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Association of the Controlling Nutritional Status (CONUT) score with all-cause and cause-specific mortality in patients with diabetic kidney disease: evidence from the NHANES 2009-2018

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Abstract

Objective: To investigate the association between the Controlling Nutritional Status (CONUT) score and all-cause and cause-specific mortality in patients with diabetic kidney disease (DKD).

Design: A retrospective cohort study.

Setting and participants: Data on DKD patients from the National Health and Nutrition Examination Survey (NHANES) 2009-2018.

Primary and secondary outcome measures: All-cause mortality, CVD-related mortality, diabetes-related mortality, and nephropathy-related mortality.

Results: A total of 1714 patients were included, with 1119 (65.29%), 553 (32.26%), and 42 (2.45%) in normal nutrition group (a score of 0-1), mild malnutrition group (a score of 2-4), and moderate and severe malnutrition group (a score of 5-12) respectively, according to the CONUT score. After controlling for age, race, marital status, smoking, hypertension, CVD, DR, poverty income ratio (PIR), antidiabetics, diuretics, urinary albumin to creatinine ratio (UACR), uric acid, energy, protein, total fat, sodium, and estimated glomerular filtration rate (eGFR), a higher CONUT score was associated with a significantly greater risk of all-cause death [hazard ratio (HR)=1.30, 95% confidence level (CI): 1.15-1.46, P<0.001]. In contrast to patients with a CONUT score of 0-1, those who scored 5-12 had a significantly increased risk of all-cause death (HR=2.80, 95%CI: 1.42-5.51, P=0.003), diabetes-related death (HR=1.78, 95%CI: 1.02-3.11, P=0.041), and nephropathy-related death (HR=1.84, 95%CI: 1.04-3.24, P=0.036).

Conclusion: Moderate and severe malnutrition was associated with a greater risk of

all-cause death, diabetes-related death and nephropathy-related death than normal nutritional status in DKD. Close monitoring of immuno-nutritional status in DKD patients may help prognosis management and improvement.

Keywords: CONUT score, immuno-nutritional status, mortality, diabetic kidney disease, NHANES

Strengths and limitations of this study

- In the current study, a nationally representative sample was employed to probe into the association between the CONUT score and the risk of mortality in patients with DKD for the first time.
- Close monitoring of immuno-nutritional status and appropriate nutritional care (e.g. dietary regulation) for DKD patients may help improve prognosis.
- Of note, the indicators required for CONUT score calculation are common and easily obtainable in clinical practice, with high practicality.
- The diagnosis of DKD was based on a single measurement of eGFR and UACR, rather than continuous observation for 3 months.
- Some possible confounding factors, such as treatment during follow-up, have not been adjusted for in this analysis.
- This research was conducted using the data from the American population, which may affect the applicability of the findings to other population.

Introduction

Diabetes mellitus is a common metabolic disease, affecting about 537 million people worldwide [1], and type 2 diabetes (T2DM) accounts for more than 90% of diabetic cases, which can lead to microvascular and macrovascular complications [2]. Diabetic kidney disease (DKD) is a main microvascular complication of diabetes [3], which occurs in 30-40% of diabetic patients. DKD is the major cause of end-stage renal disease (ESRD), and is associated with a high risk of death, resulting in a serious disease burden [4 5]. Thus, investigating effective prognostic markers has important clinical significance for stratified risk management and mortality reduction in DKD.

Recent evidence suggests that DKD is a metabolic-driven immunological disease, with pathological mechanisms involving multiple aspects such as metabolism and inflammation [6]. The Controlling Nutritional Status (CONUT) score is a commonly used immuno-nutritional marker that reflects chronic inflammation, immune status, and nutritional status in individuals, evaluated jointly by serum total cholesterol, albumin, and lymphocyte count [7 8]. Mineoka et al. [9] reported that a high CONUT score was associated with a greater risk of diabetic foot. In addition, an association was found between malnutrition assessed by the CONUT score and an elevated risk of all-cause mortality among diabetic patients [10]. According to a previous study, the CONUT score was significantly correlated with the risk of all-cause death in individuals with chronic kidney disease (CKD) who initiated dialysis [11]. Nevertheless, the relationship between the CONUT score and the risk of mortality in DKD patients is still unknown.

The objective of this study was to probe into the association between the CONUT

score and all-cause and cause-specific mortality among patients with DKD, based on the data from the National Health and Nutrition Examination Survey (NHANES) 2009-2018. Subgroup analysis was conducted in terms of sex, cardiovascular disease (CVD) and diabetic retinopathy (DR) to assess whether the association varied among different subpopulations.

Methods

Patient and Public Involvement statement

No patients involved.

Study population

This retrospective cohort study extracted data on DKD patients from 5 cycles (2009-2010, 2011-2012, 2013-2014, 2015-2016, 2017-2018) of the NHANES. The NHANES is a series of studies designed to evaluate the health and nutritional status of the nationally representative, non-institutionalized population in the United States. The survey combines interviews and physical examinations, and is approved by the National Center for Health Statistics (NCHS) Research [12]. The requirement of ethical approval for this was waived by the Institutional Review Board of Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, because the data was accessed from NHANES (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Shanxi Bethune Hospital, Shanxi Academy of Medical

Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University due to retrospective nature of the study. The study involved individuals (1) aged ≥ 18 years, (2) diagnosed as DKD, (3) with the assessment of serum albumin, total cholesterol, and total lymphocyte count, and (4) with complete survival data. Individuals without data on (1) follow-up time, or (2) the cause of death were excluded. Patients were followed up from the data of survey participation until December 31, 2019.

Assessment of DKD

Diabetes was defined as a self-reported diabetes diagnosis, use of diabetes medication or insulin, hemoglobin A1c (HbAlc) ≥ 6.5%, or a fasting glucose level ≥ 7.0 mmol/L. CKD was defined as urinary albumin to creatinine ratio (UACR) > 30 mg/g and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 according to the "KDIGO 2021 Guidelines"[13]. The CKD_EPI_Scr equation was applied to calculate eGFR [13 14]. DKD was defined as CKD combined with diabetes [15 16].

Calculation of the CONUT score

The CONUT score was calculated with the data on serum albumin, total cholesterol, and total lymphocyte count (obtained from a blood examination), ranging from 0 to 12 [7]. A total score of 0-1 was regarded as normal nutrition, and a score of 2-4, 5-8, and 9-12 in total was defined as mild, moderate, and severe malnutrition, respectively.

Assessment of mortality

Mortality evaluated in this study included all-cause mortality, CVD-related mortality, diabetes-related mortality, and nephropathy-related mortality. All-cause and cause-specific mortality was determined via linkage to the National Death Index (NDI) until December 31, 2019. The 10th revision of the International Classification of Disease (ICD-10) was used to determine the cause of death. All-cause mortality was defined as death from any cause. CVD-related mortality was defined as death from diseases of heart (I00-I09, I11, I13, I20-I51) and cerebrovascular diseases (I60-I69). Diabetes-related mortality was defined as death from diabetes mellitus (E10-E14). Nephropathy-related mortality was defined as death from nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27).

Other variables

We collected information on age (years), gender, race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), Body Mass Index (BMI, kg/cm^2), education level (less than 9th grade, 9-11th grade, high school graduate/general education development (GED) or equivalent, some college or college or associate (AA) degree, college graduate or above), marital status (married, widowed, divorced, separated, never married, living with partner), smoking, alcohol drinking, hypertension, hyperlipidemia, CVD, DR, poverty income ratio (PIR; <1, ≥1, unknown), physical activity (MET·min/week), fasting glucose (mmol/L), antidiabetics (no, only hypoglycemic drugs, hypoglycemic drugs and insulin), diuretics, angiotensin-converting enzyme inhibitor (ACEI), UACR, uric acid (μmol/L), energy (kcal), protein

(gm), carbohydrate (gm), total fat (gm), sodium (mg), potassium (mg), eGFR (mL/min/1.73 m^2), and follow-up time (months). The presence of hypertension and dyslipidemia was determined according to laboratory examination, self-reported medical history and medication history. Hypertension referred to systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or self-reported hypertension, or use of antihypertensive drugs. Dyslipidemia referred to total cholesterol (TC) ≥ 200 mg/dL (5.2 mmol/L), or triglyceride (TG) ≥ 150 mg/dL (1.7 mmol/L), or low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL (3.4 mmol/L), or how-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL (1.0 mmol/L), or self-reported hypercholesterolemia, or receiving lipid-lowering treatment. DR was defined by the question, "has a doctor ever told {you/SP} that diabetes has affected {your/his/her} eyes or that {you/s/he} had retinopathy (ret-in-op-ath-ee)?" Physical activity was converted into energy consumption. Energy consumption (MET·min) = recommended metabolic equivalent (MET) × exercise time of the corresponding activity (min).

Statistical analysis

Continuous data were illustrated as Mean [standard error (SE)], and the weighted t test was used for inter-group comparisons; categorical data were reported as the number of cases and constituent ratio [n (%)], and comparisons between groups were conducted using the χ^2 test. Continuous data were standardized. Missing data were filled with multiple imputation, and sensitivity analysis was performed for data before and after

the imputation (Supplementary Table 1).

The included patients were divided into three groups according to the CONUT score: normal nutrition group (a score of 0-1), mild malnutrition group (a score of 2-4), and moderate and severe malnutrition group (a score of 5-12). Univariate weighted Cox regression was employed to screen covariates, and examine the association between the CONUT score and mortality. Multivariate weighted Cox regression was utilized to further explore the association between the CONUT score and mortality, with adjustment for age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetics, diuretics, UACR, uric acid, energy, protein, total fat, sodium, and eGFR. Subgroup analysis was carried out based on sex, CVD and DR to assess whether the association between the CONUT score and mortality was different in subpopulations. Hazard ratios (HRs) and 95% confidence levels (CIs) were calculated.

Data extraction and cleaning were completed by SAS 9.4 (SAS Institute Inc., Cary, NC, USA). R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) was adopted for statistical analysis. A difference was regarded as significantly different when a P value < 0.05.

Results

Characteristics of the study population

From the NHANES 2009-2018, 1723 patients with DKD were enrolled. After excluding patients less than 18 years (n=3), and without information on the CONUT score (n=3) and follow-up time (n=3), a total of 1714 patients were eligible for this

study. Figure 1 demonstrates the selection process of eligible patients. According to the CONUT score, the number of patients in normal nutrition group, mild malnutrition group, and moderate and severe malnutrition group was 1119 (65.29%), 553 (32.26%), and 42 (2.45%), respectively. The mean age of these patients was 64.08 years. Most of the patients were non-Hispanic White people (59.62%), and were married (54.30%). The average follow-up time was 58.23 months. The characteristics of the included DKD patients are presented in Supplementary Table 2. Significant differences were found among the three groups in age, gender, race, BMI, marital status, hypertension, CVD, PIR, physical activity, antidiabetics, diuretics, UACR, energy, protein, carbohydrate, total fat, eGFR, follow-up time, and vital status (all $P<0.05$).

Association between the CONUT score and mortality

After controlling for age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetics, diuretics, UACR, uric acid, energy, protein, total fat, sodium, and eGFR, a higher CONUT score was associated with a significantly greater risk of all-cause death (HR=1.30, 95%CI: 1.15-1.46, $P<0.001$) and death from other causes (HR=1.54, 95%CI: 1.31-1.82, $P<0.001$). In contrast to patients with a CONUT score of 0-1, those who scored 5-12 had a significantly increased risk of all-cause death (HR=2.80, 95%CI: 1.42-5.51, $P=0.003$), diabetes-related death (HR=1.78, 95%CI: 1.02-3.11, $P=0.041$), nephropathy-related death (HR=1.84, 95%CI: 1.04-3.24, $P=0.036$), and other cause-related death (HR=6.54, 95%CI: 3.18-13.45, $P<0.001$) (Supplementary Table 3).

Association between the CONUT score and mortality in subpopulations

Sex

For males, compared with a CONUT score of 0-1, a score of 2-4 was associated with a significantly higher risk of all-cause death, and a score of 5-12 was associated with a significantly elevated risk of all-cause death and other cause-related death. For females, no significant differences were found in the risk of death between women with the CONUT scores of 0-1 and 2-4, and between women with the scores of 0-1 and 5-12 (Figure 2).

CVD

Patients with CVD who had a CONUT score of 5-12 exhibited a significantly greater risk of all-cause death and other cause-related death than those who had a score of 0-1. Among patients without CVD, a CONUT score of 5-12 was associated with a significantly increased risk of diabetes-related death, nephropathy-related death and other cause-related death than that of 0-1 (Figure 2).

DR

In patients with DR, a CONUT score of 5-12 was associated with a significantly elevated risk of other cause-related death, as compared with a score of 0-1. For patients without DR, the risk of all-cause death, CVD-related death and other cause-related death was significantly higher in those with a CONUT score of 5-12 than those with a score of 0-1 (Figure 2).

Discussion

To the best of our knowledge, the current study first investigated the association between the CONUT score and all-cause and cause-specific mortality among patients with DKD, and further assessed the association in different sex, CVD and DR subgroups. It was illustrated that for DKD patients, moderate and severe malnutrition was associated with a higher risk of all-cause death, diabetes-related death and nephropathy-related death than normal nutritional status. The association between the CONUT score and mortality varied across different sex, CVD and DR subgroups. These findings may act as evidence for risk stratification management and prognosis improvement in DKD patients.

Malnutrition is a primary issue for patients with chronic diseases. In patients with DKD, malnutrition can exacerbate inflammatory activity and further impair nutrition intake, lowering the quality of life and elevating mortality [17]. Medical nutritional therapy has been proposed for DKD, which is beneficial for health and survival [18]. The CONUT score assesses nutritional status with three objective indicators: serum albumin (protein metabolism), total cholesterol (lipid metabolism), and total lymphocyte count (immune function) [7]. Serum albumin plays an essential role in nutrition maintenance, metabolic transport and plasma colloid osmotic pressure [19]. Hypoalbuminemia was identified a prognostic factor for death in elderly individuals [20]. Sun et al. showed that a reduced level of serum albumin was associated with a greater risk of all-cause mortality in CKD, with the optimum threshold of 4 g/dL [21]. High cholesterol levels, a

low-risk factor for undernutrition in the CONUT, were related to all-cause mortality in the general population [22]. As a marker of immunological status, a decline in the total lymphocyte count can reflect susceptibility to infectious diseases, and malnutrition may lead to decreased lymphocyte maturation and circulating lymphocyte counts [11]. In a study by Tojek et al. [23], an association was found between the total lymphocyte count less than 800 mg/L and the highest risk of in-hospital mortality.

With this CONUT score, this study found that compared with normal nutritional status, moderate and severe malnutrition (a score of 2-12) was associated with an increased risk of all-cause mortality. As a dimension of nutritional status assessment, inflammation facilitates the development of DKD [24], possibly through releasing interleukin-1 (IL-1) from monocytes, which might initiate major complications and elevated mortality [25]. Additionally, inflammation is correlated with malnutrition and protein-energy wasting, potentially contributing to mortality in DKD [26]. As regards immune status, infectious complications can be caused by an immunosuppressive state, which may be associated with morbidity and mortality of DKD patients [27]. In terms of nutritional status, a prior review has indicated that improvement in nutrition plays an important role in mortality among people with CKD [28]. Moderate and severe malnutrition was also identified to be associated with diabetes-related mortality and nephropathy-related mortality. Inflammatory response may facilitate the occurrence of T2DM via inducing insulin resistance, and it can be aggravated in the case of hyperglycemia, promoting long-term complications of diabetes [29], which may contribute to the risk of death. This is a potential explanation for diabetes-related

mortality in DKD. Increases in inflammation may also account for mortality due to nephropathy [30]. Additionally, we did not find an association between the nutritional status measured by the CONUT score and CVD-related death. This may be attributed to the relatively small number of patients involved herein. Further, we found that undernourished males had a higher risk of all-cause death, while in females, no significant associations were observed between nutritional status and mortality. For patients with CVD, moderate and severe malnutrition was associated with a greater risk of all-cause death. Among patients without CVD, moderate and severe malnutrition was related to an elevated risk of diabetes-related death and nephropathy-related death. For patients without DR, those with moderate and severe malnutrition had a higher risk of all-cause death and CVD-related death. Clinicians may provide personalized advice for different subpopulations at a high risk of death. Large-scale studies are warranted to corroborate our findings.

In the current study, a nationally representative sample was employed to probe into the association between the CONUT score and the risk of mortality in patients with DKD for the first time. Close monitoring of immuno-nutritional status and appropriate nutritional care (e.g. dietary regulation) for DKD patients may help improve prognosis. Of note, the indicators required for CONUT score calculation are common and easily obtainable in clinical practice, with high practicality. Several limitations should be mentioned when interpreting our results. First, the diagnosis of DKD was based on a single measurement of eGFR and UACR, rather than continuous observation for 3 months. Second, some possible confounding factors, such as treatment during follow-

up, have not been adjusted for in this analysis. Third, this research was conducted using the data from the American population, which may affect the applicability of the findings to other population.

Conclusion

Compared with normal nutritional status, moderate and severe malnutrition was associated with a higher risk of all-cause mortality, diabetes-related mortality and nephropathy-related mortality in DKD. Close attention should be paid to the immuno-nutritional status of DKD patients to promote prognosis management and improvement. These findings need to be confirmed in future studies.

Author contributions HZ and HD designed the study. HZ wrote the manuscript. NL collected, analyzed, and interpreted the data. HZ and HD critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Figure legends

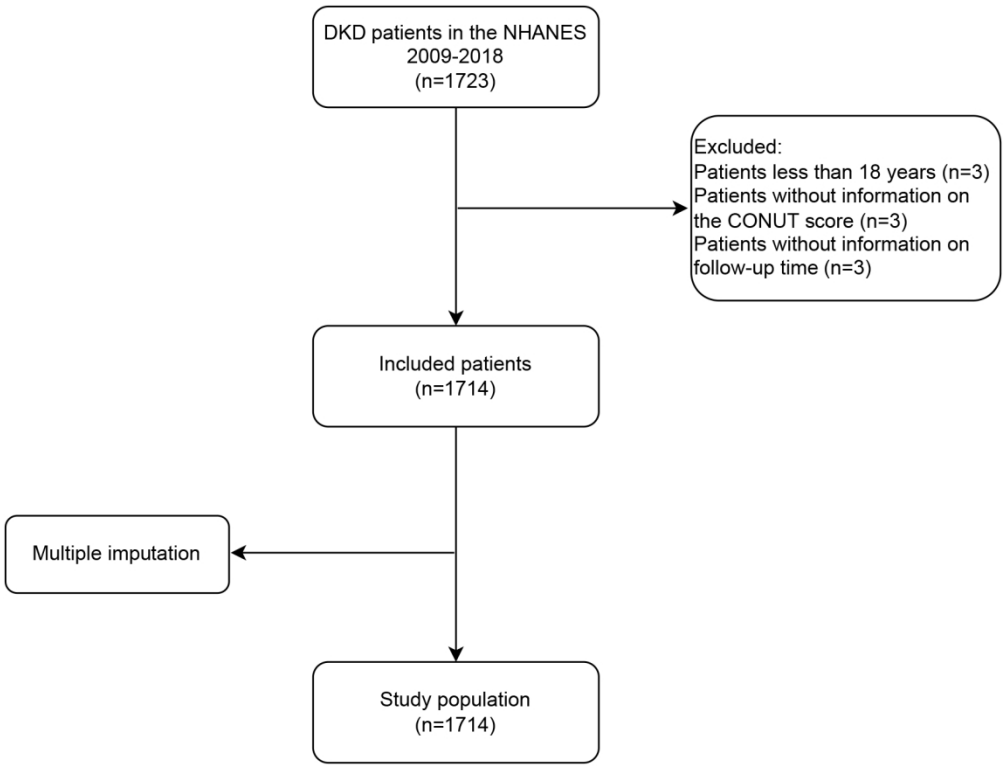
Figure 1 Flow chart of participant selection.

DKD, diabetic kidney disease; NHANES, National Health and Nutrition Examination Survey; CONUT, Controlling Nutritional Status.

Figure 2 Association between the CONUT score and mortality in subpopulations.

Adjusted variables included age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetics, diuretics, UACR, uric acid, energy, protein, total fat, sodium, and eGFR.

CONUT, Controlling Nutritional Status; CVD, cardiovascular disease; DR, diabetic retinopathy; PIR, poverty income ratio; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; Ref, reference.



150x114mm (300 x 300 DPI)

254x127mm (300 x 300 DPI)

Supplementary Table 1 Sensitivity analysis for missing data before and after the imputation.

Variables	Total (n=3428)	Post-imputation (n=1714)	Pre-imputation (n=1714)	*P*
BMI, kg/cm^2, Mean (SE)	33.14 (0.29)	33.04 (0.29)	33.24 (0.29)	0.947
Education level, n (%)				0.922
Less than 9th grade	641 (11.86)	322 (11.87)	319 (11.85)	
9-11th grade	569 (13.64)	285 (13.63)	284 (13.65)	
High school graduate/GED or equivalent	785 (26.09)	394 (26.08)	391 (26.10)	
Some college or AA degree	934 (30.89)	468 (30.90)	466 (30.88)	
College graduate or above	488 (17.53)	245 (17.53)	243 (17.53)	
Marital status, n (%)				0.472
Married	1768 (54.37)	887 (54.39)	881 (54.35)	
Widowed	640 (16.69)	320 (16.68)	320 (16.71)	
Divorced	453 (12.77)	227 (12.77)	226 (12.77)	
Separated	140 (3.22)	70 (3.22)	70 (3.23)	
Never married	303 (8.21)	152 (8.21)	151 (8.20)	
Living with partner	116 (4.74)	58 (4.73)	58 (4.74)	
Smoking, n (%)				0.881
Yes	1760 (53.22)	882 (53.22)	878 (53.23)	
No	1661 (46.78)	832 (46.78)	829 (46.77)	
CVD, n (%)				0.113
Yes	2187 (65.57)	1100 (65.45)	1087 (65.69)	
No	1220 (34.43)	614 (34.55)	606 (34.31)	
Energy, kcal, Mean (SE)	1889.72 (30.94)	1889.45 (29.74)	1890.02 (32.68)	0.941
Protein, gm, Mean (SE)	74.54 (1.54)	74.62 (1.48)	74.46 (1.62)	0.634
Carbohydrate, gm, Mean (SE)	221.08 (3.92)	221.07 (3.86)	221.08 (4.05)	0.992
Total fat, gm, Mean (SE)	76.45 (1.46)	76.38 (1.37)	76.52 (1.56)	0.689
Sodium, mg, Mean (SE)	3273.84 (59.64)	3272.01 (58.02)	3275.83 (62.33)	0.802
Potassium, mg, Mean (SE)	2436.29 (47.07)	2435.93 (44.11)	2436.68 (50.76)	0.947

BMI, body mass index; GED, general education development; AA, associate; CVD, cardiovascular disease; SE, standard error.

Supplementary Table 2 Characteristics of the included DKD patients.

Variables	Total (n=1714)	Normal nutrition group (n=1119)	Mild malnutrition group (n=553)	Moderate and severe malnutrition group (n=42)	*P*
Age, years, Mean (SE)	64.08 (0.47)	61.69 (0.60)	68.92 (0.67)	67.02 (2.14)	<0.001
Gender, n (%)					<0.001
Male	952 (53.86)	549 (47.78)	371 (65.17)	32 (75.56)	
Female	762 (46.14)	570 (52.22)	182 (34.83)	10 (24.44)	
Race, n (%)					<0.001
Mexican American	298 (10.61)	213 (12.27)	81 (7.48)	4 (5.04)	
Other Hispanic	172 (5.75)	130 (6.81)	38 (3.60)	4 (4.42)	
Non-Hispanic White	623 (59.62)	367 (56.41)	238 (66.17)	18 (63.00)	
Non-Hispanic Black	416 (14.36)	281 (15.10)	124 (12.91)	11 (12.65)	
Other race - including multi-racial	205 (9.67)	128 (9.41)	72 (9.83)	5 (14.90)	
BMI, kg/cm^2, Mean (SE)	33.04 (0.29)	33.60 (0.38)	31.97 (0.38)	31.60 (1.90)	0.020
Education level, n (%)					0.161
Less than 9th grade	322 (11.95)	218 (12.41)	98 (11.18)	6 (9.24)	
9-11th grade	284 (13.60)	181 (13.62)	92 (12.61)	11 (26.51)	
High school graduate/GED or equivalent	394 (26.08)	260 (25.40)	126 (27.62)	8 (24.46)	
Some college or AA degree	468 (30.82)	304 (32.14)	150 (27.70)	14 (35.09)	
College graduate or above	246 (17.55)	156 (16.43)	87 (20.89)	3 (4.70)	
Marital status, n (%)					0.045
Married	883 (54.30)	554 (52.79)	305 (57.17)	24 (58.54)	
Widowed	322 (16.73)	208 (15.31)	109 (20.24)	5 (10.12)	
Divorced	229 (12.81)	164 (14.21)	62 (10.08)	3 (9.41)	
Separated	70 (3.22)	51 (3.90)	18 (1.90)	1 (1.71)	
Never married	151 (8.19)	101 (8.44)	42 (6.85)	8 (19.11)	
Living with partner	59 (4.76)	41 (5.36)	17 (3.76)	1 (1.11)	
Smoking, n (%)					0.936
Yes	881 (53.20)	547 (52.88)	306 (53.69)	28 (56.03)	
No	833 (46.80)	572 (47.12)	247 (46.31)	14 (43.97)	
Alcohol drinking, n (%)					0.333
Yes	1540 (91.29)	1004 (90.90)	503 (92.60)	33 (84.63)	
No	38 (2.55)	26 (2.95)	11 (1.70)	1 (2.31)	
Unknown	136 (6.16)	89 (6.15)	39 (5.69)	8 (13.06)	
Hypertension, n (%)					0.020
No	119 (6.59)	93 (8.02)	24 (3.78)	2 (3.82)	
Yes	1595 (93.41)	1026 (91.98)	529 (96.22)	40 (96.18)	
Hyperlipidemia, n (%)					0.497
No	170 (9.74)	103 (9.02)	62 (11.15)	5 (11.50)	
Yes	1544 (90.26)	1016 (90.98)	491 (88.85)	37 (88.50)	
CVD, n (%)					<0.001
No	1100 (65.66)	772 (70.57)	307 (56.14)	21 (53.45)	

Variables	Total (n=1714)	Normal nutrition group (n=1119)	Mild malnutrition group (n=553)	Moderate and severe malnutrition group (n=42)	*P*
Yes	614 (34.34)	347 (29.43)	246 (43.86)	21 (46.55)	
DR					
Yes	366 (19.66)	200 (15.34)	146 (27.26)	20 (41.02)	
No	982 (59.14)	632 (58.95)	328 (59.54)	22 (58.98)	
Unknown	366 (21.21)	287 (25.71)	79 (13.21)	0 (0.00)	
PIR, n (%)					0.010
<1	395 (18.06)	281 (19.97)	102 (13.51)	12 (24.77)	
≥1	1134 (73.82)	720 (73.01)	388 (75.82)	26 (70.07)	
Unknown	185 (8.12)	118 (7.02)	63 (10.67)	4 (5.16)	
Physical activity, MET·min/week, Mean (SE)	599.37 (60.08)	570.24 (56.84)	692.50 (145.60)	171.77 (60.48)	<0.001
Fasting glucose, mmol/L, Mean (SE)	9.05 (0.12)	9.12 (0.16)	8.74 (0.25)	10.94 (1.15)	0.116
Antidiabetics, n (%)					<0.001
No	475 (27.45)	352 (32.50)	117 (18.18)	6 (7.65)	
Only hypoglycemic drugs	744 (44.89)	480 (43.55)	252 (48.56)	12 (33.65)	
Hypoglycemic drugs and insulin	495 (27.66)	287 (23.95)	184 (33.26)	24 (58.70)	
Diuretics, n (%)					0.018
No	1058 (64.86)	735 (67.81)	303 (59.04)	20 (59.02)	
Yes	656 (35.14)	384 (32.19)	250 (40.96)	22 (40.98)	
ACEI, n (%)					0.217
No	1097 (62.93)	730 (64.11)	336 (59.58)	31 (74.22)	
Yes	617 (37.07)	389 (35.89)	217 (40.42)	11 (25.78)	
UACR, Mean (SE)	340.37 (27.07)	248.63 (19.72)	487.57 (67.58)	988.80 (303.05)	<0.001
Uric acid, umol/L, Mean (SE)	364.70 (3.06)	359.44 (4.35)	374.75 (4.94)	379.87 (16.61)	0.053
Energy, kcal, Mean (SE)	1882.16 (31.19)	1953.27 (38.80)	1730.46 (43.77)	1893.24 (196.87)	<0.001
Protein, gm, Mean (SE)	74.85 (1.54)	77.45 (1.90)	69.16 (2.06)	77.25 (9.40)	0.011
Carbohydrate, gm, Mean (SE)	219.56 (3.86)	228.00 (4.65)	202.07 (5.66)	213.54 (25.53)	0.001
Total fat, gm, Mean (SE)	75.91 (1.43)	78.64 (2.00)	69.68 (2.13)	82.12 (9.11)	0.016
Sodium, mg, Mean (SE)	3271.95 (58.59)	3377.27 (81.96)	3049.20 (89.43)	3262.00 (422.12)	0.052
Potassium, mg, Mean (SE)	2435.63 (48.19)	2494.87 (50.47)	2306.80 (73.44)	2478.21 (294.46)	0.058
eGFR, mL/min/1.73 m^2, Mean (SE)	74.70 (1.07)	81.44 (1.18)	61.66 (1.38)	57.49 (4.56)	<0.001
Follow-up time, months, Mean (SE)	58.23 (1.29)	60.71 (1.70)	54.35 (1.75)	39.49 (6.60)	0.002
Vital status, n (%)					<0.001
Alive	1241 (74.31)	868 (78.42)	358 (68.05)	15 (40.82)	
CVD-related death	177 (9.56)	89 (7.66)	78 (12.89)	10 (19.26)	
Diabetes-related death	40 (2.61)	22 (2.24)	16 (3.42)	2 (2.18)	

Variables	Total (n=1714)	Normal nutrition (n=1119)	Mild malnutrition group (n=553)	Moderate and severe malnutrition group (n=42)	*P*
Nephropathy-related death	18 (1.11)	11 (1.23)	6 (0.84)	1 (1.22)	
Other cause-related death	238 (12.41)	129 (10.45)	95 (14.80)	14 (36.52)	

The included patients were divided into three groups according to the CONUT score: normal nutrition group (a score of 0-1), mild malnutrition group (a score of 2-4), and moderate and severe malnutrition group (a score of 5-12).

DKD, diabetic kidney disease; CONUT, Controlling Nutritional Status; BMI, body mass index; GED, general education development; AA, associate; CVD, cardiovascular disease; DR, diabetic retinopathy; PIR, poverty income ratio; MET, metabolic equivalent; ACEI, angiotensin-converting enzyme inhibitor; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; SE, standard error.

Supplementary Table 3 Association between the CONUT score and mortality in DKD patients.

Variables	Model 1		Model 2	
	HR (95%CI)	*P*	HR (95%CI)	*P*
All-cause mortality				
COUNT (continuous)	1.53 (1.37-1.71)	<0.001	1.30 (1.15-1.46)	<0.001
COUNT				
0-1	Ref		Ref	
2-4	1.68 (1.31-2.16)	<0.001	1.12 (0.91-1.37)	0.290
5-12	4.48 (2.41-8.36)	<0.001	2.80 (1.42-5.51)	0.003
CVD-related mortality				
COUNT (continuous)	1.07 (0.93-1.23)	0.323	1.07 (0.92-1.24)	0.381
COUNT				
0-1	Ref		Ref	
2-4	0.95 (0.74-1.23)	0.723	0.94 (0.71-1.24)	0.656
5-12	1.82 (0.84-3.94)	0.131	1.67 (0.82-3.39)	0.159
Diabetes-related mortality				
COUNT (continuous)	1.10 (0.99-1.21)	0.066	1.09 (0.98-1.22)	0.099
COUNT				
0-1	Ref		Ref	
2-4	1.01 (0.83-1.24)	0.904	1.00 (0.80-1.24)	0.995
5-12	1.90 (1.10-3.28)	0.022	1.78 (1.02-3.11)	0.041
Kidney disease-cause mortality				
COUNT (continuous)	1.10 (0.99-1.22)	0.076	1.13 (1.00-1.27)	0.051
COUNT				
0-1	Ref		Ref	
2-4	1.05 (0.84-1.31)	0.655	1.09 (0.85-1.38)	0.500
5-12	1.84 (1.07-3.17)	0.026	1.84 (1.04-3.24)	0.036
Other cause				
COUNT (continuous)	1.56 (1.35-1.80)	<0.001	1.54 (1.31-1.82)	<0.001
COUNT				
0-1	Ref		Ref	
2-4	1.60 (1.15-2.22)	0.005	1.24 (0.91-1.68)	0.167
5-12	5.54 (2.45-12.53)	<0.001	6.54 (3.18-13.45)	<0.001

Model 1, a univariate model;

Model 2: a multivariate model adjusted for age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetic, diuretic, UACR, uric acid, energy, protein, total fat, sodium, and eGFR.

DKD, diabetic kidney disease; CONUT, Controlling Nutritional Status; CVD, cardiovascular disease; DR, diabetic retinopathy; PIR, poverty income ratio; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; Ref: reference.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	10-11
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
		(b) Give reasons for non-participation at each stage	11-12
		(c) Consider use of a flow diagram	11-12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	11-12
		(c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of the Controlling Nutritional Status (CONUT) score with all-cause and cause-specific mortality in patients with diabetic kidney disease: evidence from the NHANES 2009-2018

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Abstract

Objective: To investigate the association between the Controlling Nutritional Status (CONUT) score and all-cause and cause-specific mortality in patients with diabetic kidney disease (DKD).

Design: A retrospective cohort study.

Setting and participants: Data on DKD patients from the National Health and Nutrition Examination Survey (NHANES) 2009-2018.

Primary and secondary outcome measures: All-cause mortality, CVD-related mortality, diabetes-related mortality, and nephropathy-related mortality.

Results: A total of 1714 patients were included, with 1119 (65.29%) in normal nutrition group (a score of 0-1), 553 (32.26%) in mild malnutrition group (a score of 2-4), and 42 (2.45%) in moderate and severe malnutrition group (a score of 5-12), according to the CONUT score. After controlling for age, race, marital status, smoking, hypertension, CVD, DR, poverty income ratio (PIR), antidiabetics, diuretics, urinary albumin to creatinine ratio (UACR), uric acid, energy, protein, total fat, sodium, and estimated glomerular filtration rate (eGFR), a higher CONUT score was associated with a significantly greater risk of all-cause death [hazard ratio (HR)=1.30, 95% confidence level (CI): 1.15-1.46, P<0.001]. In contrast to patients with a CONUT score of 0-1, those who scored 5-12 had significantly increased risks of all-cause death (HR=2.80, 95%CI: 1.42-5.51, P=0.003), diabetes-related death (HR=1.78, 95%CI: 1.02-3.11, P=0.041) and nephropathy-related death (HR=1.84, 95%CI: 1.04-3.24, P=0.036).

Conclusion: Moderate and severe malnutrition was associated with greater risks of all-

cause death, diabetes-related death and nephropathy-related death than normal nutritional status in DKD. Close monitoring of immuno-nutritional status in DKD patients may help prognosis management and improvement.

Keywords: CONUT score, immuno-nutritional status, mortality, diabetic kidney disease, NHANES

Strengths and limitations of this study

- A nationally representative sample was employed to probe into the association between the CONUT score and the risk of all-cause and cause-specific mortality in patients with DKD.
- The association between the CONUT score and the risk of mortality was further assessed in different sex, CVD and DR subpopulations.
- The diagnosis of DKD was based on a single measurement of eGFR and UACR, rather than continuous observation for 3 months.
- Some possible confounding factors, such as treatment during follow-up, have not been adjusted for in this analysis.
- This research was conducted using the data from the American population, which may affect the applicability of the findings to other populations.

Introduction

Diabetes mellitus is a common metabolic disease, affecting about 537 million people worldwide [1], and type 2 diabetes (T2DM) accounts for more than 90% of diabetic cases, which can lead to microvascular and macrovascular complications [2]. Diabetic kidney disease (DKD) is a main microvascular complication of diabetes [3], which occurs in 30-40% of diabetic patients. DKD is the major cause of end-stage renal disease (ESRD), and is associated with a high risk of death, resulting in a serious disease burden [4, 5]. Thus, investigating effective prognostic markers has important clinical significance for stratified risk management and mortality reduction in DKD.

Recent evidence suggests that DKD is a metabolic-driven immunological disease, with pathological mechanisms involving multiple aspects such as metabolism and inflammation [6]. The Controlling Nutritional Status (CONUT) score is a commonly used immuno-nutritional marker that reflects chronic inflammation, immune status, and nutritional status in individuals, evaluated jointly by total cholesterol, serum albumin and lymphocyte count [7, 8]. Mineoka et al. [9] reported that a high CONUT score was associated with a greater risk of diabetic foot. In addition, an association was found between malnutrition assessed by the CONUT score and an elevated risk of all-cause mortality among diabetic patients [10]. According to a previous study, the CONUT score was significantly correlated with the risk of all-cause death in individuals with chronic kidney disease (CKD) who initiated dialysis [11]. Nevertheless, the relationship between the CONUT score and the risk of mortality in DKD patients is still unknown.

The objective of this study was to probe into the association between the CONUT

score and all-cause and cause-specific mortality among patients with DKD, based on the data from the National Health and Nutrition Examination Survey (NHANES) 2009-2018. Subgroup analysis was conducted in terms of sex, cardiovascular disease (CVD) and diabetic retinopathy (DR) to assess whether the association varied among different subpopulations.

Methods

Patient and Public Involvement statement

No patients involved.

Study population

This retrospective cohort study extracted data on DKD patients from 5 cycles (2009-2010, 2011-2012, 2013-2014, 2015-2016, 2017-2018) of the NHANES. The NHANES is a series of studies designed to evaluate the health and nutritional status of the nationally representative, non-institutionalized population in the United States. The survey combines interviews and physical examinations, and is approved by the National Center for Health Statistics (NCHS) Research [12]. The requirement of ethical approval for this was waived by the Institutional Review Board of Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, because the data was accessed from NHANES (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Shanxi Bethune Hospital, Shanxi Academy of Medical

Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University due to retrospective nature of the study. The study involved individuals (1) aged ≥ 18 years, (2) diagnosed as DKD, (3) with the assessment of serum albumin, total cholesterol, and total lymphocyte count, and (4) with complete survival data. Individuals without data on (1) follow-up time, or (2) the cause of death were excluded. Patients were followed up from the data of survey participation until December 31, 2019.

Assessment of DKD

Diabetes was defined as a self-reported diabetes diagnosis, use of diabetes medication or insulin, hemoglobin A1c (HbAlc) ≥ 6.5%, or a fasting glucose level ≥ 7.0 mmol/L. CKD was defined as urinary albumin to creatinine ratio (UACR) > 30 mg/g and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 according to the "KDIGO 2021 Guidelines" [13]. The CKD_EPI_Scr equation was applied to calculate eGFR [13, 14]. DKD was defined as CKD combined with diabetes [15, 16].

Calculation of the CONUT score

The CONUT score was calculated with the data on serum albumin, total cholesterol, and total lymphocyte count (obtained from a blood examination), ranging from 0 to 12 [7]. A total score of 0-1 was regarded as normal nutrition, and a score of 2-4, 5-8, and 9-12 in total was defined as mild, moderate, and severe malnutrition, respectively.

Assessment of mortality

Mortality evaluated in this study included all-cause mortality, CVD-related mortality, diabetes-related mortality, and nephropathy-related mortality. All-cause and cause-specific mortality was determined via linkage to the National Death Index (NDI) until December 31, 2019. The 10th revision of the International Classification of Disease (ICD-10) was used to determine the cause of death. All-cause mortality was defined as death from any cause. CVD-related mortality was defined as death from diseases of heart (I00-I09, I11, I13, I20-I51) and cerebrovascular diseases (I60-I69). Diabetes-related mortality was defined as death from diabetes mellitus (E10-E14). Nephropathy-related mortality was defined as death from nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27).

Other variables

We collected information on age (years), gender, race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), Body Mass Index (BMI, kg/cm^2), education level (less than 9th grade, 9-11th grade, high school graduate/general education development (GED) or equivalent, some college or college or associate (AA) degree, college graduate or above), marital status (married, widowed, divorced, separated, never married, living with partner), smoking, alcohol drinking, hypertension, hyperlipidemia, CVD, DR, poverty income ratio (PIR; <1, ≥1, unknown), physical activity (MET·min/week), fasting glucose (mmol/L), antidiabetics (no, only hypoglycemic drugs, hypoglycemic drugs and insulin), diuretics, angiotensin-converting enzyme inhibitor (ACEI), UACR, uric acid (μmol/L), energy (kcal), protein

(gm), carbohydrate (gm), total fat (gm), sodium (mg), potassium (mg), eGFR (mL/min/1.73 m^2), and follow-up time (months). The presence of hypertension and dyslipidemia was determined according to laboratory examination, self-reported medical history and medication history. Hypertension referred to systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or self-reported hypertension, or use of antihypertensive drugs. Dyslipidemia referred to total cholesterol (TC) ≥ 200 mg/dL (5.2 mmol/L), or triglyceride (TG) ≥ 150 mg/dL (1.7 mmol/L), or low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL (3.4 mmol/L), or how-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL (1.0 mmol/L), or self-reported hypercholesterolemia, or receiving lipid-lowering treatment. DR was defined by the question, "has a doctor ever told {you/SP} that diabetes has affected {your/his/her} eyes or that {you/s/he} had retinopathy (ret-in-op-ath-ee)?" Physical activity was converted into energy consumption. Energy consumption (MET·min) = recommended metabolic equivalent (MET) × exercise time of the corresponding activity (min).

Statistical analysis

Continuous data were illustrated as Mean [standard error (SE)], and the weighted t test was used for inter-group comparisons; categorical data were reported as the number of cases and constituent ratio [n (%)], and comparisons between groups were conducted using the χ^2 test. Continuous data were standardized. Missing data were filled with multiple imputation, and sensitivity analysis was performed for data before and after

the imputation (Supplementary Table 1).

The included patients were divided into three groups according to the CONUT score: normal nutrition group (a score of 0-1), mild malnutrition group (a score of 2-4), and moderate and severe malnutrition group (a score of 5-12). Univariate weighted Cox regression was employed to screen covariates, and examine the association between the CONUT score and mortality. Multivariate weighted Cox regression was utilized to further explore the association between the CONUT score and mortality, with adjustment for age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetics, diuretics, UACR, uric acid, energy, protein, total fat, sodium, and eGFR. Subgroup analysis was carried out based on sex, CVD and DR to assess whether the association between the CONUT score and mortality was different in subpopulations, and the controlled covariates were selected through new univariate weighted Cox regression models. Hazard ratios (HRs) and 95% confidence levels (CIs) were calculated.

Data extraction and cleaning were completed by SAS 9.4 (SAS Institute Inc., Cary, NC, USA). R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) was adopted for statistical analysis. A difference was regarded as significantly different when a P value < 0.05.

Results

Characteristics of the study population

From the NHANES 2009-2018, 1723 patients with DKD were enrolled. After

excluding patients less than 18 years (n=3), and without information on the CONUT score (n=3) and follow-up time (n=3), a total of 1714 patients were eligible for this study. Figure 1 demonstrates the selection process of eligible patients. According to the CONUT score, the number of patients in normal nutrition group, mild malnutrition group, and moderate and severe malnutrition group was 1119 (65.29%), 553 (32.26%), and 42 (2.45%), respectively. The mean age of these patients was 64.08 years. Most of the patients were non-Hispanic White people (59.62%), and were married (54.30%). The average follow-up time was 58.23 months. The characteristics of the included DKD patients are presented in Table 1. Significant differences were found among the three groups in age, gender, race, BMI, marital status, hypertension, CVD, PIR, physical activity, antidiabetics, diuretics, UACR, energy, protein, carbohydrate, total fat, eGFR, follow-up time, and vital status (all P<0.05).

Table 1 Characteristics of the included DKD patients.

Variables	Total (n=1714)	Normal nutrition group (n=1119)	Mild malnutrition group (n=553)	Moderate and severe malnutrition group (n=42)	*P*
Age, years, Mean (SE)	64.08 (0.47)	61.69 (0.60)	68.92 (0.67)	67.02 (2.14)	<0.001
Gender, n (%)					<0.001
Male	952 (53.86)	549 (47.78)	371 (65.17)	32 (75.56)	
Female	762 (46.14)	570 (52.22)	182 (34.83)	10 (24.44)	
Race, n (%)					<0.001
Mexican American	298 (10.61)	213 (12.27)	81 (7.48)	4 (5.04)	
Other Hispanic	172 (5.75)	130 (6.81)	38 (3.60)	4 (4.42)	
Non-Hispanic White	623 (59.62)	367 (56.41)	238 (66.17)	18 (63.00)	
Non-Hispanic Black	416 (14.36)	281 (15.10)	124 (12.91)	11 (12.65)	
Other race - including multi-racial	205 (9.67)	128 (9.41)	72 (9.83)	5 (14.90)	
BMI, kg/cm^2, Mean (SE)	33.04 (0.29)	33.60 (0.38)	31.97 (0.38)	31.60 (1.90)	0.020
Education level, n (%)					0.161
Less than 9th grade	322 (11.95)	218 (12.41)	98 (11.18)	6 (9.24)	

Variables	Total (n=1714)	Normal nutrition group (n=1119)	Mild malnutrition group (n=553)	Moderate and severe malnutrition group (n=42)	*P*
9-11th grade	284 (13.60)	181 (13.62)	92 (12.61)	11 (26.51)	
High school graduate/GED or equivalent	394 (26.08)	260 (25.40)	126 (27.62)	8 (24.46)	
Some college or AA degree	468 (30.82)	304 (32.14)	150 (27.70)	14 (35.09)	
College graduate or above	246 (17.55)	156 (16.43)	87 (20.89)	3 (4.70)	
Marital status, n (%)					0.045
Married	883 (54.30)	554 (52.79)	305 (57.17)	24 (58.54)	
Widowed	322 (16.73)	208 (15.31)	109 (20.24)	5 (10.12)	
Divorced	229 (12.81)	164 (14.21)	62 (10.08)	3 (9.41)	
Separated	70 (3.22)	51 (3.90)	18 (1.90)	1 (1.71)	
Never married	151 (8.19)	101 (8.44)	42 (6.85)	8 (19.11)	
Living with partner	59 (4.76)	41 (5.36)	17 (3.76)	1 (1.11)	
Smoking, n (%)					0.936
Yes	881 (53.20)	547 (52.88)	306 (53.69)	28 (56.03)	
No	833 (46.80)	572 (47.12)	247 (46.31)	14 (43.97)	
Alcohol drinking, n (%)					0.333
Yes	1540 (91.29)	1004 (90.90)	503 (92.60)	33 (84.63)	
No	38 (2.55)	26 (2.95)	11 (1.70)	1 (2.31)	
Unknown	136 (6.16)	89 (6.15)	39 (5.69)	8 (13.06)	
Hypertension, n (%)					0.020
No	119 (6.59)	93 (8.02)	24 (3.78)	2 (3.82)	
Yes	1595 (93.41)	1026 (91.98)	529 (96.22)	40 (96.18)	
Hyperlipidemia, n (%)					0.497
No	170 (9.74)	103 (9.02)	62 (11.15)	5 (11.50)	
Yes	1544 (90.26)	1016 (90.98)	491 (88.85)	37 (88.50)	
CVD, n (%)					<0.001
No	1100 (65.66)	772 (70.57)	307 (56.14)	21 (53.45)	
Yes	614 (34.34)	347 (29.43)	246 (43.86)	21 (46.55)	
DR					
Yes	366 (19.66)	200 (15.34)	146 (27.26)	20 (41.02)	
No	982 (59.14)	632 (58.95)	328 (59.54)	22 (58.98)	
Unknown	366 (21.21)	287 (25.71)	79 (13.21)	0 (0.00)	
PIR, n (%)					0.010
<1	395 (18.06)	281 (19.97)	102 (13.51)	12 (24.77)	
≥1	1134 (73.82)	720 (73.01)	388 (75.82)	26 (70.07)	
Unknown	185 (8.12)	118 (7.02)	63 (10.67)	4 (5.16)	
Physical activity, MET·min/week, Mean (SE)	599.37 (60.08)	570.24 (56.84)	692.50 (145.60)	171.77 (60.48)	<0.001
Fasting glucose, mmol/L, Mean (SE)	9.05 (0.12)	9.12 (0.16)	8.74 (0.25)	10.94 (1.15)	0.116
Antidiabetics, n (%)					<0.001
No	475 (27.45)	352 (32.50)	117 (18.18)	6 (7.65)	

Variables	Total (n=1714)	Normal nutrition group (n=1119)	Mild malnutrition group (n=553)	Moderate and severe malnutrition group (n=42)	*P*
Only hypoglycemic drugs	744 (44.89)	480 (43.55)	252 (48.56)	12 (33.65)	
Hypoglycemic drugs and insulin	495 (27.66)	287 (23.95)	184 (33.26)	24 (58.70)	
Diuretics, n (%)					0.018
No	1058 (64.86)	735 (67.81)	303 (59.04)	20 (59.02)	
Yes	656 (35.14)	384 (32.19)	250 (40.96)	22 (40.98)	
ACEI, n (%)					0.217
No	1097 (62.93)	730 (64.11)	336 (59.58)	31 (74.22)	
Yes	617 (37.07)	389 (35.89)	217 (40.42)	11 (25.78)	
UACR, Mean (SE)	340.37 (27.07)	248.63 (19.72)	487.57 (67.58)	988.80 (303.05)	<0.001
Uric acid, umol/L, Mean (SE)	364.70 (3.06)	359.44 (4.35)	374.75 (4.94)	379.87 (16.61)	0.053
Energy, kcal, Mean (SE)	1882.16 (31.19)	1953.27 (38.80)	1730.46 (43.77)	1893.24 (196.87)	<0.001
Protein, gm, Mean (SE)	74.85 (1.54)	77.45 (1.90)	69.16 (2.06)	77.25 (9.40)	0.011
Carbohydrate, gm, Mean (SE)	219.56 (3.86)	228.00 (4.65)	202.07 (5.66)	213.54 (25.53)	0.001
Total fat, gm, Mean (SE)	75.91 (1.43)	78.64 (2.00)	69.68 (2.13)	82.12 (9.11)	0.016
Sodium, mg, Mean (SE)	3271.95 (58.59)	3377.27 (81.96)	3049.20 (89.43)	3262.00 (422.12)	0.052
Potassium, mg, Mean (SE)	2435.63 (48.19)	2494.87 (50.47)	2306.80 (73.44)	2478.21 (294.46)	0.058
eGFR, mL/min/1.73 m^2, Mean (SE)	74.70 (1.07)	81.44 (1.18)	61.66 (1.38)	57.49 (4.56)	<0.001
Follow-up time, months, Mean (SE)	58.23 (1.29)	60.71 (1.70)	54.35 (1.75)	39.49 (6.60)	0.002
Vital status, n (%)					<0.001
Alive	1241 (74.31)	868 (78.42)	358 (68.05)	15 (40.82)	
CVD-related death	177 (9.56)	89 (7.66)	78 (12.89)	10 (19.26)	
Diabetes-related death	40 (2.61)	22 (2.24)	16 (3.42)	2 (2.18)	
Nephropathy-related death	18 (1.11)	11 (1.23)	6 (0.84)	1 (1.22)	
Other cause-related death	238 (12.41)	129 (10.45)	95 (14.80)	14 (36.52)	

The included patients were divided into three groups according to the CONUT score: normal nutrition group (a score of 0-1), mild malnutrition group (a score of 2-4), and moderate and severe malnutrition group (a score of 5-12).

DKD, diabetic kidney disease; CONUT, Controlling Nutritional Status; BMI, body mass index; GED, general education development; AA, associate; CVD, cardiovascular disease; DR, diabetic retinopathy; PIR, poverty income ratio; MET, metabolic equivalent; ACEI, angiotensin-converting enzyme inhibitor; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; SE, standard error.

Association between the CONUT score and mortality

The univariate analysis showed that patients with an increased CONUT score had a

significantly higher risk of all-cause death (HR=1.53, 95%CI: 1.37-1.71, *P*<0.001) and other cause-related death (HR=1.56, 95%CI: 1.35-1.80, *P*<0.001). Compared with a CONUT score of 0-1, a CONUT score of 2-4 was associated with a significantly greater risk of all-cause death (HR=1.68, 95%CI: 1.31-2.16, *P*<0.001) and other cause-related death (HR=1.60, 95%CI: 1.15-2.22, *P*=0.005), and a CONUT score of 5-12 was associated with a significantly elevated risk of all-cause death (HR=4.48, 95%CI: 2.41-8.36, *P*<0.001), diabetes-related death (HR=1.90, 95%CI: 1.10-3.28, *P*=0.022), nephropathy-related death (HR=1.84, 95%CI: 1.07-3.17, *P*=0.026), and other cause-related death (HR=5.54, 95%CI: 2.45-12.53, *P*<0.001). After controlling for age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetics, diuretics, UACR, uric acid, energy, protein, total fat, sodium, and eGFR, a higher CONUT score was associated with a significantly greater risk of all-cause death (HR=1.30, 95%CI: 1.15-1.46, *P*<0.001) and death from other causes (HR=1.54, 95%CI: 1.31-1.82, *P*<0.001). In contrast to patients with a CONUT score of 0-1, those who scored 5-12 had a significantly increased risk of all-cause death (HR=2.80, 95%CI: 1.42-5.51, *P*=0.003), diabetes-related death (HR=1.78, 95%CI: 1.02-3.11, *P*=0.041), nephropathy-related death (HR=1.84, 95%CI: 1.04-3.24, *P*=0.036), and other cause-related death (HR=6.54, 95%CI: 3.18-13.45, *P*<0.001) (Table 2).

Table 2 Association between the CONUT score and mortality in DKD patients.

Variables	Model 1		Model 2	
	HR (95%CI)	*P*	HR (95%CI)	*P*
All-cause mortality				
COUNT (continuous)	1.53 (1.37-1.71)	<0.001	1.30 (1.15-1.46)	<0.001
COUNT				

0-1	Ref		Ref	
2-4	1.68 (1.31-2.16)	<0.001	1.12 (0.91-1.37)	0.290
5-12	4.48 (2.41-8.36)	<0.001	2.80 (1.42-5.51)	0.003
CVD-related mortality				
COUNT (continuous)	1.07 (0.93-1.23)	0.323	1.07 (0.92-1.24)	0.381
COUNT				
0-1	Ref		Ref	
2-4	0.95 (0.74-1.23)	0.723	0.94 (0.71-1.24)	0.656
5-12	1.82 (0.84-3.94)	0.131	1.67 (0.82-3.39)	0.159
Diabetes-related mortality				
COUNT (continuous)	1.10 (0.99-1.21)	0.066	1.09 (0.98-1.22)	0.099
COUNT				
0-1	Ref		Ref	
2-4	1.01 (0.83-1.24)	0.904	1.00 (0.80-1.24)	0.995
5-12	1.90 (1.10-3.28)	0.022	1.78 (1.02-3.11)	0.041
Nephropathy-related mortality				
COUNT (continuous)	1.10 (0.99-1.22)	0.076	1.13 (1.00-1.27)	0.051
COUNT				
0-1	Ref		Ref	
2-4	1.05 (0.84-1.31)	0.655	1.09 (0.85-1.38)	0.500
5-12	1.84 (1.07-3.17)	0.026	1.84 (1.04-3.24)	0.036
Other cause-related mortality				
COUNT (continuous)	1.56 (1.35-1.80)	<0.001	1.54 (1.31-1.82)	<0.001
COUNT				
0-1	Ref		Ref	
2-4	1.60 (1.15-2.22)	0.005	1.24 (0.91-1.68)	0.167
5-12	5.54 (2.45-12.53)	<0.001	6.54 (3.18-13.45)	<0.001

Model 1, a univariate model;

Model 2, a multivariate model adjusted for age, race, marital status, smoking, hypertension, CVD, DR, PIR, antidiabetics, diuretics, UACR, uric acid, energy, protein, total fat, sodium, and eGFR.

DKD, diabetic kidney disease; CONUT, Controlling Nutritional Status; CVD, cardiovascular disease; DR, diabetic retinopathy; PIR, poverty income ratio; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; Ref: reference.

Association between the CONUT score and mortality in subpopulations

Sex

For males, compared with a CONUT score of 0-1, a score of 2-4 was associated with a significantly higher risk of all-cause death (HR=1.34, 95%CI: 1.02-1.77, *P*=0.033), and

a score of 5-12 was associated with significantly elevated risks of all-cause death (HR=4.40, 95%CI: 2.52-7.69, *P*<0.001), diabetes-related death (HR=2.53, 95%CI: 1.42-4.49, *P*=0.002), nephropathy-related death (HR=2.50, 95%CI: 1.42-4.39, *P*=0.001), and other cause-related death (HR=5.65, 95%CI: 2.65-12.03, *P*<0.001). For females, no significant differences were found in the risk of death between women with the CONUT scores of 0-1 and 2-4, and between women with the scores of 0-1 and 5-12 (all *P*>0.05) (Supplementary Table 2, Figure 2).

CVD

Patients with CVD who had a CONUT score of 5-12 exhibited significantly greater risks of all-cause death (HR=2.60, 95%CI: 1.41-4.79, *P*=0.002), CVD-related death (HR=3.09, 95%CI: 1.27-7.52, *P*=0.013), diabetes-related death (HR=3.85, 95%CI: 2.07-7.18, *P*<0.001), nephropathy-related death (HR=4.07, 95%CI: 2.18-7.57, *P*<0.001), and other cause-related death (HR=3.76, 95%CI: 1.52-9.30, *P*=0.004) than those who had a score of 0-1. Among patients without CVD, a CONUT score of 5-12 was associated with significantly increased risks of all-cause death (HR=5.29, 95%CI: 2.59-10.81, *P*<0.001) and other cause-related death (HR=6.03, 95%CI: 2.43-14.97, *P*<0.001) than that of 0-1 (Supplementary Table 2, Figure 2).

DR

In patients with DR, a CONUT score of 5-12 was associated with significantly elevated risks of all-cause death (HR=3.74, 95%CI: 1.97-7.08, *P*<0.001), CVD-related death

(HR=2.55, 95%CI: 1.22-5.34, *P*=0.013), diabetes-related death (HR=2.58, 95%CI: 1.37-4.86, *P*=0.003), nephropathy-related death (HR=2.61, 95%CI: 1.39-4.92, *P*=0.003), and other cause-related death (HR=4.76, 95%CI: 2.02-11.21, *P*<0.001), as compared with a score of 0-1. For patients without DR, the risks of all-cause death (HR=3.43, 95%CI: 1.80-6.54, *P*<0.001), nephropathy-related death (HR=2.47, 95%CI: 1.23-4.95, *P*=0.011) and other cause-related death (HR=3.43, 95%CI: 1.34-8.73, *P*=0.010) were significantly higher in those with a CONUT score of 5-12 than those with a score of 0-1 (Supplementary Table 2, Figure 2).

Discussion

The current study investigated the association between the CONUT score and all-cause and cause-specific mortality among patients with DKD, and further assessed the association in different sex, CVD and DR subgroups. It was illustrated that for DKD patients, moderate and severe malnutrition was associated with higher risks of all-cause death, diabetes-related death and nephropathy-related death than normal nutritional status. The association between the CONUT score and mortality varied across different sex, CVD and DR subgroups. These findings may act as evidence for risk stratification management and prognosis improvement in DKD patients.

Malnutrition is a primary issue for patients with chronic diseases. In patients with DKD, malnutrition can exacerbate inflammatory activity and further impair nutrition intake, lowering the quality of life and elevating mortality [17]. Medical nutritional therapy has been proposed for DKD, which is beneficial for health and survival [18].

The CONUT score assesses nutritional status with three objective indicators: serum albumin (protein metabolism), total cholesterol (lipid metabolism), and total lymphocyte count (immune function) [7]. Serum albumin plays an essential role in nutrition maintenance, metabolic transport and plasma colloid osmotic pressure [19]. Hypoalbuminemia was identified a prognostic factor for death in elderly individuals [20]. Sun et al. showed that a reduced level of serum albumin was associated with a greater risk of all-cause mortality in CKD, with the optimum threshold of 4 g/dL [21]. High cholesterol levels, a low-risk factor for undernutrition in the CONUT, were related to all-cause mortality in the general population [22]. As a marker of immunological status, a decline in the total lymphocyte count can reflect susceptibility to infectious diseases, and malnutrition may lead to decreased lymphocyte maturation and circulating lymphocyte counts [11]. In a study by Tojek et al. [23], an association was found between the total lymphocyte count less than 800 mg/L and the highest risk of in-hospital mortality.

With this CONUT score, this study found that compared with normal nutritional status, moderate and severe malnutrition (a score of 2-12) was associated with an increased risk of all-cause mortality. As a dimension of nutritional status assessment, inflammation facilitates the development of DKD [24], possibly through releasing interleukin-1 (IL-1) from monocytes, which might initiate major complications and elevated mortality [25]. Additionally, inflammation is correlated with malnutrition and protein-energy wasting, potentially contributing to mortality in DKD [26]. As regards immune status, infectious complications can be caused by an immunosuppressive state,

which may be associated with morbidity and mortality of DKD patients [27]. In terms of nutritional status, a prior review has indicated that improvement in nutrition plays an important role in mortality among people with CKD [28]. Moderate and severe malnutrition was also identified to be associated with diabetes-related mortality and nephropathy-related mortality. Inflammatory response may facilitate the occurrence of T2DM via inducing insulin resistance, and it can be aggravated in the case of hyperglycemia, promoting long-term complications of diabetes [29], which may contribute to the risk of death. This is a potential explanation for diabetes-related mortality in DKD. Increases in inflammation may also account for mortality due to nephropathy [30]. Additionally, we did not find an association between the nutritional status measured by the CONUT score and CVD-related death. This may be attributed to the relatively small number of patients involved herein. Further, we found that undernourished males had higher risks of all-cause, diabetes-related and nephropathy-related death, while in females, no significant associations were observed between nutritional status and mortality. For patients with CVD or DR, moderate and severe malnutrition was associated with a greater risk of all-cause, CVD-related, diabetes-related, and nephropathy-related death. Among patients without CVD, moderate and severe malnutrition was related to an elevated risk of all-cause death. For patients without DR, those with moderate and severe malnutrition had a higher risk of all-cause and nephropathy-related death. The significantly discrepant association of the CONUT score and mortality between males and females may be attributed to the limited ability of the CONUT score to distinguish between nutritional status in different genders since

the score has no threshold differences in total cholesterol, serum albumin and lymphocyte count between men and women [7]. Besides, biological differences between men and women with DKD may also be contributors, such as sex hormones, kidney hemodynamic function, adiponectin, and oxidative stress [31]. For example, higher levels of adiponectin in women might exert a compensatory action against further progression of DKD [32, 33], and greater degrees of oxidative stress in men than women may be associated with worse prognosis in DKD [34]. Clinicians may provide personalized advice for different subpopulations at a high risk of death. Large-scale studies are warranted to corroborate our findings.

In the current study, a nationally representative sample was employed to probe into the association between the CONUT score and the risk of mortality in patients with DKD for the first time. Close monitoring of immuno-nutritional status and appropriate nutritional care (e.g. dietary regulation) for DKD patients may help improve prognosis. Of note, the indicators required for CONUT score calculation are common and easily obtainable in clinical practice, with high practicality. Several limitations should be mentioned when interpreting our results. First, the diagnosis of DKD was based on a single measurement of eGFR and UACR, rather than continuous observation for 3 months. Second, some possible confounding factors, such as treatment during follow-up, have not been adjusted for in this analysis. Third, this research was conducted using the data from the American population, which may affect the applicability of the findings to other populations.

Conclusion

Compared with normal nutritional status, moderate and severe malnutrition was associated with higher risks of all-cause mortality, diabetes-related mortality and nephropathy-related mortality in DKD. Close attention should be paid to the immuno-nutritional status of DKD patients to promote prognosis management and improvement. These findings need to be confirmed in future studies.

Author contributions HZ and HD designed the study. HZ wrote the manuscript. NL collected, analyzed, and interpreted the data. HZ and HD critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Competing interests None.

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Data availability statement

Data are available in a public, open access repository. Open access data are available on the NHANES website (www.cdc.gov/nchs/nhanes/).

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Figure legends

Figure 1 Flow chart of participant selection.

DKD, diabetic kidney disease; NHANES, National Health and Nutrition Examination Survey; CONUT, Controlling Nutritional Status.

Figure 2 Association between the CONUT score and mortality in subpopulations.

For the male subgroup, age, race, marital status, smoking, hypertension, CVD, physical activity, fasting glucose, diuretics, uric acid, energy, protein, sodium, and eGFR were adjusted for;

For the female subgroup, age, race, BMI, education level, marital status, smoking, CVD, PIR, physical activity, diuretics, uric acid, protein, carbohydrate, and eGFR were adjusted for;

For the subgroup with CVD, age, race, BMI, marital status, smoking, CVD, diuretics, UACR, uric acid, and eGFR were adjusted for;

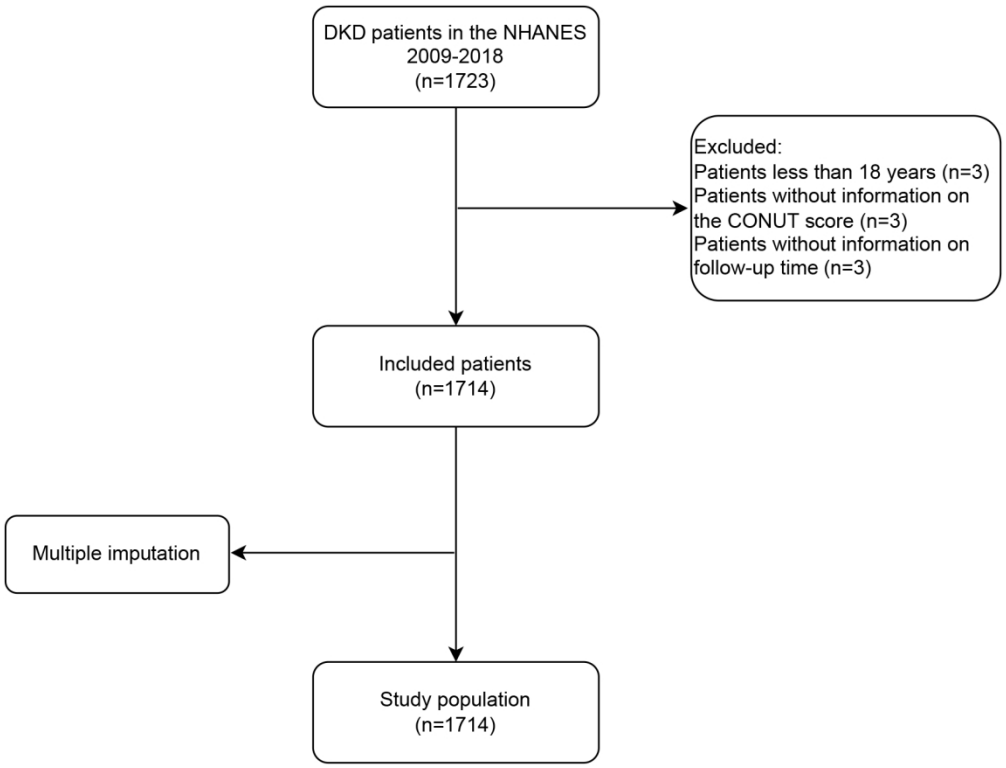
For the subgroup without CVD, age, race, CVD, physical activity, diuretics, uric acid, and eGFR were adjusted for;

For the subgroup with DR, age, gender, race, BMI, marital status, smoking, hyperlipidemia, physical activity, antidiabetics, diuretics, UACR, uric acid, carbohydrate, sodium, and eGFR were adjusted for;

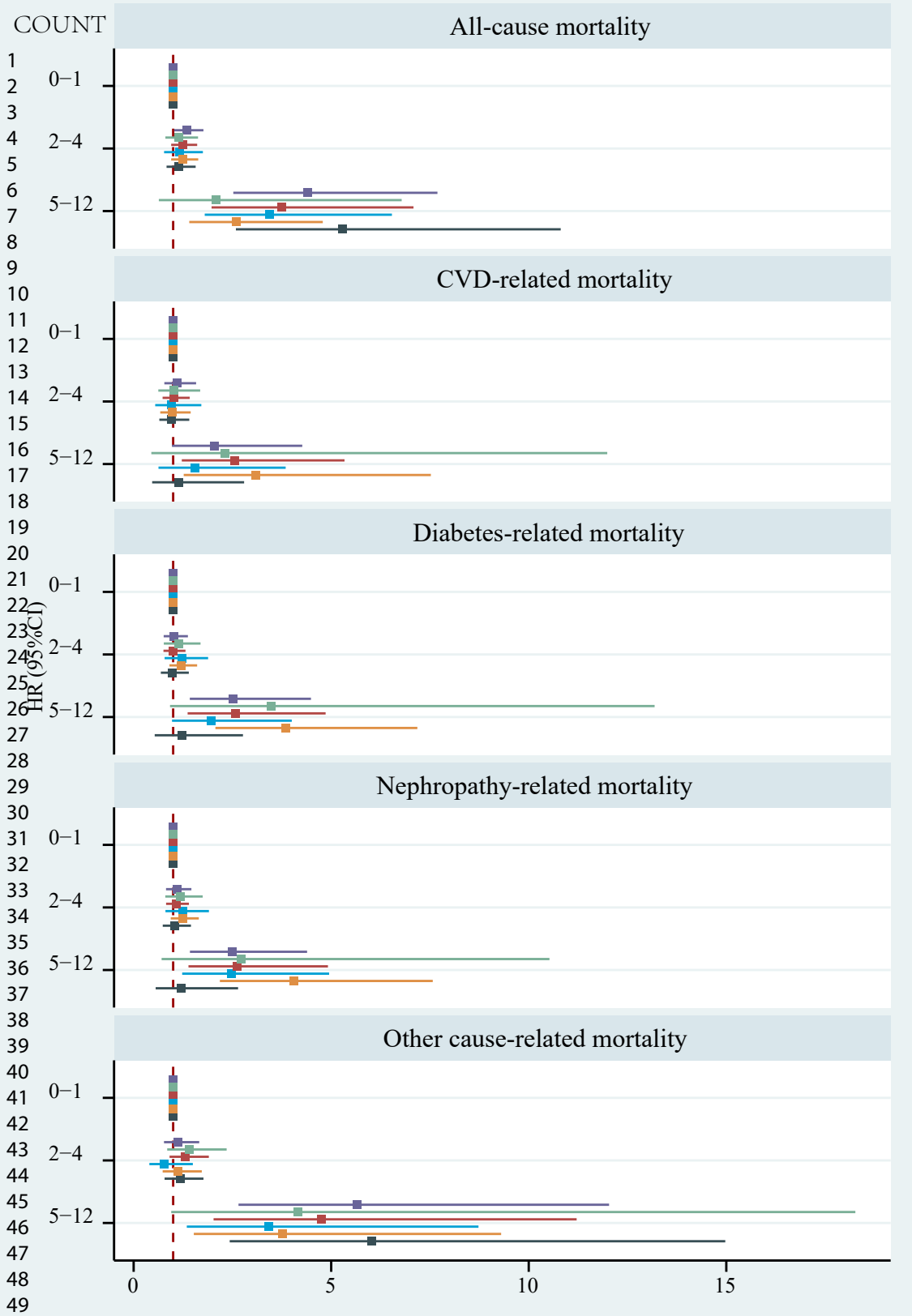
For the subgroup without DR, age, race, marital status, diuretics, uric acid, and eGFR were adjusted for.

BMI, body mass index; CONUT, Controlling Nutritional Status; CVD, cardiovascular

disease; DR, diabetic retinopathy; PIR, poverty income ratio; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; Ref: reference.



150x114mm (300 x 300 DPI)



Supplementary Table 1 Sensitivity analysis for missing data before and after the imputation.

Variables	Total (n=3428)	Post-imputation (n=1714)	Pre-imputation (n=1714)	*P*
BMI, kg/cm^2, Mean (SE)	33.14 (0.29)	33.04 (0.29)	33.24 (0.29)	0.947
Education level, n (%)				0.922
Less than 9th grade	641 (11.86)	322 (11.87)	319 (11.85)	
9-11th grade	569 (13.64)	285 (13.63)	284 (13.65)	
High school graduate/GED or equivalent	785 (26.09)	394 (26.08)	391 (26.10)	
Some college or AA degree	934 (30.89)	468 (30.90)	466 (30.88)	
College graduate or above	488 (17.53)	245 (17.53)	243 (17.53)	
Marital status, n (%)				0.472
Married	1768 (54.37)	887 (54.39)	881 (54.35)	
Widowed	640 (16.69)	320 (16.68)	320 (16.71)	
Divorced	453 (12.77)	227 (12.77)	226 (12.77)	
Separated	140 (3.22)	70 (3.22)	70 (3.23)	
Never married	303 (8.21)	152 (8.21)	151 (8.20)	
Living with partner	116 (4.74)	58 (4.73)	58 (4.74)	
Smoking, n (%)				0.881
Yes	1760 (53.22)	882 (53.22)	878 (53.23)	
No	1661 (46.78)	832 (46.78)	829 (46.77)	
CVD, n (%)				0.113
Yes	2187 (65.57)	1100 (65.45)	1087 (65.69)	
No	1220 (34.43)	614 (34.55)	606 (34.31)	
Energy, kcal, Mean (SE)	1889.72 (30.94)	1889.45 (29.74)	1890.02 (32.68)	0.941
Protein, gm, Mean (SE)	74.54 (1.54)	74.62 (1.48)	74.46 (1.62)	0.634
Carbohydrate, gm, Mean (SE)	221.08 (3.92)	221.07 (3.86)	221.08 (4.05)	0.992
Total fat, gm, Mean (SE)	76.45 (1.46)	76.38 (1.37)	76.52 (1.56)	0.689
Sodium, mg, Mean (SE)	3273.84 (59.64)	3272.01 (58.02)	3275.83 (62.33)	0.802
Potassium, mg, Mean (SE)	2436.29 (47.07)	2435.93 (44.11)	2436.68 (50.76)	0.947

BMI, body mass index; GED, general education development; AA, associate; CVD, cardiovascular disease; SE, standard error.

Supplemental Table 1 Association between the CONUT score and mortality in different sex, CVD and DR subgroups.

Variables	Subgroups											
	Male		Female		CVD		No CVD		DR		No DR	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
All-cause mortality												
COUNT												
0-1	Ref		Ref		Ref		Ref		Ref		Ref	
2-4	1.34 (1.02-1.77)	0.033	1.14 (0.80-1.63)	0.456	1.25 (0.95-1.63)	0.112	1.14 (0.83-1.57)	0.408	1.24 (0.95-1.61)	0.115	1.16 (0.77-1.75)	0.474
5-12	4.40 (2.52-7.69)	<0.001	2.08 (0.64-6.78)	0.225	2.60 (1.41-4.79)	0.002	5.29 (2.59-10.81)	<0.001	3.74 (1.97-7.08)	<0.001	3.43 (1.80-6.54)	<0.001
CVD-related mortality												
COUNT												
0-1	Ref		Ref		Ref		Ref		Ref		Ref	
2-4	1.11 (0.78-1.58)	0.570	1.03 (0.62-1.68)	0.922	0.99 (0.67-1.44)	0.941	0.96 (0.65-1.41)	0.823	1.02 (0.73-1.42)	0.908	0.97 (0.55-1.71)	0.907
5-12	2.04 (0.97-4.27)	0.060	2.32 (0.45-11.99)	0.317	3.09 (1.27-7.52)	0.013	1.14 (0.47-2.80)	0.768	2.85 (1.22-5.34)	0.013	1.56 (0.63-3.85)	0.339
Diabetes-related mortality												
COUNT												
0-1	Ref		Ref									
2-4	1.02 (0.76-1.37)	0.888	1.14 (0.76-1.69)	0.528	1.21 (0.91-1.61)	0.200	0.98 (0.69-1.40)	0.911	1.00 (0.75-1.31)	0.972	1.22 (0.78-1.88)	0.384
5-12	2.53 (1.42-4.49)	0.002	3.48 (0.92-13.19)	0.066	3.85 (2.07-7.18)	<0.001	1.21 (0.53-2.77)	0.645	2.88 (1.37-4.86)	0.003	1.97 (0.97-4.00)	0.060
Nephropathy-related mortality												
COUNT												
0-1	Ref		Ref		Ref		Ref		Ref		Ref	
2-4	1.09 (0.82-1.46)	0.541	1.18 (0.80-1.75)	0.399	1.24 (0.94-1.65)	0.129	1.03 (0.74-1.45)	0.848	1.07 (0.82-1.40)	0.611	1.24 (0.80-1.90)	0.332

	5-12	2.50 (1.42-4.39)	0.001	2.73 (0.71-10.52)	0.145	4.07 (2.18-7.57)	<0.001	1.21 (0.56-2.64)	0.627	2.91 (1.39-4.92)	0.003	2.47 (1.23-4.95)	0.011
Other cause-related mortality COUNT													
	0-1	Ref		Ref		Ref		Ref		Ref		Ref	
	2-4	1.13 (0.77-1.66)	0.537	1.41 (0.85-2.35)	0.183	1.13 (0.73-1.72)	0.588	1.18 (0.78-1.77)	0.434	1.32 (0.91-1.90)	0.146	0.77 (0.40-1.50)	0.444
	5-12	5.65 (2.65-12.03)	<0.001	4.17 (0.95-18.27)	0.058	3.76 (1.52-9.30)	0.004	6.03 (2.43-14.97)	<0.001	4.76 (2.02-11.21)	<0.001	3.43 (1.34-8.73)	0.010

For the male subgroup, age, race, marital status, smoking, hypertension, CVD, physical activity, fasting glucose, diuretics, uric acid, energy, protein, sodium, and eGFR were adjusted for;

For the female subgroup, age, race, BMI, education level, marital status, smoking, CVD, PIR, physical activity, diuretics, uric acid, protein, carbohydrate, and eGFR were adjusted for;

For the subgroup with CVD, age, race, BMI, marital status, smoking, CVD, diuretics, UACR, uric acid, and eGFR were adjusted for;

For the subgroup without CVD, age, race, CVD, physical activity, diuretics, uric acid, and eGFR were adjusted for;

For the subgroup with DR, age, gender, race, BMI, marital status, smoking, hyperlipidemia, physical activity, antidiabetics, diuretics, UACR, uric acid, carbohydrate, sodium, and eGFR were adjusted for;

For the subgroup without DR, age, race, marital status, diuretics, uric acid, and eGFR were adjusted for.

BMI, body mass index; CONUT, Controlling Nutritional Status; CVD, cardiovascular disease; DR, diabetic retinopathy; PIR, poverty income ratio; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; Ref: reference.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	10-11
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
		(b) Give reasons for non-participation at each stage	11-12
		(c) Consider use of a flow diagram	11-12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	11-12
		(c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.