Glutamine synthetase limits beta-catenin-mutated liver cancer growth by maintaining nitrogen homeostasis and suppressing mTORC1. J Clin Invest 2022, 132(24).
47. Wang M, Wang C, Zhao M, Li Y, Yao S, et al. Uric acid variability and All-Cause mortality: A prospective cohort study in Northern China. J Nutr Health Aging. 2021;25(10):1235–41.
48. Li B, Chen L, Hu X, Tan T, Yang J, et al. Association of serum uric acid with All-Cause and cardiovascular mortality in diabetes. Diabetes Care. 2023;46(2):425–33.
49. Ndrepepa G. Uric acid and cardiovascular disease. Clin Chim Acta. 2018;484:150–63.
50. Li X, Meng X, Timofeeva M, Tzoulaki I, Tsilidis KK, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. BMJ. 2017;357:j2376.
51. Fini MA, Elias A, Johnson RJ, Wright RM. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med. 2012;1(1):16.
52. Masulli M, D'Elia L, Angeli F, Barbagallo CM, Bilancio G, et al. Serum uric acid levels threshold for mortality in diabetic individuals: the uric acid right for heart health (URRAH) project. Nutr Metab Cardiovasc Dis. 2022;32(5):1245–52.
53. Virdis A, Masi S, Casiglia E, Tikhonoff V, Cicero AFG, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years. Hypertension. 2020;75(2):302–8.
54. Li J, Huang JY, Liu L, Lo K, Sun S, et al. Relationship between serum uric acid level and all-cause and cardiovascular mortality in population with obesity. Postgrad Med J. 2020;96(1141):660–5.
55. Liu H, Xin X, Gan J, Huang J. The long-term effects of blood Urea nitrogen levels on cardiovascular disease and all-cause mortality in diabetes: a prospective cohort study. BMC Cardiovasc Disord. 2024;24(1):256.
56. Xu Q, Li X, Gao B, Xu Y, Wang Y, et al. Comparative performance of four equations estimating glomerular filtration rate in adult Chinese diabetics. J Endocrinol Invest. 2013;36(5):293–7.


## Publisher's note