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Diabetology & Metabolic Syndrome (2025) 17:38
https://doi.org/10.1186/s13098-025-01598-8

Diabetology &
Metabolic Syndrome

RESEARCH

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The kidney reabsorption-related magnesium depletion score is associated with cardiovascular disease and longitudinal mortality in diabetic kidney disease patients

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Abstract

Background The kidney reabsorption is essential for maintaining magnesium homeostasis. This study aims to explore the relationship between kidney reabsorption-related magnesium depletion score (MDS) and the occurrence of cardiovascular disease (CVD) and prognosis in diabetic disease kidney (DKD) patients.

Methods We included 3199 DKD patients from the National Health and Nutrition Examination Survey (NHANES) database, including 1072 CVD patients. Weighted logistic regression analysis was used to explore the relationship between MDS and the occurrence of CVD. Weighted COX proportional hazards regression was used to explore the relationship between MDS and mortality. Stratified analysis was used to further validate. Finally, we assessed the predictive accuracy of MDS on survival outcomes in DKD patients using time-dependent receiver operating characteristic (ROC) curve analysis.

Results Survey-weighted multiple logistic regression analysis revealed that MDS ≥ 3, the incidence of CVD increased by 371%. During the follow-up period (median of 87 months), 1373 all-cause deaths (497 cardiovascular deaths) were recorded. In DKD patients, MDS ≥ 3, all-cause mortality increased 78% ($P < 0.001$) and cardiac mortality 76% ($P = 0.08$). Consistent results were also shown when stratified by age, sex, race, marital status, magnesium intake. The area under the curve (AUC) values for predicting 1-,2-,3-,4-, and 5-year mortality using MDS were 0.86, 0.66, 0.59, 0.57, and 0.55, for all-cause mortality and 0.9, 0.67, 0.62, 0.58, and 0.56 for cardiovascular mortality.

Conclusion MDS, kidney reabsorption-related, is positively correlated with the incidence of CVD and longitudinal mortality in DKD patients.

Keywords MDS, Magnesium depletion score, DKD, Mortality, CVD

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Introduction

In the United States, 30 to 50% of cases of end-stage renal disease are caused by diabetic disease kidney (DKD), and it is the main cause of end-stage renal disease, posing a major challenge to public health. [1]. Additionally, the risk of cardiovascular disease (CVD) in patients with diabetes mellitus (DM) is significant [2]. Proactive management of cardiovascular risk is a key aspect of treatment for DKD [2]. Beyond traditional risk factors, mineral deregulation can also contribute to the development of DM [3] and CVD [4].

Magnesium is a vital and abundant mineral essential for health and life, serving as a crucial cofactor for ATP, the primary source of cellular energy [5]. Magnesium also plays a crucial role in regulating vascular tone, myocardial metabolism, and other physiological functions [6, 7]. Higher levels of serum magnesium or magnesium intake were associated with decreased risk of occurrence and prognosis of type 2 DM (T2DM) [3, 8] and CVD [8, 9]. Previous studies have shown that plasma magnesium levels are inversely related to the risk of cardiovascular and metabolic diseases [6]. High prevalence of hypomagnesemia and low intracellular magnesium concentrations among diabetic patients [10]. Cohort studies suggest that hypomagnesemia is associated with an increased risk of all-cause death and cardiovascular mortality in maintenance hemodialysis [11] and T2DM patients [12].

Previous studies have concentrated on the prognostic effects of serum and dietary magnesium but have overlooked the impact of actual magnesium deficiency. Magnesium depletion score (MDS) is a comprehensive scoring tool for the evaluation of magnesium deficiency status. A higher MDS indicates more severe magnesium deficiency. Fan et al. developed the MDS and discovered that higher MDS values were positively correlated with an increased risk of all-cause and cardiovascular mortality [13]. However, there is limited research on the relationship between MDS and the incidence of CVD in DKD. Additionally, the connection between MDS and the prognosis of DKD remains underexplored.

To address the above issues, we conducted research based on the National Health and Nutrition Examination Survey (NHANES). This study aims to explore (1) whether MDS is associated with a higher prevalence of CVD in DKD and (2) whether MDS is associated with an increased risk of all-cause death and CVD death in patients with DKD.

Materials and methods

Data source and study population

The NHANES, conducted by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC) in the United States, was the basis for our study. Our study enrolled patients with DKD spanning from 1999 to 2018. Dietary data were sourced from the Food Patterns Equivalents Database (FPED). NHANES mortality data were obtained from the National Death Index (NDI), with causes of death coded using International Classification of Diseases (ICD) codes.

Part 1: We included participants with DKD from 10 cycles of NHANES (1999–2018). After excluding those with pregnant, 3665 participants with DKD remained. Following further exclusions due to age under 20 (n = 28), lack of MDS (n = 280), lack of eGFR score (n = 153), lack of diuretic score (n = 5), a total of 3199 participants were finally included in the study. And we exclude missing CVD diagnosis (n = 2), missing coronary heart disease (CHD) diagnosis (n = 49), missing congestive heart failure (CHF) diagnosis (n = 19), missing heart attack diagnosis (n = 8), missing stroke diagnosis (n = 6), and missing angina diagnosis (n = 24), 3,091 participants were finally included in the Part 1 (Fig. 1). We explored the cross-sectional association between MDS and CVD in participants with DKD.

Part 2: Subsequently, we excluded 4 individuals with missing survival data among 3199 participants. As of 31 December 2019, 497 cardiovascular deaths and 1,373 all-cause deaths were recorded in 3195 patients with DKD (Fig. 1). The association of MDS and mortality was explored in our study.

Definition of outcomes

Part I: Five self-reported subtypes were used to determine the CVD, including CHF, CHD, angina, heart attack, or stroke [14, 15]. Each respondent aged 20 was asked by a trained interviewer using a standard questionnaire: “Has a doctor or other health professional ever told you that you had CHF/CHD/angina/heart attack/stroke?" Any of the above questions answered yes were diagnosed with CVD.

Part II: The primary outcome is all-cause death and cardiovascular death. CVD mortality was determined by the International Classification of Diseases 10th Edition (ICD-10), including codes I00 to I09, I11, I13, I20 to I51, and I60 to I69. Follow-up time was calculated from the date of the NHANES interview to the date of death or 31 December 2019.

MDS definition

MDS, a clinical indicator for assessing magnesium deficiency in vivo, was calculated by summing the following four scores: 1. Use of diuretics: 1 point for "yes", 0 points for "no". 2. Use of proton pump inhibitors (PPIs): 1 point for "yes", 0 points for "no". 3. Renal function: Estimated glomerular filtration rate (eGFR) of 90 points: 0 points.

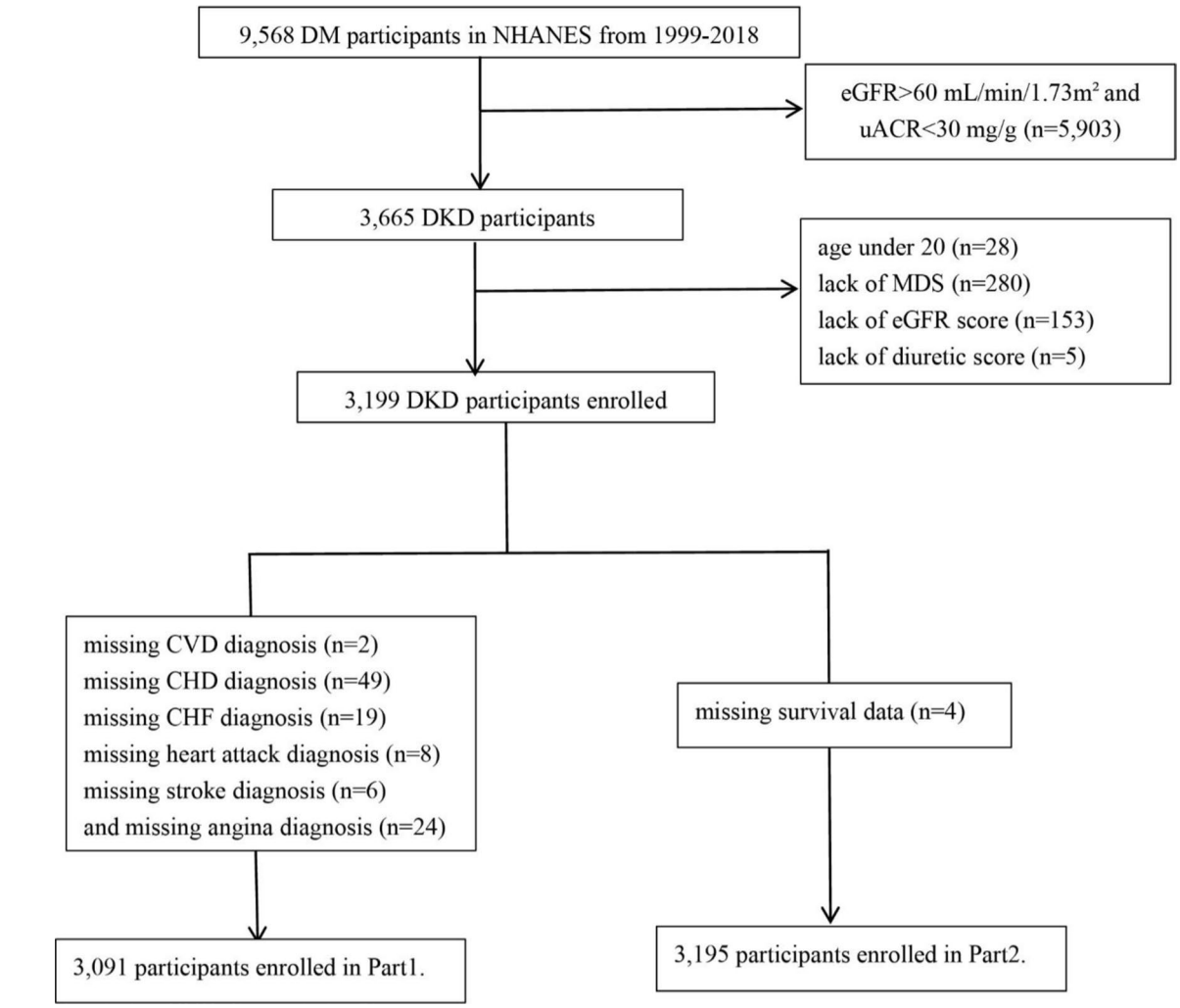

Fig 1. Flowchart of the DKD participants from the National Health and Nutrition Examination Survey 1999 to 2018

1 point for eGFR between 60 and 90 ml/min/1.73 m^2. 2 points for eGFR less than 60 ml/min/1.73 m^2[16]. 4. Heavy drinking: 1 point for consumption greater than 1 cup/day for women and greater than 2 cups/day for men [17]. All other drinking habits (none, mild, moderate) scored zero. In this study, MDS was categorized into four groups: MDS = 0, MDS = 1, MDS = 2, and MDS ≥ 3.

DKD definition

Diabetes Diagnosis: Participants were classified as having diabetes if they met one or more of the following criteria: 1. Self-reported physician diagnosis of diabetes. 2.Use of antidiabetic medications. 3.HbA1c level ≥ 6.5%. Nephropathy Indicators: Evidence of nephropathy was determined by the presence of albuminuria: Albuminuria, defined as a urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g. Reduced kidney function, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, calculated using the CKD-EPI equation. Patients meeting both the diabetes and nephropathy criteria were classified as having DKD.

Covariates

The covariates encompassed demographic characteristics (age, gender, marital status, race or ethnicity, education, household poverty income ratio, and body mass index), lifestyle behaviors (smoking and drinking status), dietary factors (fiber intake, fat intake, magnesium intake, calcium intake, energy intake, and the Healthy Diet Index-2015 (HEI-2015)), comorbidities (hypertension and hyperlipidemia), and laboratory data (glycated hemoglobin A1c [HbA1c], serum creatinine, and urine albumin-to-creatinine ratio (uACR)). Dietary data were collected through a 24-h dietary recall survey.

Hypertension was identified through self-report, use of antihypertensive medications, or systolic/diastolic blood pressure of ≥ 140/90 mmHg. Hyperlipidemia was diagnosed by self-report, triglyceride levels of ≥ 150 mg/dL, total cholesterol levels of ≥ 200 mg/dL, high-density lipoprotein cholesterol levels of > 40 mg/dL in men or > 50 mg/dL in women, or low-density lipoprotein cholesterol levels of ≥ 130 mg/dL. BMI was classified into three categories: BMI < 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2.

Statistical analysis

To ensure national representativeness, this study accounted for the complex sampling design of the NHANES, incorporating sample weighting, clustering, and stratification in all analyses. Baseline characteristics of individuals with DKD were described using weighted means (standard deviation, SD) or medians (interquartile range, IQR) with corresponding confidence intervals (CIs) for continuous variables, and weighted percentages for categorical variables. Group comparisons were conducted with t-tests or Mann–Whitney U tests for continuous variables, and Chi-squared tests or Fisher's exact tests for categorical variables.

To address the issue of missing data, a specialized multilevel approach for survey data was used with the R package "mice" [18]. The "mice" package employs "cart" methods and sets the seed to 1234 to predict the missing values. Each imputed dataset is generated using different random variations or assumptions in the interpolation method. Statistical analysis was then performed using a complete case approach.

To establish the independent correlation between MDS and the risks of CVD in DKD, survey-weighted univariable and multivariable logistic regression analyses were performed. Meanwhile, we explored the possible correlation between composition of MDS (diuretic use, PPI use, alcohol use, eGFR) and incidence of CVD in DKD patients. Furthermore, to investigate the relationship between MDS and the prevalence of five CVD (heart failure, CHD, angina, heart attack, and stroke), a survey-weighted multiple logistic regression analysis was conducted.

Stratified analyses were conducted to examine whether the association between MDS and CVD persisted across different subgroups defined by age, sex, smoking status, body mass index, magnesium intake, and complications.

Weighted Kaplan–Meier curves and log-rank tests were used to assess cumulative survival in different MDS levels. Survey-weighted cox proportional hazards regression analysis examined the relationship between MDS and both all-cause and CVD mortality in multivariable models. Stratified analysis investigated whether the association between MDS and mortality persisted across age, sex, smoking status, body mass index, magnesium intake, and complications. The area under the receiver operating characteristic (ROC) [19] curve (AUC) was used to evaluate the performance of MDS in predicting longitudinal mortality in patients with DKD.

In order to evaluate the robustness of our results, sensitivity analyses were performed. Initially, to account for the relationships between blood lipids, eGFR, and mortality, we adjusted for triglycerides and serum creatinine in the fully adjusted model. Additionally, to reduce potential dietary bias, we used 2-day mean values for calculating dietary data. For the final data analysis, we used interpolated data instead of missing data. Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance defined as a P-value of less than 0.05 in all two-tailed tests.

Result

Relationship between MDS and CVD in DKD

In this study, 3,199 individuals from NHANES were analyzed, with 3,091 were included in the part1 and 3,195 were included in the part2 (Fig. 1). Table 1 detail the main characteristics of those with and without CVD. The MDS level was significantly higher in the CVD group (P < 0.001). Specifically, individuals with CVD had higher usage of diuretics, higher eGFR scores, lower usage of PPIs and fewer alcohol users, compared to those without CVD. Additionally, the CVD group was older, predominantly white, couple, former smokers, higher rates of hypertension, lower levels of family income, and consumed less magnesium. Conversely, triglyceride and total cholesterol levels were notably lower in the CVD group with higher hyperlipidemia, likely due to the use of lipid-lowering medications.

Survey-weighted multivariate logistic regression models illustrate the relationship between MDS (its individual measures) and incidence of CVD risk (Table 2). After adjusting for confounding factors, compared to MDS = 0, individuals with MDS levels 1, 2, and ≥ 3 had odds ratios of 1.89 (95% CI 1.15–3.11), 2.43 (95% CI 1.52–3.9) and 4.71 (95% CI 2.88–7.7) (P < 0.05). Among the components of MDS, diuretic use and renal dysfunction (eGFR < 90 mL/min/1.73 m^2) were positively associated with a higher risk of CVD. However, PPI use and heavy drinking did not show a statistically significant association with CVD after adjusting for confounding variables.

Table 3 demonstrated the relationship between MDS and the 5 specific CVD risks. After adjusting for all covariates, participants with MDS ≥ 3 were significantly associated with higher CHF, CHD, angina, heart attack

Table 1 Participant Characteristics in NHANES 1999 to 2018, Weighted (Participants = 3091, CVD cases = 1072)

Variable	Total	Non-CVD	CVD	*P*-value
Age, year	63.98(63.29,64.67)	61.15(60.26,62.04)	69.53(68.79,70.26)	< 0.0001
< 60	33.93(30.65,37.20)	43.56(40.25,46.87)	15.02(12.41,17.63)	
≥ 60	66.07(61.37,70.78)	56.44(53.13,59.75)	84.98(82.37,87.59)	
Gender (%)				0.97
Male	51.30(47.20,55.39)	51.26(48.22,54.30)	51.37(47.29,55.44)	
Female	48.70(45.08,52.32)	48.74(45.70,51.78)	48.63(44.56,52.71)	
Ethnicity (%)				< 0.0001
Mexican American	8.62(7.02,10.23)	10.48(8.42,12.54)	4.98(3.51, 6.44)	
White	63.47(57.41,69.54)	58.84(55.08,62.61)	72.56(69.68,75.43)	
Black	14.62(13.03,16.21)	15.20(13.11,17.28)	13.49(11.15,15.83)	
Other	13.28(11.26,15.31)	15.48(12.90,18.06)	8.97(7.00,10.95)	
BMI, kg/m^2	32.78(32.36,33.19)	32.72(32.23,33.21)	32.90(32.26,33.53)	0.64
< 25 kg/m^2	13.26(11.25,15.28)	13.47(11.55,15.39)	12.85(10.16,15.55)	
25–30 kg/m^2	25.80(23.49,28.12)	26.36(23.91,28.81)	24.71(21.39,28.03)	
≥ 30 kg/m^2	60.93(56.60,65.27)	60.17(57.33,63.01)	62.44(58.72,66.15)	
Education (%)				0.6
< High school graduate	30.01(27.55,32.47)	29.24(26.84,31.64)	31.51(27.87,35.16)	
High school graduate	25.92(23.10,28.73)	25.46(22.17,28.75)	26.82(23.30,30.35)	
Some college or associates degree	29.12(25.91,32.33)	29.70(26.43,32.97)	27.98(24.39,31.57)	
College graduate or above	14.95(12.72,17.18)	15.60(12.82,18.38)	13.68(10.71,16.65)	
Marital (%)				0.02
Couple	58.21(53.52,62.89)	60.21(56.76,63.66)	54.28(50.47,58.09)	
Single	41.79(38.37,45.21)	39.79(36.34,43.24)	45.72(41.91,49.53)	
Family poverty-to-income ratio (%)				0.03
< 1.3	29.06(26.47,31.64)	28.43(25.85,31.01)	30.28(26.74,33.83)	
1.3–3.5	43.56(39.93,47.19)	42.04(38.91,45.18)	46.54(42.53,50.55)	
> 3.5	27.38(23.92,30.84)	29.52(25.98,33.07)	23.18(19.33,27.03)	
Smoking status (%)				0.01
Never	46.40(43.11,49.70)	48.68(45.61,51.75)	41.94(38.08,45.80)	
Former	38.26(34.89,41.63)	35.58(32.65,38.51)	43.52(39.97,47.06)	
Now	15.34(13.28,17.39)	15.74(13.74,17.74)	14.55(11.52,17.58)	
Hypertension (%)				< 0.0001
No	19.48(17.17,21.79)	23.32(20.44,26.20)	11.93(9.58,14.28)	
Yes	80.52(75.22,85.83)	76.68(73.80,79.56)	88.07(85.72,90.42)	
Hyperlipidemia (%)				0.003
No	10.00(8.68,11.32)	11.39(9.58,13.20)	7.28(5.59, 8.97)	
Yes	90.00(84.19,95.81)	88.61(86.80,90.42)	92.72(91.03,94.41)	
Serum glucose, mg.dl	155.51(152.38,158.63)	158.81(154.77,162.86)	149.02(144.02,154.02)	0.004
HbA1c (%)				0.15
HbA1c < 7	53.53(49.32,57.75)	52.23(49.12,55.33)	56.10(51.97,60.22)	
HbA1c ≥ 7	46.47(42.86,50.07)	47.77(44.67,50.88)	43.90(39.78,48.03)	
uACR, mg/g	55.03(26.74,148.99)	54.58(31.25,143.33)	55.22(18.83,161.88)	0.84
uACR (%)				< 0.0001
A1	26.17(23.26,29.07)	23.26(20.80,25.71)	31.89(28.12,35.65)	
A2	57.33(53.01,61.65)	61.54(58.54,64.55)	49.06(44.47,53.65)	
A3	16.50(14.47,18.54)	15.20(13.01,17.39)	19.06(15.62,22.50)	
eGFR, mL/min/1.73m^2	69.56(68.16,70.96)	75.93(74.20,77.66)	57.06(55.41,58.72)	< 0.0001
Albumin, g/L	40.90(40.70,41.10)	41.24(41.01,41.47)	40.23(39.94,40.52)	< 0.0001
Serum creatinine, mg/dl	1.21(1.17,1.25)	1.11(1.06,1.16)	1.41(1.34,1.48)	< 0.0001

Table 1 (continued)

Variable	Total	Non-CVD	CVD	*P*-value
Serum uric acid, mg/dl	6.18(6.10,6.26)	6.01(5.92,6.10)	6.52(6.37,6.67)	< 0.0001
Serum blood urea nitrogen, mg/dl	19.71(19.25,20.18)	18.05(17.50,18.60)	22.98(22.16,23.80)	< 0.0001
Serum sodium, mmol/L	138.82(138.62,139.02)	138.58(138.35,138.82)	139.28(139.01,139.55)	< 0.0001
Serum phosphorus, mg/dl	3.72(3.69,3.75)	3.68(3.64,3.72)	3.79(3.73,3.85)	0.004
Serum calcium, mg/dl	9.45(9.42,9.47)	9.47(9.44,9.50)	9.40(9.37,9.44)	< 0.001
Serum potassium, mmol/L	4.16(4.14,4.19)	4.13(4.10,4.16)	4.23(4.19,4.27)	< 0.0001
Serum bicarbonate, mmol/L	24.86(24.73,24.99)	24.71(24.54,24.88)	25.16(24.98,25.35)	< 0.001
Serum triglycerides, mg/dl	221.45(208.91,233.99)	234.26(216.17,252.35)	196.31(186.84,205.77)	< 0.001
Serum total cholesterol, mg/dl	188.71(186.56,190.87)	194.57(191.66,197.48)	177.21(173.34,181.07)	< 0.0001
Serum hdl cholesterol, mg/dl	47.71(46.83,48.60)	48.17(47.05,49.28)	46.83(45.63,48.02)	0.08
HEI-2015	51.05(50.45,51.64)	50.78(50.00,51.57)	51.57(50.61,52.53)	0.23
Total energy, kcal/day	1823.46(1787.91,1859.00)	1887.71(1841.29,1934.12)	1697.35(1638.25,1756.44)	< 0.0001
Total protein, g/day	74.35(72.71,75.99)	76.85(74.78,78.93)	69.42(66.69,72.15)	< 0.0001
Total carbohydrate, g/day	213.89(209.11,218.67)	219.92(213.73,226.12)	202.04(195.28,208.80)	< 0.001
Total sugars, g/day	90.44(87.37,93.51)	93.05(88.96,97.15)	85.30(81.57,89.03)	0.005
Total dietary fiber, g/day	15.20(14.80,15.60)	15.48(14.99,15.96)	14.65(13.99,15.30)	0.04
Total fat, g/day	73.18(71.36,75.00)	75.82(73.27,78.38)	68.00(64.82,71.18)	< 0.001
Total calcium, mg/day	821.57(795.47,847.66)	843.89(810.87,876.91)	777.75(738.49,817.01)	0.01
Total phosphorus, mg/day	1216.36(1189.38,1243.34)	1251.48(1217.12,1285.85)	1147.42(1102.39,1192.44)	< 0.001
Total magnesium_mg	260.73(254.73,266.73)	267.84(260.01,275.67)	246.78(237.77,255.80)	< 0.001
Insufficient magnesium intake	85.55(80.14,90.97)	84.05(81.59,86.52)	88.50(85.49,91.52)	
Sufficient magnesium intake	14.45(12.31,16.59)	15.95(13.48,18.41)	11.50(8.48,14.51)	
MDS (%)				< 0.0001
0	18.47(16.34,20.59)	25.13(22.56,27.70)	5.39(3.55, 7.23)	
1	20.15(17.44,22.86)	23.30(20.54,26.05)	13.98(10.98,16.98)	
2	28.93(26.20,31.66)	28.29(25.50,31.08)	30.18(26.45,33.91)	
≥ 3	32.46(29.57,35.35)	23.29(21.03,25.54)	50.45(46.53,54.37)	
Score eGFR (%)				< 0.0001
0	28.07(25.18,30.97)	37.03(33.99,40.07)	10.49(8.30,12.69)	
1	23.52(21.12,25.92)	23.13(20.58,25.68)	24.29(21.20,27.37)	
2	48.41(44.69,52.12)	39.84(36.83,42.85)	65.22(62.04,68.40)	
Score diuretic (%)				< 0.0001
0	61.43(57.03,65.84)	69.90(67.41,72.39)	44.81(40.73,48.88)	
1	38.57(35.21,41.93)	30.10(27.61,32.59)	55.19(51.12,59.27)	
Score ppi (%)				< 0.0001
0	83.98(78.90,89.06)	86.58(84.68,88.49)	78.87(75.98,81.76)	
1	16.02(14.08,17.96)	13.42(11.51,15.32)	21.13(18.24,24.02)	
Score drinks (%)				0.002
0	92.83(87.04,98.61)	91.39(89.60,93.18)	95.64(93.97,97.32)	
1	7.17(5.81, 8.54)	8.61(6.82,10.40)	4.36(2.68, 6.03)	

BMI indicates body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; MDS, magnesium depletion score; NHANES, National Health and Nutrition Examination Survey; and PPI, proton pump inhibitor

uACR, urine albumin creatine ratio; A1, < 30 mg/g; A2 30–300 mg/g; A3 > 300 mg/g; Weighted by the full-sample MEC exam. For continuous variables, the survey-weighted quartile was presented. For categorical variables, the survey-weighted percentage (95% CI) was presented

and stroke compared to participants with MDS = 0 (all P for trend < 0.05). Stratified analyses revealed a stable and similar trends between MDS and an increased risk of CVD in all subgroups (Table 4).

Relationship of MDS with mortality among individuals with DKD

A total of 3,195 DKD patients had available follow-up data. During a median follow-up period of 87.2 months, the study identified 1,373 all-cause deaths and 4,97

Table 2 Relationship Between MDS and the Prevalence of Total CVD (Participants = 3 091, CVD cases = 1 072)

	Events	Unadjusted model OR (95% CI)	P	Adjusted model OR (95% CI)	P
Diuretic use	580	2.86(2.36,3.47)	< 0.0001	2.15(1.71,2.70)	< 0.0001
PPI use	246	1.73(1.35,2.21)	< 0.0001	1.25(0.95,1.65)	0.11
Heavy drinking	49	0.48(0.30,0.78)	0.003	0.67(0.40,1.13)	0.13
eGFR[a]					
0 points	115	Reference		Reference	
1 point	269	3.71(2.70,5.09)	< 0.0001	2.01(1.37,2.94)	< 0.001
2 points	688	5.78(4.38,7.61)	< 0.0001	2.87(1.96,4.21)	< 0.0001
P for trend		< 0.0001		< 0.0001	
MDS					
0	57	Reference		Reference	
1	157	2.80(1.74, 4.48)	< 0.0001	1.89(1.15,3.11)	0.01
2	325	4.97(3.29, 7.52)	< 0.0001	2.43(1.52,3.90)	< 0.001
≥ 3	533	10.10(6.78,15.03)	< 0.0001	4.71(2.88,7.70)	< 0.0001
P for trend		< 0.0001		< 0.0001	

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDS, magnesium depletion score; OR, odds ratio; and PPI, proton pump inhibitor

[a] 60 mL/min per 1.73 m^2 ≤ eGFR < 90 mL/min per 1.73 m^2 was scored 1 point, and eGFR < 60 mL/min per 1.73 m^2 was scored 2 points

Adjusted model was adjusted for age, gender, marital, ethnicity, education status, smoking status, drinking status, poverty, obesity, Hypertension, Hyperlipidemia, serum creatinine, ACR (ln-transformed), total cholesterol, triglycerides, dietary magnesium, dietary calcium, total energy intake, dietary phosphorus, HEI-2015, dietary fiber, dietary total fat, serum potassium,

Red color represents P < 0.05

Table 3 Adjusted Odds Ratios for Correlations Between MDS and Individual CVDs (Participants = 3 091, CVD cases = 1 072)

	Congestive heart failure OR (95% CI)	Coronary heart disease OR (95% CI)	Angina pectoris OR (95% CI)	Heart attack OR (95% CI)	Stroke OR (95% CI)
0	Reference	Reference	Reference	Reference	Reference
1	3.80(1.68, 8.62)†	1.80(0.82,3.99)	1.74(0.64, 4.73)	1.21(0.54,2.67)	1.88(0.89,3.98)
2	3.97(1.88, 8.39)‡	1.55(0.69,3.47)	3.11(1.22, 7.93)*	1.87(0.82,4.27)	2.37(1.23,4.57)*
≥ 3	12.60(6.20,25.61)‡	3.19(1.44,7.05)†	4.36(1.65,11.54)†	3.54(1.57,7.96)†	2.94(1.50,5.76)†
P for trend	< 0.0001	< 0.001	< 0.0001	< 0.0001	0.004

Adjusted model was adjusted for age, gender, marital, ethnicity, education status, smoking status, drinking status, poverty, obesity, Hypertension, Hyperlipidemia, serum creatinine, ACR (ln-transformed), total cholesterol, triglycerides, dietary magnesium, dietary calcium, total energy intake, dietary phosphorus, HEI-2015, dietary fiber, dietary total fat, serum potassium

* P < 0.05; †P < 0.01; ‡P < 0.001

CVD deaths. Table S1 shows the baseline characteristics grouped according to the MDS results. The Kaplan–Meier curves describe the survival differences between patients with different MDS levels. For all-cause mortality, the survival rate of the participants with MDS ≥ 3 is the lowest, and the mortality rate increases with the increase of MDS scores (log-rank P < 0.05, Fig. 2A). Figure 2B shows similar results for cardiovascular mortality (log-rank P < 0.05).

Multivariate Cox regression models reveal the relationship of MDS and MDS components with all-cause and CVD mortality (Table 5). After full adjustment, participants with MDS ≥ 3 had all-cause and CVD mortality risk 1.78(95%CI, 1.29–2.47) and 1.76 (95%CI, 0.94–3.28) higher than participants with MDS = 0, but CVD mortality risk did not reach statistical significance. In the multivariate model, for each item of MDS, diuretic use was an independent risk factor. Its cardiovascular mortality and all-cause mortality risk were 1.42 and 1.64 times, respectively. Patients with PPI, alcohol consumption, or renal dysfunction (eGFR < 90 mL/min/1.73 m^2) had higher all-cause and

Table 4 Subgroup Analysis for the Association Between MDS and CVD (Participants = 3 091, CVD cases = 1 072)

	0 OR (95% CI)	1 OR (95% CI)	2 OR (95% CI)	≥ 3 OR (95% CI)	P for trend	P for interaction
Dietary magnesium						0.199
Insufficient magnesium intake	ref	1.490(0.861,2.581)	2.134(1.313,3.468)	3.837(2.368,6.218)	< 0.0001	
Sufficient magnesium intake	ref	6.643(1.700,25.963)	3.846(0.636,23.250)	8.303(1.602,43.038)	0.049	
Age_strata						0.211
≥ 60	ref	2.121(1.098,4.095)	2.224(1.215,4.071)	4.245(2.311,7.797)	< 0.0001	
< 60	ref	1.277(0.677, 2.411)	3.082(1.450, 6.551)	5.023(2.393,10.544)	< 0.0001	
Gender						0.257
Male	ref	2.320(1.226, 4.393)	2.590(1.281, 5.238)	6.321(3.172,12.597)	< 0.0001	
Female	ref	1.539(0.783,3.026)	2.240(1.256,3.995)	3.377(1.833,6.220)	< 0.0001	
Poverty						0.007
< 1.3	ref	4.002(2.140,7.485)	2.611(1.437,4.743)	4.990(2.520,9.882)	< 0.001	
1.3–3.5	ref	1.278(0.616,2.651)	2.622(1.262,5.446)	3.605(1.811,7.178)	< 0.0001	
> 3.5	ref	1.821(0.476, 6.967)	1.767(0.441, 7.089)	7.696(1.775,33.370)	< 0.001	
Marital						0.333
Couple	ref	2.056(1.070,3.949)	1.971(1.005,3.868)	4.326(2.181,8.580)	< 0.0001	
Single	ref	1.649(0.820,3.317)	2.646(1.371,5.107)	4.068(2.185,7.571)	< 0.0001	
BMI						0.418
< 25 kg/m^2	ref	1.053(0.277, 3.994)	2.387(0.660, 8.625)	4.802(1.497,15.398)	< 0.001	
25–30 kg/m^2	ref	4.579(1.770,11.844)	3.757(1.442, 9.787)	6.958(2.682,18.052)	< 0.001	
≥ 30 kg/m^2	ref	1.733(0.988,3.041)	2.162(1.210,3.862)	4.187(2.332,7.517)	< 0.0001	
Ethnicity						0.299
Mexican American	ref	2.302(0.642, 8.257)	2.566(0.739, 8.913)	5.004(1.468,17.062)	0.004	
White	ref	1.826(0.886, 3.761)	2.714(1.338, 5.506)	5.201(2.459,11.001)	< 0.0001	
Black	ref	0.997(0.459,2.169)	1.701(0.774,3.740)	2.442(1.034,5.767)	0.013	
Other	ref	2.601(0.819, 8.258)	1.086(0.286, 4.124)	3.538(1.019,12.286)	0.103	
ACR strata						0.247
≤ 300 mg/g	ref	2.281(1.332,3.906)	2.495(1.419,4.387)	4.606(2.657,7.987)	< 0.0001	
> 300 mg/g	ref	0.840(0.324, 2.178)	2.301(0.870, 6.089)	5.051(1.989,12.828)	< 0.0001	
HbA1c strata						0.901
HbA1c ≥ 7	ref	1.862(0.997,3.477)	2.445(1.197,4.994)	3.815(1.916,7.598)	< 0.0001	
HbA1c < 7	ref	2.027(0.956, 4.298)	2.514(1.314, 4.810)	5.323(2.703,10.480)	< 0.0001	
Hypertension						0.015
No	ref	2.094(0.881, 4.977)	6.214(2.311,16.711)	15.949(5.425,46.888)	< 0.0001	
Yes	ref	1.653(0.953,2.869)	1.849(1.112,3.072)	3.301(1.980,5.502)	< 0.0001	
Hyperlipidemia						0.222
No	ref	4.548(0.980,21.097)	4.828(1.132,20.592)	5.175(1.089,24.586)	0.253	
Yes	ref	1.799(1.090,2.971)	2.174(1.340,3.529)	4.264(2.646,6.873)	< 0.0001	

Model was adjusted for age, serum creatinine, ACR (ln-transformed), HbA1c, BMI, SBP, DBP, total cholesterol, triglycerides, dietary magnesium, dietary calcium, dietary total energy, dietary phosphorus, HEI-2015, dietary fiber, total fat, serum potassium

cardiovascular mortality, but did not reach statistical significance.

Stratified analyses demonstrated a stable and consistent association between MDS and an increased risk of all-cause mortality in all subgroups (Table 6). It is worth noting that in the subgroup analysis of cardiovascular mortality, the Mexican American, the young, low income, HbA1c ≥ 7, uACR > 300 mg/g increase the risk of cardiovascular mortality. Table S2 shows MDS had no statistical significance for mortality in the diuretic subgroup (P for interaction < 0.05 & P for trend < 0.05) (Table 7).

ROC analysis of the MDS for prognosis in DKD

Subsequently, we evaluated the prognostic significance of MDS in predicting all-cause mortality and cardiovascular

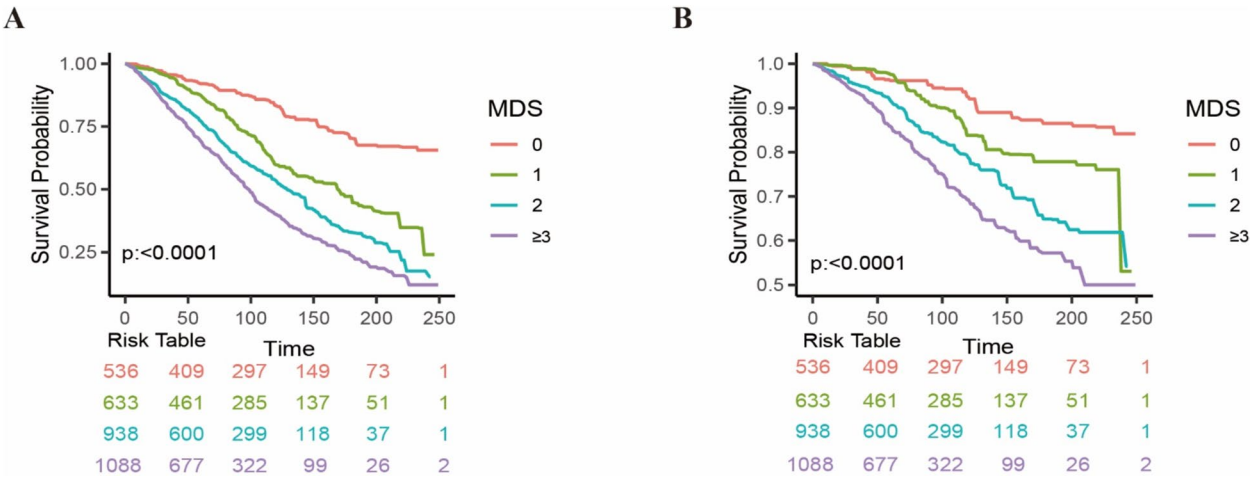

Fig 2. Kaplan–Meier curves were used to present the relationship of the magnesium depletion score with all-cause (**A**) and cardiovascular mortality (**B**) among patients with DKD

mortality by using a time-dependent ROC analysis [20] (Fig. 3). The results showed that the AUC for 1-,2-,3-,4-, and 5- year all-cause mortality in DKD patients was 0.86, 0.66, 0.59, 0.57, and 0.55, for all-cause mortality respectively (Fig. 3A, B). The AUC for 1-, 2-, 3-, 4-, and 5-year cardiovascular mortality were 0.9,0.67,0.62,0.58, and 0.56 respectively (Fig. 3C**,** D)**.** These findings suggest that MDS has excellent, and potential predictive power for short term all-cause and cardiovascular mortality.

Discussion

The findings of our study indicate a positive correlation between MDS and the prevalence of CVD in patients with DKD. This association persists even when examining specific forms of CVD. After adjusting for multiple covariants, the relationship remains strong. Additionally, MDS increases the risk of all-cause mortality and cardiovascular mortality in DKD patients. Consistent results from the sensitivity analysis further strengthen the robustness of these conclusions. MDS showed good predictive efficacy as an outcome indicator for DKD.

Serum magnesium is the most commonly used method for the clinical evaluation of magnesium status. Some studies have reported that hypomagnesemia is common in type 2 diabetes patients and is a significant risk factor for CVD [21–23]. However, serum magnesium accounts for less than 1% of the total magnesium content in the body [24], with the majority stored in bones, muscles, and soft tissues. Therefore, the serum magnesium cannot reflect the overall magnesium status in the body [25]. While serum magnesium levels are often within the normal range, intracellular magnesium levels may still be depleted [26–28]. Relying solely on serum magnesium measurements, without considering urinary magnesium loss and dietary intake, may lead to an underestimation of clinical magnesium deficiency [28]. Hypomagnesemia was associated with chronic alcohol use, decreased magnesium intake, increased gastrointestinal loss, and renal tubular injury [29, 30]. Urinary magnesium level is another method to assess magnesium status, but they can be influenced by dietary intake, PPI use, diuretics, and renal function [31, 32]. The 24-h urine magnesium tolerance test is considered the gold standard for assessing magnesium status in humans [33], but its complexity and unsuitability for patients with impaired renal function limit its use in clinical practice. MDS combines four risk factors affecting magnesium reabsorption in the U.S. population—PPI use, diuretic use, alcohol consumption, and eGFR—and serves as a simple and effective predictor of magnesium deficiency [13]. In this study, we investigated the connection between MDS and both the occurrence of CVD and its prognosis in patients with DKD.

Magnesium is essential for maintaining endothelial cell function and vascular integrity [34, 35]. Low magnesium levels, as indicated by a higher MDS, can exacerbate endothelial dysfunction through increased oxidative stress and impaired nitric oxide production [35, 36], both of which are key contributors to atherosclerosis and CVD risk. Magnesium deficiency has been shown to up-regulate pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [37, 38]. In DKD patients, chronic inflammation is already heightened due to metabolic and renal dysfunction, and magnesium deficiency may further amplify this pro-inflammatory state, increasing CVD susceptibility [9]. Magnesium plays a pivotal role in insulin sensitivity and glucose metabolism. Its deficiency may worsen hyperglycemia and glycemic variability in DKD patients, leading

Table 5 Multivariable-Adjusted HRs and 95% CIs for MDS in Relation to All-Cause and CVD Mortality Among 3195 Participants With DKD

	Mortality	Model1 HR (95% CI)	P	Model2 HR (95% CI)	P
All-cause mortality					
Diuretic use	645	1.79(1.55,2.07)	< 0.0001	1.42(1.23,1.64)	< 0.0001
PPI use	244	1.29(1.07,1.55)	0.01	0.98(0.81,1.18)	0.82
Heavy drinking	81	0.92(0.67,1.25)	0.58	1.68(1.20,2.34)	0.002
eGFR*					
0 points	162	Reference		Reference	
1 point	364	2.47(1.94,3.14)	< 0.0001	1.06(0.84,1.35)	0.62
2 points	847	3.38(2.67,4.28)	< 0.0001	1.17(0.89,1.54)	0.25
P for trend			< 0.0001		0.21
MDS[a]	1373	1.46(1.37,1.56)	< 0.0001	1.17(1.08,1.27)	< 0.001
MDS categories					
0	92	Reference		Reference	
1	243	2.30(1.68,3.15)	< 0.0001	1.38(1.03,1.86)	0.03
2	454	3.45(2.50,4.77)	< 0.0001	1.35(0.97,1.88)	0.07
≥ 3	584	4.71(3.47,6.39)	< 0.0001	1.78(1.29,2.46)	< 0.001
P for trend			< 0.0001		< 0.001
CVD mortality					
Diuretic use	254	2.10(1.69,2.60)	< 0.0001	1.64(1.29,2.09)	< 0.0001
PPI use	84	1.07(0.80,1.43)	0.67	0.79(0.58,1.08)	0.14
Heavy drinking	31	0.87(0.52,1.46)	0.61	1.53(0.83,2.84)	0.17
eGFR*					
0 points	51	Reference	Reference	Reference	Reference
1 point	132	2.78(1.70,4.53)	< 0.0001	1.27(0.74,2.18)	0.38
2 points	314	3.90(2.40,6.34)	< 0.0001	1.49(0.80,2.78)	0.21
P for trend			< 0.0001		0.18
MDS[a]	497	1.51(1.35,1.69)	< 0.0001	1.22(1.05,1.41)	0.01
MDS categories					
0	31	Reference	Reference	Reference	Reference
1	76	1.73(1.01,2.98)	0.05	1.09(0.60,1.98)	0.78
2	166	3.03(1.68,5.45)	< 0.001	1.22(0.63,2.36)	0.56
≥ 3	224	4.50(2.63,7.68)	< 0.0001	1.76(0.94,3.29)	0.08
P for trend			< 0.0001		0.02

Model was adjusted for age, gender, marital, ethnicity, education, smoking status, drinking status, poverty, obesity,

Hypertension, Hyperlipidemia, serum creatinine, ACR (ln-transformed), HbA1c, serum total cholesterol,

serum triglycerides, dietary magnesium, dietary calcium, dietary phosphorus, dietary energy intake, serum potassium, HEI-2015, dietary fiber, total fat, CVD

[a]In the sensitivity analysis, the MDS was converted from a categorical variable to a continuous variable; *60 mL/min per 1.73 m^2 ≤ eGFR < 90 mL/min per 1.73 m^2 was scored 1 point; and eGFR ≤ 60 mL/min per 1.73 m^2 was scored 2 point; 90 mL/min per 1.73 m2 ≤ eGFR was scored 0 point

Red color represents P < 0.05

to vascular complications that elevate CVD risk [40]. Many DKD patients are prescribed diuretics, which exacerbate magnesium wasting through renal excretion. This diuretic-induced magnesium loss is reflected in a higher MDS and may independently elevate CVD risk by promoting vascular calcification and arterial stiffness [41]. This study revealed a positive association between MDS and the risk of CVD in patients with DKD. The results indicate that patients with MDS ≥ 3 should be particularly cautious about the risk of developing CVD. A previous study demonstrated that the significant relationship between MDS and abdominal aorta calcification was observed only in patients with lower magnesium intake [42]. In our study, magnesium intake did not affect the relationship between MDS and both the occurrence and

Table 6 Subgroup Analysis for the Association Between MDS and all-cause mortality (Participants = 3195, all-cause mortality = 1373)

	0	1	2	≥ 3	P	P for trend	P for interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			
Magnesium							0.105
Sufficient magnesium intake	ref	1.920(0.693, 5.323)	2.594(0.895, 7.520)	5.027(1.675,15.085)	0.004	< 0.001	
Insufficient magnesium intake	ref	1.353(0.982,1.863)	1.277(0.917,1.780)	1.706(1.233,2.360)	0.001	< 0.001	
Age							0.242
≥ 60	ref	1.134(0.764,1.682)	1.116(0.751,1.656)	1.437(0.974,2.120)	0.067	0.004	
< 60	ref	1.672(1.058,2.643)	1.524(0.736,3.153)	3.153(1.641,6.061)	< 0.001	0.003	
Gender							0.317
Male	ref	1.169(0.782,1.746)	1.105(0.733,1.667)	1.639(1.090,2.463)	0.018	0.005	
Female	ref	1.608(1.001,2.584)	1.685(1.047,2.713)	2.151(1.311,3.527)	0.002	0.002	
Poverty							0.138
< 1.3	ref	2.429(1.357,4.348)	2.915(1.726,4.924)	3.015(1.736,5.238)	< 0.0001	< 0.001	
1.3–3.5	ref	1.022(0.693,1.506)	0.938(0.626,1.404)	1.373(0.956,1.970)	0.086	0.007	
> 3.5	ref	0.965(0.462,2.015)	0.772(0.325,1.835)	1.409(0.633,3.137)	0.401	0.195	
Marital							0.023
Couple	ref	1.483(0.987,2.229)	1.319(0.844,2.062)	2.216(1.432,3.430)	< 0.001	< 0.0001	
Single	ref	1.153(0.738,1.801)	1.324(0.834,2.102)	1.420(0.896,2.253)	0.136	0.078	
BMI							0.16
< 25 kg/m2	ref	1.266(0.554,2.893)	1.146(0.483,2.721)	1.857(0.779,4.426)	0.162	0.041	
25–30 kg/m2	ref	1.841(1.098,3.087)	1.338(0.802,2.232)	1.353(0.839,2.181)	0.215	0.994	
≥ 30 kg/m2	ref	1.206(0.771,1.888)	1.419(0.904,2.230)	2.032(1.275,3.238)	0.003	< 0.001	
Ethnicity							0.27
Mexican American	ref	1.738(0.859,3.517)	2.741(1.469,5.116)	2.879(1.278,6.486)	0.011	0.008	
White	ref	1.399(0.910,2.153)	1.221(0.767,1.946)	1.794(1.160,2.774)	0.009	0.002	
Black	ref	1.647(1.007,2.695)	1.860(1.127,3.070)	1.864(1.081,3.214)	0.025	0.054	
Other	ref	0.846(0.380,1.881)	0.978(0.389,2.462)	1.333(0.590,3.015)	0.489	0.365	
Hypertension							0.019
No	ref	1.406(0.725,2.727)	1.879(0.897,3.934)	2.078(0.939,4.600)	0.071	0.056	
Yes	ref	1.293(0.900,1.858)	1.178(0.819,1.693)	1.662(1.164,2.373)	0.005	< 0.001	
Hyperlipidemia							0.76
No	ref	1.783(0.889,3.574)	1.552(0.739,3.259)	2.952(1.260,6.919)	0.013	0.021	
Yes	ref	1.336(0.954,1.871)	1.319(0.919,1.894)	1.714(1.207,2.435)	0.003	< 0.001	
CVD							0.954
No	ref	1.237(0.877,1.745)	1.042(0.713,1.524)	1.297(0.902,1.863)	0.160	0.251	
Yes	ref	1.285(0.660,2.505)	1.521(0.862,2.683)	2.005(1.117,3.600)	0.020	0.001	
HbA1c							0.617
HbA1c ≥ 7	ref	1.666(1.071,2.591)	1.568(1.031,2.383)	2.169(1.419,3.316)	< 0.001	< 0.001	
HbA1c < 7	ref	0.984(0.588,1.646)	1.003(0.594,1.694)	1.283(0.764,2.156)	0.347	0.061	
uACR							0.398
≤ 300 mg/g	ref	1.294(0.922,1.816)	1.212(0.843,1.742)	1.520(1.055,2.189)	0.025	0.017	
> 300 mg/g	ref	1.646(0.766,3.537)	1.916(0.887,4.139)	3.584(1.664,7.723)	0.001	< 0.0001	

Model was adjusted for age, creatinine, ACR (ln-transformed), HbA1c, BMI, SBP, DBP, serum total cholesterol, serum triglycerides, dietary magnesium, dietary calcium, dietary energy, dietary phosphorus, HEI-2015, dietary fiber, dietary total fat, serum potassium

Red color represents P < 0.05

Table 7 Subgroup Analysis for the Association Between MDS and CVD mortality (Participants = 3195, CVD mortality = 497)

	0 HR (95% CI)	1 HR (95% CI)	2 HR (95% CI)	≥ 3 HR (95% CI)	p	p for trend	p for interaction
Magnesium							0.101
Sufficient magnesium intake	ref	2.924(0.265, 32.267)	6.880(0.627, 75.477)	11.285(0.974,130.736)	0.053	0.007	
Insufficient magnesium intake	ref	1.024(0.561,1.872)	1.152(0.592,2.244)	1.726(0.934,3.190)	0.081	0.013	
Age							0.336
≥ 60	ref	0.923(0.437,1.947)	0.918(0.457,1.845)	1.402(0.683,2.877)	0.357	0.046	
< 60	ref	1.045(0.417,2.622)	2.560(0.743,8.824)	2.794(1.104,7.073)	0.030	0.029	
Gender							0.164
Male	ref	0.849(0.414,1.740)	1.078(0.498,2.332)	1.865(0.847,4.108)	0.122	0.023	
Female	ref	1.679(0.719,3.922)	1.744(0.694,4.383)	2.224(0.924,5.349)	0.074	0.081	
Poverty							0.131
< 1.3	ref	2.391(0.847,6.752)	2.846(1.136,7.131)	3.381(1.301,8.788)	0.012	0.007	
1.3–3.5	ref	0.548(0.272,1.104)	1.080(0.490,2.381)	1.658(0.847,3.247)	0.140	0.005	
> 3.5	ref	0.780(0.252,2.418)	0.252(0.065,0.980)	0.565(0.144,2.216)	0.413	0.586	
Marital							0.128
Couple	ref	1.267(0.597,2.687)	1.003(0.440,2.283)	1.986(0.839,4.699)	0.118	0.063	
Single	ref	0.835(0.375,1.858)	1.421(0.555,3.638)	1.573(0.683,3.618)	0.287	0.063	
BMI							0.033
< 25 kg/m2	ref	1.629(0.213,12.460)	3.177(0.465,21.690)	9.295(1.757,49.167)	0.009	< 0.0001	
25–30 kg/m2	ref	1.805(0.695,4.691)	1.231(0.460,3.295)	1.045(0.380,2.874)	0.932	0.493	
≥ 30 kg/m2	ref	0.722(0.360,1.448)	1.010(0.461,2.212)	1.522(0.718,3.227)	0.273	0.069	
Ethnicity							0.293
Mexican American	ref	1.263(0.399, 4.000)	3.712(1.092,12.617)	6.163(1.024,37.088)	0.047	0.017	
White	ref	1.204(0.532,2.726)	1.157(0.466,2.876)	1.972(0.856,4.546)	0.111	0.022	
Black	ref	1.184(0.477,2.936)	1.904(0.841,4.311)	1.470(0.718,3.008)	0.292	0.332	
Other	ref	0.384(0.144,1.023)	0.685(0.199,2.358)	1.145(0.324,4.046)	0.834	0.617	
Hypertension							0.067
No	ref	0.555(0.186,1.654)	1.436(0.398,5.173)	1.063(0.278,4.065)	0.929	0.836	
Yes	ref	1.233(0.592,2.571)	1.200(0.564,2.553)	1.975(0.987,3.953)	0.054	0.006	
Hyperlipidemia							0.821
No	ref	1.866(0.477, 7.296)	2.635(0.646,10.747)	5.693(0.934,34.687)	0.059	0.05	
Yes	ref	0.986(0.550,1.767)	1.122(0.581,2.164)	1.602(0.864,2.970)	0.135	0.032	
CVD							0.863
No	ref	1.034(0.542,1.972)	0.990(0.459,2.135)	1.148(0.533,2.473)	0.724	0.704	
Yes	ref	0.916(0.349,2.405)	1.233(0.513,2.964)	1.874(0.790,4.447)	0.154	0.008	
HbA1c							0.995
HbA1c ≥ 7	ref	1.153(0.504,2.637)	1.367(0.574,3.255)	2.344(1.071,5.130)	0.033	0.01	
HbA1c < 7	ref	0.895(0.355,2.257)	1.024(0.387,2.712)	1.304(0.498,3.415)	0.589	0.199	
uACR							0.116
≤ 300 mg/g	ref	0.963(0.528,1.757)	0.902(0.468,1.737)	1.178(0.648,2.141)	0.591	0.322	
> 300 mg/g	ref	1.447(0.270, 7.763)	3.506(0.688,17.882)	8.543(1.728,42.246)	0.009	< 0.0001	

Model was adjusted for age, creatinine, ACR (In-transformed), HbA1c, BMI, SBP, DBP, serum total cholesterol, serum triglycerides, dietary magnesium, dietary calcium, dietary energy, dietary phosphorus, HEI-2015, dietary fiber, dietary total fat, serum potassium

Red color represents P < 0.05

prognosis of CVD in patients with DKD. This discrepancy might be due to differences among participants.

MDS combines four risk factors for magnesium reabsorption in the US population: alcohol consumption, diuretics, PPIs, and renal function [13]. Alcohol is considered as a magnesium diuretic that rapidly increases magnesium excretion by causing proximal tubular dysfunction [43]. Diuretics and proton pump inhibitors can

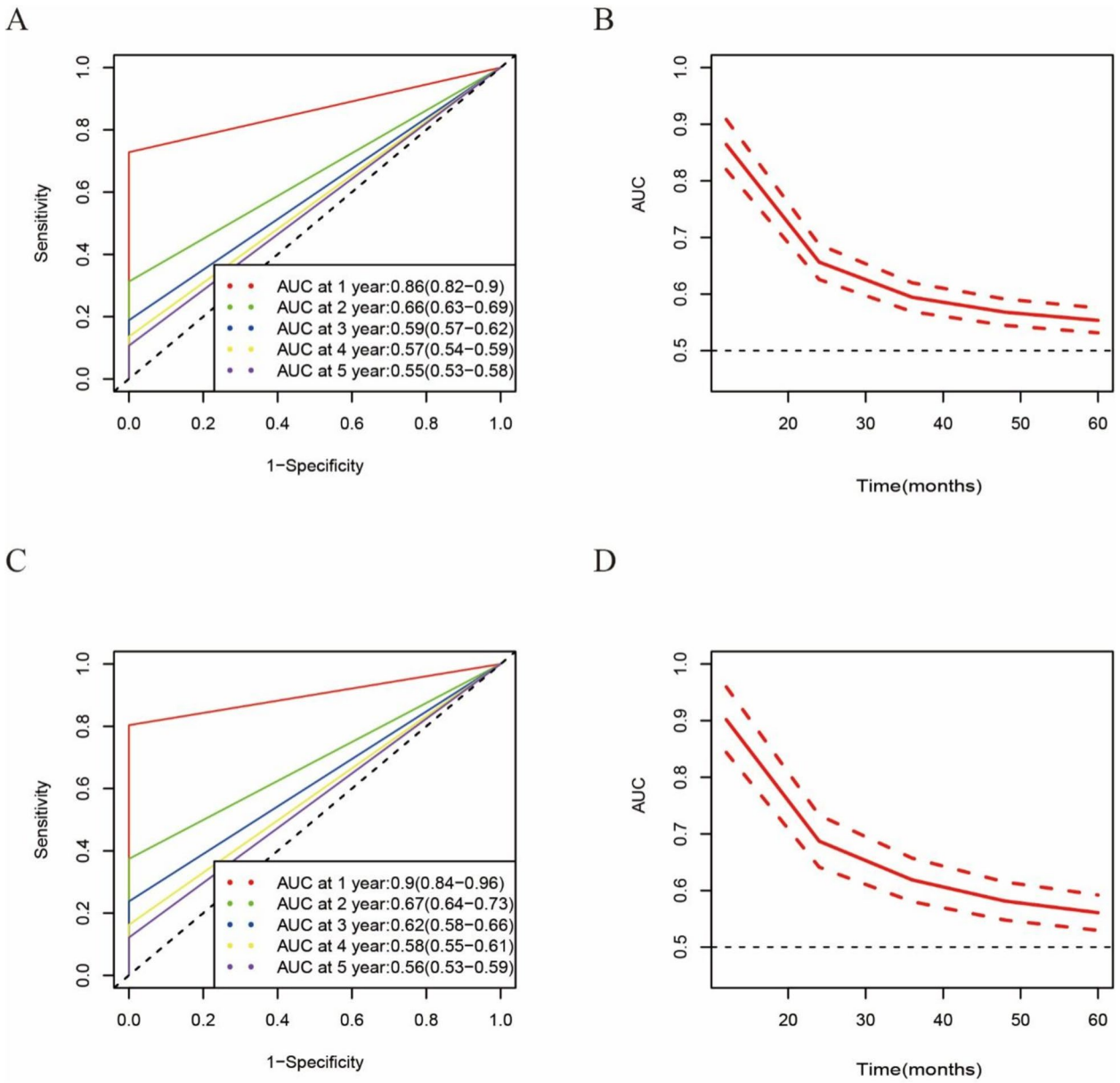

Fig 3. Time-dependent ROC curves and AUC values (with 95% CI) of the MDS for predicting all-cause mortality (**A**, **B**) and cardiovascular mortality (**C**, **D**)

lead to magnesium loss and hypomagnesaemia [44]. PPIs reduce magnesium absorption in the intestine by downregulating TRPM6 activity [45]. Magnesium homeostasis is primarily maintained by the kidneys, with 20% of magnesium reabsorbed in the proximal tubule and 70% in the thick ascending limb of the loop of Henle [29]. We further explored the relationship between MDS, individual indicators, and prognosis, finding that MDS and diuretic use were independently associated with poor prognosis. Patients with DKD are more likely to use diuretics, and those who do have a higher risk of CVD and mortality.

Similar to the findings of Fan et al. [13], we observed that MDS was independently associated with all-cause mortality in our DKD patients. Using MDS, we identified patients with DKD with possible dysfunction in magnesium reabsorption. Therefore, based on the score, timely intervention is given when DKD patients have both inadequate intake and reabsorption dysfunction. Our study provides a new approach to evaluate and identify patients

with DKD at higher risk of magnesium deficiency. Previous study has also been shown that a Mediterranean diet with high magnesium levels is closely related to blood magnesium levels, reducing cardiovascular mortality in dialysis patients [46, 47]. Our study shows that different levels of magnesium intake are all associated with all-cause death in DKD patients. Therefore, prospective studies are still needed to explore the impact of increasing magnesium intake on patients with DKD. Prompt intervention in DKD patients with high MDS, especially those with MDS ≥ 3, may help to reduce the risk of death.

Our study suggested that MDS may have a stronger prognostic impact in patients with more advanced disease or comorbid conditions. Specifically, the HRs for all-cause and cardiovascular mortality were significantly greater in patients with poor glycemic control (HbA1c ≥ 7%), indicating that magnesium deficiency may exacerbate the adverse effects of hyperglycemia, including oxidative stress and inflammation, on cardiovascular outcomes. Magnesium plays an important role in glucose metabolism, including insulin secretion, insulin receptor sensitivity, and processes such as glycogen synthesis. Studies have shown that magnesium deficiency may lead to increased insulin resistance [10], thus making glycemic control more difficult. Therefore, DKD patients with associated magnesium deficiency (especially at high HbA1c levels) may face worse glycemic control and metabolic imbalance, resulting in an increased risk of CVD and all-cause mortality. At the same time, the DKD patient is often accompanied by chronic low-grade inflammation [48]. Magnesium deficiency has been shown to be associated with elevated inflammatory levels [29], and magnesium deficiency may exacerbate the risk of cardiovascular events and death by activating pro-inflammatory cytokines [38]. Magnesium is an important regulator of endothelial cell function, able to promote vascular dilation and mitigate oxidative damage to the vascular endothelium [38]. Magnesium deficiency is closely associated with endothelial dysfunction [38], and in diabetic nephropathy patients with high HbA1c status, magnesium deficiency may exacerbate the impairment of endothelial function and subsequently increase the risk of cardiovascular death.

Similarly, the stronger relationship between MDS and outcomes in patients with higher levels of urinary albumin excretion (ACR > 300 mg/g) highlights the interplay between magnesium deficiency and severe proteinuria, both of which are markers of disease severity and systemic inflammation in DKD. DKD patients in the A3 level group had more prominent cardiovascular risk due to worsening renal function and excessive excretion of urinary albumin. Magnesium helps to maintain normal function of the kidney and reducing oxidative stress [35], inflammation [13] and calcium and phosphorus metabolism disorders [10]. For DKD patients, magnesium deficiency may exacerbate tubular injury and tubulointerstitial fibrosis, further driving the deterioration of kidney function. At the same time, magnesium deficiency may further increase the risk of cardiovascular death by promoting endothelial dysfunction, promoting the inflammatory response, and hypertension.

Moreover, in hypertensive DKD patients, the stronger association between MDS and mortality might reflect the role of magnesium in modulating vascular tone and blood pressure regulation, as well as its potential impact on mitigating hypertension-induced target organ damage. The significant interaction observed in patients with a history of CVD suggests that pre-existing cardiovascular damage may amplify the detrimental effects of magnesium deficiency. These findings emphasize the need for further research to investigate the pathophysiological mechanisms underlying these interactions, particularly in high-risk subgroups of DKD patients.

Despite the large sample and long-term NHANES database, we must acknowledge that this study still has some limitations. First, limitations of cross-sectional study design leads to the inability to determine a causal relationship between MDS and CVD. Second, due to lake of serum magnesium data, serum magnesium was not adjusted as a covariate. Third, the findings may not be generalizable to other ethnic groups. Finally, we cannot rule out the possibility that selection bias affects the results, although a multivariate analysis was performed in our study.

Conclusion

The current study showed that MDS is positively associated with the prevalence of CVD in patients with DKD. Furthermore, high MDS was associated with an elevated risk of all-cause and CVD mortality in DKD patients.

Abbreviations

DKD	Diabetic kidney disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
T2DM	Type 2 DM
MDS	Magnesium depletion score
NHANES	The National Health and Nutrition Examination Survey
NCHS	The National Center for Health Statistics
CDC	The Centers for Disease Control and Prevention
FPED	The Food Patterns Equivalents Database
NDI	The National Death Index
ICD	International Classification of Diseases
CHF	Congestive heart failure
CHD	Coronary heart disease
ICD-10	The International Classification of Diseases 10th Edition
PPIs	Proton pump inhibitors
eGFR	Estimated glomerular filtration rate
HEI-2015	The Healthy Diet Index-2015
HbA1c	Glycated hemoglobin A1c
uACR	Urine albumin-to-creatinine ratio

SD	Standard deviation
IQR	Interquartile range
CIs	Confidence intervals
ROC	The receiver operating characteristic
AUC	The area under the ROC curve
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-alpha

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01598-8.

Supplementary materials 1.

Acknowledgements
We extend our gratitude to the participants and staff of NHANES, as well as the NCHS, for their invaluable contributions to this study. We also wish to acknowledge Zhang Jing from the Second Department of Infectious Disease at Shanghai Fifth People's Hospital, Fudan University, for his contributions to the NHANES database. His outstanding work, including the development of the nhanesR package and associated webpage, has greatly supported our exploration of the NHANES data.

Author contributions
The study design and research concept were developed by X.T.Y., with data collection carried out by X.T.Y. and Z.X.Z. Data analysis and interpretation were performed by X.T.Y., who also provided supervision and guidance for the statistical analyses. Each author made significant contributions to the drafting or revision of the manuscript and accepts responsibility for their individual contributions. All authors are dedicated to addressing any concerns related to the accuracy or integrity of the work.

Funding
No funding.

Availability of data and materials
The NHANES is not a clinical trial but a research program conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). Since NHANES is not registered as a clinical trial, it does not have a clinical trial number. Instead, it is an ongoing series of surveys designed to collect data on public health and nutrition, rather than a specific clinical study testing interventions or treatments. The NHANES dataset is publicly available through the NCHS, a division of the CDC, and can be accessed on their website: https://www.cdc.gov/nchs/nhanes/. No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate.
The NHANES survey is conducted collaboratively by the CDC and the NCHS. The study protocol was reviewed and approved by the NCHS Research Ethics Review Committee. All participants provided written informed consent prior to their involvement in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests pertaining to this study.

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Received: 30 August 2024 Accepted: 15 January 2025
Published online: 29 January 2025

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