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ORIGINAL RESEARCH

Association of Life's Essential 8 Score with All-Cause and Cardiovascular Mortality in Patients with Diabetic Nephropathy: A NHANES-Based Cohort Study

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Purpose: This study aimed to assess the relationship between the "Life's Essential 8" (LE8) score and all-cause and cardiovascular mortality in patients with diabetic nephropathy (DN).

Methods: This observational cohort study utilized data from the National Health and Nutrition Examination Survey (NHANES, 2005–2018). A total of 1,745 patients with DN were included. The LE8 score encompassed health behaviors (diet, physical activity, nicotine control, sleep) and physiological indices (body mass index, non-high-density lipoprotein cholesterol, blood glucose, blood pressure). A multivariate Cox proportional risk model was employed to assess the effect of the LE8 score on the risk of death, and the dose-response relationship was analyzed by a restricted cubic spline (RCS) model. Subgroup analyses and multiple imputations were performed to verify the robustness of the findings.

Results: After adjusting for confounders, a 10-point increase in the LE8 score was associated with a 12% reduction in the risk of all-cause mortality [hazard ratio (HR) = 0.88, P < 0.001] and a 16% reduction in the risk of cardiovascular death (HR = 0.84, P = 0.007). The risk of all-cause mortality was 33% lower in the highest tertile group compared with the lowest group (HR = 0.67, P < 0.001), and the risk of cardiovascular mortality was 36% lower (HR = 0.64, P = 0.014). RCS analysis showed that LE8 scores were linearly negatively correlated with mortality (nonlinear P > 0.05). Subgroup analyses further confirmed the consistency of this association across various characteristic subgroups.

Conclusion: LE8 score has been identified as an independent protective factor for the risk of death in patients with DN, exhibiting a linear dose-response relationship consistent across sociodemographic subgroups. This finding underscores the importance of incorporating LE8 into a comprehensive assessment system for DN patients, providing a foundation for precision intervention.

Keywords: diabetic nephropathy, life's essential 8, all-cause mortality, cardiovascular mortality, cohort studies

Introduction

Diabetic nephropathy (DN) is a prevalent microvascular complication of diabetes mellitus that has emerged as a predominant cause of chronic kidney disease and end-stage renal disease on a global scale.[1–3] The clinical manifestations of this condition include persistent proteinuria in the early stages, followed by the gradual development of renal impairment, hypertension, edema, and ultimately, severe renal failure, which necessitates dialysis treatment to maintain life.[4,5] The prevalence of DN in patients with type 2 diabetes ranges from 20% to 50%,[6,7] and a strong pathophysiological correlation exists between DN and cardiovascular disease (CVD), a significant cause of mortality among diabetic

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patients.[8,9] The joint impact of these conditions on patient health, quality of life, and prognosis is significant, underscoring the need for comprehensive management and research to mitigate their adverse effects.

Recent research findings on the pathogenesis of DN and CVD have indicated the crucial role of metabolic disorders, inflammatory responses, and oxidative stress in the development of both conditions.[10–12] Moreover, several modifiable lifestyle factors, including dietary nutrition, physical activity, nicotine exposure control, and sleep health, have been identified as potentially significant contributors to the development of DN and CVD.[13–16] A substantial body of research has demonstrated that lifestyle interventions can enhance health outcomes in patients with diabetes and kidney disease; however, these studies have predominantly examined individual lifestyle factors and have not employed comprehensive health indicator assessment systems. For instance, some studies have shown that regular physical activity can reduce the risk of cardiovascular events in patients with diabetes and that a rational diet positively affects renal function.[17,18] Nevertheless, these studies have not systematically analyzed various health behaviors and factors to elucidate their joint effects fully.

The Life's Essential 8 (LE8) assessment system, developed by the American Heart Association (AHA), is a comprehensive instrument designed to evaluate an individual's cardiovascular health.[19] While the LE8 assessment system has been extensively applied in the general population and has demonstrated adequate predictive capability for CVD risk,[20,21] its implementation in a distinct population of patients with DN and its correlation with mortality require further elucidation.

In light of these observations, the objective of this study was to methodically examine the following scientific inquiries utilizing data from a substantial cohort of the National Health and Nutrition Examination Survey (NHANES): First, we sought to determine whether LE8 scores are independently associated with all-cause mortality and cardiovascular mortality in patients with DN. Second, we investigated whether the protective effect of LE8 scores on the risk of death exhibits a linear dose-response pattern. Third, we examined whether the association of LE8 with the risk of death varies according to sociodemographic characteristics and whether there is heterogeneity in the association between LE8 and mortality risk in subgroups. The rationale for employing the NHANES cohort study to explore the prognosis of DN is outlined below: the nationally representative sampling facilitates population-level inferences; the relevant mortality data for 2019 is sourced from the National Death Index; and there is a standardized evaluation of DN and LE8 components. Through this study, we aim to deepen our understanding of the multidimensional regulatory mechanisms of cardiovascular health in DN patients, thereby providing a precise basis for the clinical management of DN patients and the development of public health policies.

Methods

Study Population

The data for this study were obtained from the NHANES cross-sectional survey database. The NHANES database encompasses a total of seven cycles from 2005 to 2018, which were organized by the Centers for Disease Control and Prevention (CDC). All study procedures were approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), and participants signed written informed consent. The anonymized nature of the data and relevant NIH regulations were deemed sufficient to conclude that no additional ethical approval was required for this study. The original cohort comprised 70,190 subjects; however, the following individuals were excluded through screenings: those under 20, pregnant females, and those with missing key variables. The key variables include data on indicators related to the diagnosis of DN, data related to LE8, data on survival follow-up, demographic characteristics, history of chronic disease, and BMI. In addition, non-DN participants were excluded from the study. The final analysis included 1,745 participants with DN, and the specific screening process is shown in Figure 1.

Definition of Disease

The diagnosis of diabetes mellitus was made by composite criteria, with patients being included if they met any of the following criteria: (1) a precise diagnosis by a clinician; (2) fasting plasma glucose (FPG) ≥126 mg/dl; (3) glycosylated hemoglobin (HbA1c) ≥6.5%; and (4) current receipt of oral hypoglycemic agents or insulin therapy. Renal function status

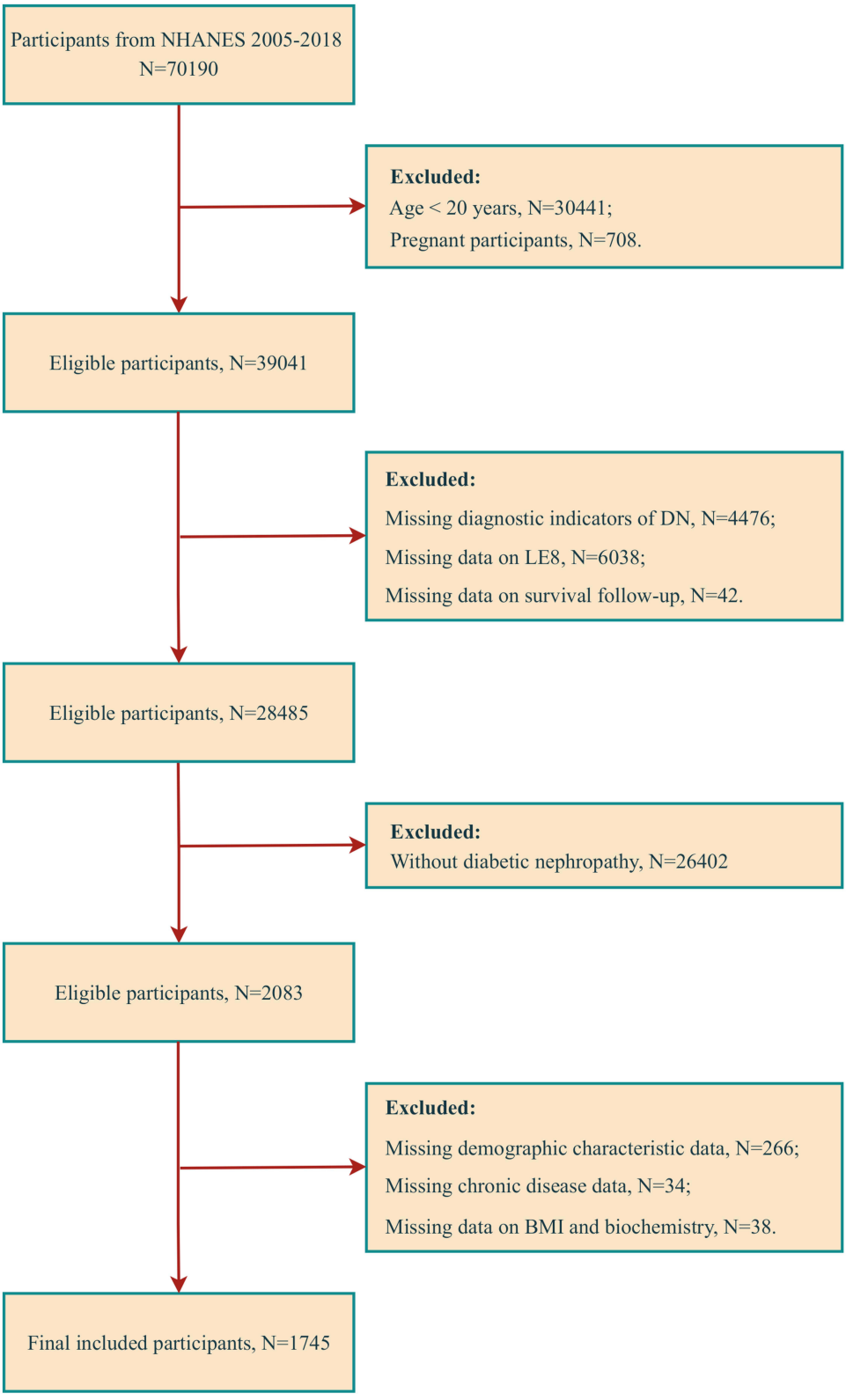

Figure 1 Participant screening flowchart.
Abbreviation: LE8, Life's Essential 8.

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was assessed by measuring the urine albumin to creatinine ratio (UACR) and the estimated glomerular filtration rate (eGFR). The eGFR value was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recommended formula. In the diagnostic process of DN, we followed the internationally recognized diagnostic criteria, ie, UACR of not less than 30 mg/g or/and eGFR of less than 60 mL/min/1.73m², to ensure that the diagnostic results were accurate and reliable.[22]

LE8 Assessment

The LE8 assessment system, proposed by the AHA, is a comprehensive framework encompassing four health behaviors (dietary nutrition, physical activity, nicotine exposure control, and sleep health) and four health factors [body mass index (BMI), non-high-density lipoprotein cholesterol (non-HDL-C), blood glucose levels, and blood pressure parameters].[19] In this study, the dimensions were quantified using a standardized assessment protocol. Dietary quality was evaluated using the 2015 version of the Healthy Eating Index (HEI-2015), which is calculated based on the mean value of dietary components collected by two 24-hour dietary recalls.[23] Self-reported questionnaires obtained physical activity level, tobacco exposure, and sleep quality; anthropometric parameters (body weight, height, and blood pressure) were standardized for physical examination, while laboratory tests determined metabolic indicators (lipids, blood glucose). Scores for each dimension were calculated using a standardized scoring system of 0–100 points, and the total LE8 score was obtained by calculating the unweighted mean of the eight dimensions. Notably, to address the impaired metabolic regulation that characterizes the prevalence of DN in the population, the present study used a three-quarter grouping method to replace the binary division criteria of 80 (ideal level) and 50 (moderate level) in the traditional cardiovascular health assessment. This adaptation seeks to elucidate the dose-response relationship between the LE8 score gradient and mortality in patients with DN with greater precision. Additionally, it aims to provide methodological optimization for cardiovascular health assessment in specific populations.

Mortality Assessment

The primary endpoints of the study were all-cause mortality and cardiovascular mortality. All-cause mortality was defined as death from any cause, and cardiovascular deaths were determined based on International Classification of Diseases, 10th edition (ICD-10) codes covering heart disease (I00-I09, I11, I13, I20-I51) and cerebrovascular disease (I60-I69). The mortality data were obtained by matching the NHANES Public Death Records file to the 2019 National Death Index (NDI), with follow-up from the baseline visit date to the date of death or the December 31, 2019 cutoff.[24]

Assessment of Covariates

The following covariates were included in this study: 1) demographic characteristics (gender, age, and race); 2) socio-economic indicators (education level, marital status, and family income); 3) lifestyle (smoking, alcohol consumption, and intensity of physical activity); and 4) history of chronic disease (hypertension, coronary heart disease, stroke, and cancer). The racial category was further subdivided into Mexican American, non-Hispanic white, non-Hispanic black, and other race; education level was categorized according to years of education into less than 9th grade, 9th to 12th grade, and more than 12th grade; marital status was simplified into cohabitation and solitude; and family income was categorized according to the official US Poverty-to-Income Ratio (PIR) into three groups: low (≤1.3), medium (1.3–3.5), and high (>3.5). Smoking was defined as lifetime smoking ≥100 cigarettes and current smoking. Alcohol use was defined as consumption of ≥12 alcoholic beverages in the past year. Physical activity was categorized as inactive, moderate, and vigorous. Chronic disease status was confirmed based on self-reported physician diagnosis or medication records.

Statistical Analysis

In order to verify the normality of the continuous variables, we implemented the Kolmogorov–Smirnov test. It was determined that none of the continuous variables included in this study adhered to a normal distribution. Consequently, we proceeded to present descriptive statistics using the median (25th and 75th percentile). We then analyzed the differences between groups using the Mann–Whitney *U*-test. Using the chi-square test, we presented categorical variables in the form of frequencies and percentages and subsequently analyzed them for between-group differences.

To investigate the association between LE8 levels and all-cause mortality and cardiovascular mortality in patients with DN, we constructed a multivariate Cox proportional risk regression model to quantitatively assess the effect of LE8 and its tertiles [T1 (<46.9), T2 (46.9–57.5), and T3 (>57.5)] on the risk of death in patients with DN by estimating the hazard ratio (HR) and its 95% confidence interval (CI). To control the potential interference of confounding variables, we constructed three models stepwise: model 1 served as the baseline without any adjustment; model 2 incorporated age, gender, and race based on the baseline model; and model 3 further introduced educational attainment, marital status, family PIR, alcohol consumption, coronary heart disease, stroke, and cancer as adjustment variables.

We employed a restricted cubic spline (RCS) model to ascertain a potential nonlinear dose-response relationship between LE8 levels and mortality in patients with DN. In this model, LE8 was regarded as a continuous variable, and the 5th, 35th, 65th, and 95th percentiles were designated as pivotal points for analysis based on their distributional properties.

Furthermore, we conducted subgroup analyses. Participants were stratified based on gender, race, education level, marital status, family PIR, and drinking habits. This approach was taken to explore the heterogeneity of the patterns of association between LE8 levels and all-cause and cardiovascular mortality in different subgroups. Interaction analyses were conducted to assess the stability and consistency of the relationship between indices and mortality risk within each subgroup.

Finally, we employed multiple imputation techniques to address missing values in the data. Multiple imputation models excluded outcome variables (mortality) and included all covariates. Missing data percentages were: demographics 12.8%, comorbidities 1.6%, biochemistry 1.8%. We conducted a sensitivity analysis (complete case analysis) to assess the consistency of the results before and after imputation. This approach enabled us to verify the robustness of the findings. Throughout the statistical analysis, we adhered to the principle of two-sided testing and defined statistical significance at the P-value <0.05 level. All data analysis was conducted using R 4.4.2 software (provided by R Foundation at http://www.R-project.org) with SPSS version 23.0 (IBM Corporation, Armonk, New York, USA). Graphical representations were generated using GraphPad Prism version 9.3.1 (GraphPad Software, USA).

Results

Baseline Characteristics of Participants

This study encompassed 1,745 patients diagnosed with DN, of whom 1,169 (67.0%) survived, and 576 (33.0%) did not. A non-significant disparity in gender distribution was observed between the two groups (P = 0.135). A statistically significant difference was observed in age between survivors and non-survivors, with the former group being younger (64.00 vs 74.00 years, P < 0.001). Significant disparities in racial distribution were observed, with non-Hispanic white individuals comprising a higher percentage of non-survivors (56.42% vs 37.21%) and Mexican American individuals comprising a lower percentage (10.42% vs 18.99%, P < 0.001). A multifaceted comparison of the two groups revealed significant disparities in education level, marital status, family PIR, smoking, physical activity, hypertension, coronary heart disease, stroke, and cancer (P < 0.05). Specifically, non-survivors exhibited lower levels of education, higher incidence of living alone, lower family PIR, a higher proportion of smokers, lower levels of physical activity, and higher rates of hypertension, coronary heart disease, stroke, and cancer. Furthermore, non-survivors demonstrated lower BMI, HbA1c, TC, and eGFR levels and higher levels of creatinine (P < 0.05). A notable finding was the lower LE8 scores observed in non-survivors compared to survivors (51.25 vs 52.50, P = 0.040) (Table 1).

Table 1 Baseline Characteristics of Participants with Diabetic Nephropathy

Variables	Total (n = 1745)	Survivors (n = 1169)	Non-Survivors (n = 576)	*P*
Gender, n (%)				0.135
Male	922 (52.84)	603 (51.58)	319 (55.38)	
Female	823 (47.16)	566 (48.42)	257 (44.62)	
Age (years)	67.00 (59.00, 76.00)	64.00 (54.00, 72.00)	74.00 (65.00, 80.00)	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 1745)	Survivors (n = 1169)	Non-Survivors (n = 576)	*P*
Race, n (%)				<0.001
Mexican American	282 (16.16)	222 (18.99)	60 (10.42)	
Non-Hispanic White	760 (43.55)	435 (37.21)	325 (56.42)	
Non-Hispanic Black	443 (25.39)	307 (26.26)	136 (23.61)	
Other Race	260 (14.90)	205 (17.54)	55 (9.55)	
Education Level, n (%)				0.001
Less than 9th grade	288 (16.50)	175 (14.97)	113 (19.62)	
9–12th grade	740 (42.41)	480 (41.06)	260 (45.14)	
More than 12th grade	717 (41.09)	514 (43.97)	203 (35.24)	
Marital Status, n (%)				<0.001
Cohabitation	987 (56.56)	698 (59.71)	289 (50.17)	
Solitude	758 (43.44)	471 (40.29)	287 (49.83)	
Family PIR, n (%)				0.009
Low (≤1.3)	640 (36.68)	421 (36.01)	219 (38.02)	
Medium (1.3–3.5)	747 (42.81)	484 (41.40)	263 (45.66)	
High (>3.5)	358 (20.52)	264 (22.58)	94 (16.32)	
Smoking, n (%)				<0.001
Yes	938 (53.75)	591 (50.56)	347 (60.24)	
No	807 (46.25)	578 (49.44)	229 (39.76)	
Alcohol, n (%)				0.151
Yes	1009 (57.82)	662 (56.63)	347 (60.24)	
No	736 (42.18)	507 (43.37)	229 (39.76)	
Physical Activity, n (%)				<0.001
Inactive	822 (47.11)	463 (39.61)	359 (62.33)	
Moderate	637 (36.50)	457 (39.09)	180 (31.25)	
Vigorous	286 (16.39)	249 (21.30)	37 (6.42)	
Hypertension, n (%)				0.003
Yes	1294 (74.15)	841 (71.94)	453 (78.65)	
No	451 (25.85)	328 (28.06)	123 (21.35)	
Coronary heart disease, n (%)				<0.001
Yes	262 (15.01)	135 (11.55)	127 (22.05)	
No	1483 (84.99)	1034 (88.45)	449 (77.95)	
Stroke, n (%)				<0.001
Yes	216 (12.38)	115 (9.84)	101 (17.53)	
No	1529 (87.62)	1054 (90.16)	475 (82.47)	
Cancer, n (%)				<0.001
Yes	296 (16.96)	154 (13.17)	142 (24.65)	
No	1449 (83.04)	1015 (86.83)	434 (75.35)	
BMI (kg/m^2)	31.40 (27.40, 36.54)	32.00 (28.00, 37.11)	30.21 (26.12, 35.31)	<0.001
FPG (mg/dL)	136.00 (109.00, 182.00)	137.00 (109.00, 188.00)	135.00 (110.00, 177.00)	0.384
HbA1c (%)	6.80 (6.20, 8.00)	6.90 (6.30, 8.30)	6.70 (6.10, 7.70)	<0.001
TC (mg/dL)	176.00 (150.00, 210.00)	178.00 (151.00, 212.00)	170.00 (146.00, 206.00)	0.011
TG (mg/dL)	159.00 (106.00, 240.00)	163.00 (109.00, 242.00)	153.50 (102.50, 235.25)	0.080
HDL-c (mg/dL)	45.00 (38.00, 56.00)	45.00 (38.00, 55.00)	45.00 (38.00, 56.00)	0.576
Creatinine (mg/dL)	1.10 (0.85, 1.37)	1.04 (0.81, 1.31)	1.24 (0.98, 1.54)	<0.001
UACR (mg/g)	57.50 (23.64, 159.67)	56.64 (25.00, 148.99)	58.71 (23.20, 197.30)	0.247
eGFR ($mL/min/1.73m^2$)	59.59 (48.37, 89.12)	66.71 (51.91, 94.56)	53.27 (40.36, 69.30)	<0.001
LE8 score	51.88 (43.57, 60.63)	52.50 (44.38, 61.25)	51.25 (42.50, 60.00)	0.040

Notes: Data are shown as median (25th, 75th percentiles) or percentages, p <0.05 considered statistically significant.

Abbreviations: PIR, Poverty-to-income ratio; BMI, Body mass index; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein cholesterol; UACR, Urinary albumin/creatinine ratio; eGFR, Estimated glomerular filtration rate; LE8, Life's Essential 8.

Table 2 Relationships Between LE8 and Mortality in Participants with Diabetic Nephropathy

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality						
LE8 per 10 scores	0.93 (0.87 ~ 0.99)	0.031	0.83 (0.78 ~ 0.89)	<0.001	0.88 (0.82 ~ 0.94)	<0.001
Categories						
Tertile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Tertile 2	0.83 (0.68 ~ 1.02)	0.070	0.73 (0.60 ~ 0.89)	0.002	0.78 (0.63 ~ 0.95)	0.016
Tertile 3	0.80 (0.66 ~ 0.98)	0.029	0.58 (0.48 ~ 0.71)	<0.001	0.67 (0.55 ~ 0.83)	<0.001
P for trend		0.028		<0.001		<0.001
Cardiovascular mortality						
LE8 per 10 scores	0.91 (0.82 ~ 1.02)	0.100	0.81 (0.72 ~ 0.92)	<0.001	0.84 (0.75 ~ 0.95)	0.007
Categories						
Tertile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Tertile 2	0.77 (0.54 ~ 1.08)	0.126	0.68 (0.48 ~ 0.95)	0.026	0.71 (0.50 ~ 1.01)	0.056
Tertile 3	0.77 (0.55 ~ 1.08)	0.125	0.57 (0.40 ~ 0.80)	0.001	0.64 (0.45 ~ 0.91)	0.014
P for trend		0.120		0.001		0.014

Note: Model 1: crude; Model 2: adjusted for Gender, Age, Race; Model 3: adjusted for Gender, Age, Race, Education Level, Marital Status, Family PIR, Alcohol, Coronary heart disease, Stroke, and Cancer.
Abbreviations: LE8, Life's Essential 8; HR, Hazard ratio; CI, Confidence interval.

Relationship Between LE8 Score and Mortality in Patients with DN

In unadjusted Model 1, a 10-point increase in LE8 was associated with a 7% reduction in the risk of all-cause mortality (HR = 0.93, P = 0.031). In Model 2, which was adjusted for gender, age, and race, a 10-point increase in LE8 was associated with a 17% reduction in the risk of all-cause mortality (HR = 0.83, P < 0.001) and a 19% reduction in the risk of cardiovascular mortality (HR = 0.81, P < 0.001). In Model 3, after further adjustment for socioeconomic and comorbidity variables, each 10-point increase in LE8 was associated with a 12% reduction in the risk of all-cause mortality (HR = 0.88, P < 0.001) and a 16% reduction in the risk of cardiovascular mortality (HR = 0.84, P = 0.007). The grouping of subjects according to tertiles of LE8 score yielded a 33% reduction in the risk of all-cause mortality (Model 3: HR = 0.67, P < 0.001) and a 36% reduction in the risk of cardiovascular mortality (Model 3: HR = 0.64, P = 0.014). The tests for trend were all significant (all P < 0.05) (Table 2).

RCS Analysis of the Relationship Between LE8 Score and Mortality in Patients with DN

Figure 2A illustrates the relationship between LE8 score and all-cause mortality in patients with DN. The findings revealed a statistically significant negative correlation between LE8 score and all-cause mortality (P-overall < 0.001), indicating that higher LE8 scores are associated with lower all-cause mortality. This relationship exhibited a linear trend (P-nonlinear = 0.637). Conversely, Figure 2B illustrates the association between LE8 score and cardiovascular mortality, demonstrating a comparable negative correlation (P-overall = 0.005). This relationship exhibited a linear trend as well (P-nonlinear = 0.128).

Subgroup Analysis

Figure 3 illustrates the outcomes of the subgroup analysis investigating the correlation between LE8 and all-cause mortality. The analysis revealed that for every 10-point increase in the LE8 score, there was a 12% decrease in the risk of all-cause mortality (HR = 0.88, P < 0.001). Subgroup analyses revealed that gender (male: HR = 0.88, P = 0.007; female:

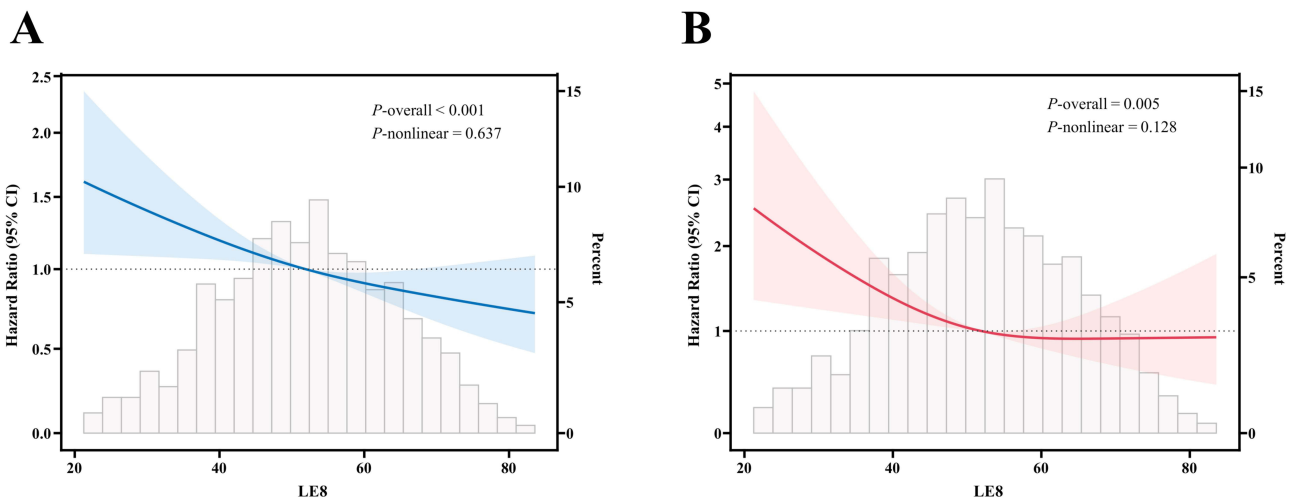

Figure 2 Restricted cubic spline fitting for the association between LE8 and mortality in participants with diabetic nephropathy. (**A**) all-cause mortality; (**B**) cardiovascular mortality. Solid lines indicate HR and shaded areas indicate 95% CI. These analyses were adjusted according to Model 3.
Abbreviations: LE8, Life's Essential 8; HR, Hazard ratio; CI, Confidence interval.

Subgroup	N	Adjusted HR (95% CI)	*P* value	*P* for interaction
Overall	1745	0.88 (0.82, 0.94)	<0.001	
Gender				0.986
Male	922	0.88 (0.79, 0.96)	0.007	
Female	823	0.88 (0.79, 0.97)	0.014	
Race				0.138
Mexican American	282	1.00 (0.78, 1.29)	0.992	
Non-Hispanic White	760	0.89 (0.81, 0.98)	0.017	
Non-Hispanic Black	443	0.79 (0.69, 0.92)	0.002	
Other Race	260	0.82 (0.64, 1.05)	0.109	
Education Level				0.101
Less than 9th grade	288	0.95 (0.81, 1.11)	0.526	
9–12th grade	740	0.90 (0.82, 1.00)	0.055	
More than 12th grade	717	0.80 (0.71, 0.91)	0.001	
Marital Status				0.437
Cohabitation	987	0.90 (0.81, 0.99)	0.028	
Solitude	758	0.85 (0.77, 0.95)	0.003	
PIR				0.081
Low	640	0.91 (0.82, 1.02)	0.109	
Median	747	0.90 (0.81, 1.01)	0.063	
High	358	0.66 (0.54, 0.80)	<0.001	
Alcohol				0.467
Yes	1009	0.85 (0.77, 0.93)	0.001	
No	736	0.91 (0.82, 1.01)	0.082	

Figure 3 Subgroup analysis of the association between LE8 and all-cause mortality. Adjusted variables: gender, age, race, education level, marital status, family PIR, alcohol, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis.
Abbreviations: PIR, Poverty-to-income ratio; HR, Hazard ratio; CI, Confidence interval.

HR = 0.88, P = 0.014), non-Hispanic white (HR = 0.89, P = 0.017), non-Hispanic black (HR = 0.79, P = 0.002), high educational attainment (HR = 0.80, P = 0.001), cohabitation (HR = 0.90, P = 0.028), and living alone (HR = 0.85, P = 0.003) populations all had statistically significant associations. Of particular note, the magnitude of the risk reduction was most substantial in the high family PIR group (HR = 0.66, P < 0.001), whereas it did not attain statistical significance in the low/middle PIR group (P > 0.05). Moreover, the risk reduction was more pronounced among individuals who

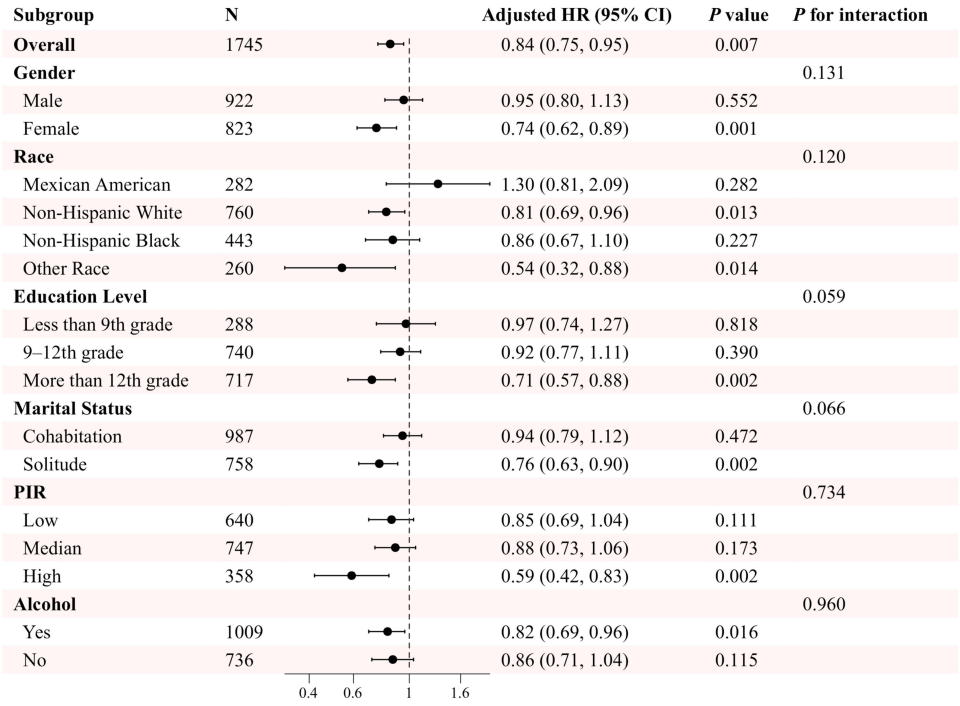

Figure 4 Subgroup analysis of the association between LE8 and cardiovascular mortality. Adjusted variables: gender, age, race, education level, marital status, family PIR, alcohol, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis.
Abbreviations: PIR, Poverty-to-income ratio; HR, Hazard ratio; CI, Confidence interval.

consumed alcohol (HR = 0.85, P = 0.001). Interaction tests revealed that none of the interaction differences between the various subgroups attained statistical significance (all P for interaction > 0.05).

Figure 4 presents the findings of the subgroup analysis investigating the association between LE8 and cardiovascular mortality. The analysis indicated that the association was statistically significant for females (HR = 0.74, P = 0.001), non-Hispanic white (HR = 0.81, P = 0.013), other race (HR = 0.54, P = 0.014), and those with a high education level (HR = 0.71, P = 0.002), living alone (HR = 0.76, P = 0.002), high family PIR group (HR = 0.59, P = 0.002), and drinkers (HR = 0.82, P = 0.016). However, none of the interaction differences between the different subgroups reached statistical significance (all P for interaction > 0.05). In conclusion, the LE8 score is a robust predictor of significantly reduced mortality in patients with DN, and this effect was consistent across sociodemographic characteristics.

Robustness Analysis of the Relationship Between LE8 Score and Mortality in Patients with DN After Multiple Imputation

Following the implementation of multiple imputation procedures for missing data, the observed trends in the association between LE8 score and mortality demonstrated persistent consistency. In Model 3, a 10-point increase in the LE8 score was associated with a 13% reduction in the risk of all-cause mortality (HR = 0.87, P < 0.001), with a 33% reduction observed in the highest quartile group (HR = 0.67, P < 0.001). In the cardiovascular mortality analysis, each 10-point increase in LE8 was associated with a 12% reduction in the risk of cardiovascular death (HR = 0.88, P = 0.020), and a 30% reduction in risk was observed in the highest tertile group (HR = 0.70, P = 0.034). The test for trend was statistically significant (all P values < 0.05). The multiple imputation results further support the LE8 score as an independent protective factor for the risk of death in patients with DN (Table 3). Robustness analysis confirmed consistency between imputed and complete-case models (HR differences <5%, all interaction P>0.05).

Table 3 Relationships Between LE8 and Mortality in Participants with Diabetic Nephropathy After Multiple Imputations for Missing Variables

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality						
LE8 per 10 scores	0.93 (0.88 ~ 0.98)	0.013	0.83 (0.78 ~ 0.88)	<0.001	0.87 (0.82 ~ 0.93)	<0.001
Categories						
Tertile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Tertile 2	0.87 (0.73 ~ 1.04)	0.127	0.75 (0.62 ~ 0.90)	0.002	0.81 (0.67 ~ 0.97)	0.020
Tertile 3	0.80 (0.67 ~ 0.96)	0.017	0.58 (0.48 ~ 0.70)	<0.001	0.67 (0.56 ~ 0.82)	<0.001
P for trend		0.016		<0.001		<0.001
Cardiovascular mortality						
LE8 per 10 scores	0.95 (0.85 ~ 1.04)	0.270	0.85 (0.76 ~ 0.94)	0.002	0.88 (0.78 ~ 0.98)	0.020
Categories						
Tertile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Tertile 2	0.83 (0.61 ~ 1.14)	0.250	0.72 (0.53 ~ 0.99)	0.043	0.75 (0.54 ~ 1.02)	0.070
Tertile 3	0.85 (0.63 ~ 1.16)	0.312	0.63 (0.46 ~ 0.87)	0.004	0.70 (0.51 ~ 0.97)	0.034
P for trend		0.306		0.005		0.035

Note: Model 1: crude; Model 2: adjusted for Gender, Age, Race; Model 3: adjusted for Gender, Age, Race, Education Level, Marital Status, Family PIR, Alcohol, Coronary heart disease, Stroke, and Cancer.
Abbreviations: LE8, Life's Essential 8; HR, Hazard ratio; CI, Confidence interval.

The RCS analysis, conducted after multiple imputation, revealed a significant and linear negative association between LE8 scores and all-cause mortality (P < 0.001) (Figure 5A). In the cardiovascular mortality analysis, an increase in LE8 score was significantly associated with risk reduction (overall P = 0.011), and no significant nonlinear effect was detected (P = 0.088) (Figure 5B). These results further validate the robustness of the LE8 score as a continuous protective indicator.

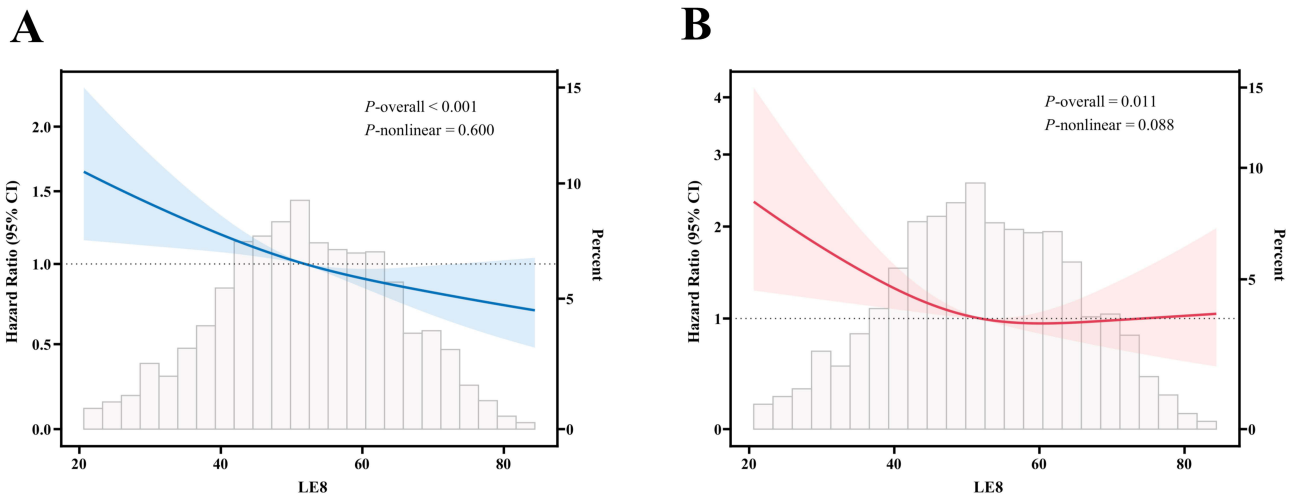

Figure 5 Restricted cubic spline fitting for the association between LE8 and mortality in participants with diabetic nephropathy after multiple imputations for missing covariates. (**A**) all-cause mortality; (**B**) cardiovascular mortality. Solid lines indicate HR and shaded areas indicate 95% CI. These analyses were adjusted according to Model 3.
Abbreviations: LE8, Life's Essential 8; HR, Hazard ratio; CI, Confidence interval.

Discussion

This study is pioneering in its use of data from the NHANES cohort. It is the first to systematically investigate the association between LE8 score and all-cause mortality and cardiovascular mortality in patients with DN. The results demonstrated that an elevated LE8 score was independently associated with a significantly lower risk of death in patients with DN. Furthermore, this protective effect was consistent across sociodemographic subgroups.

The present study confirmed that for every 10-point increase in LE8 score, the risk of all-cause mortality was reduced by 12% and cardiovascular mortality by 16% in patients with DN after adjusting for age, gender, race, socioeconomic factors, and comorbidities. Subgroup analysis by tertile revealed a 33% decrease in the risk of all-cause mortality and a 36% decrease in the risk of cardiovascular mortality in the highest tertile group compared with the lowest tertile group. This finding aligns with prior studies in the general population, as evidenced by Sun et al, who observed a 38% and 64% decrease in the risk of cardiovascular death in adults with intermediate and high LE8 scores, respectively, compared with adults with low LE8 scores.[20] However, the baseline levels of LE8 scores in DN patients in this study (median 51.25–52.50) were significantly lower than those in the general population (mean 65),[25] suggesting that metabolic disorders may diminish the attainment of a composite index of cardiovascular health. Notably, the "ideal" threshold (80 points) in the traditional LE8 score has limited applicability in the DN population. The tertile grouping method used in the present study is more applicable to the metabolic heterogeneity characteristics of this population. This methodological innovation provides an essential reference for subsequent analyses.

The present study's findings are consistent with those of previous studies on applying the LE8 assessment system in the general population. These earlier studies have demonstrated that the LE8 score is a robust predictor of an individual's cardiovascular fitness and future mortality risk.[20,21] However, unlike previous studies, the present study focused on a specific population of DN patients and revealed a novel association between the LE8 score and mortality in this population. This finding extends the application of the LE8 assessment system and provides a new perspective on the prognostic assessment of patients with DN.

LE8 encompasses a wide array of health behaviors and factors that substantially influence the progression of DN. For instance, a rational diet can enhance glycemic control, reduce renal stress, and mitigate inflammatory responses.[18,26] Engaging in regular physical activity can augment insulin sensitivity, improve vascular endothelial function, and decrease the likelihood of cardiovascular incidents.[27,28] Adequate sleep quality can regulate metabolic rhythms and reduce oxidative stress.[29,30] Nicotine exposure control can prevent the toxicity of tobacco, thereby reducing the risk of mortality.[31,32] Furthermore, maintaining an optimal BMI, along with optimal blood glucose, blood pressure, and lipid levels, can retard the progression of glomerulosclerosis and, by extension, minimize cardiovascular load.[1,33–35] The study identified a linear dose-response relationship between LE8 scores and mortality, suggesting that even modest improvements in cardiovascular health indicators (eg, sleep quality or nicotine exposure control) may confer a survival benefit for DN patients.

The findings of subgroup analyses indicated that the correlation between the LE8 score and mortality in patients with DN exhibited consistency across various characteristic subgroups, thereby further substantiating the robustness of the LE8 score as a predictor. Specifically, subgroup analyses revealed a stronger protective association of LE8 in high-income groups (PIR>3.5, HR=0.66). This phenomenon may be indicative of enhanced access to health resources, such as nutritious diets and exercise facilities, as well as healthcare services, which in turn may facilitate more effective management of the LE8 component.[36] The potential exists for future randomized trials to test LE8 as a multidimensional intervention target, particularly with regard to addressing socioeconomic barriers in low-income DN populations. The robustness analysis, employing multiple imputation techniques, yielded consistent results with the original analysis, thereby validating the reliability of the LE8 score as an independent protective factor for mortality risk. This finding suggests that missing data did not substantially affect the primary conclusions.

The present study is not without its limitations. First, the cross-sectional design of the NHANES data limits causal inference, and prospective cohort studies are needed to validate the association between dynamic changes in LE8 scores and risk of death. Second, this study relied primarily on self-reported data and laboratory test results from the NHANES database, which may be subject to information bias and measurement error; third, the potential effect of the interaction between components of the LE8 (eg, diet and blood pressure) on the risk of death was not assessed. Finally, the study

population was limited to US residents, and extrapolating conclusions to other races or regions requires caution. Future studies could explore the pathways of LE8 in combination with biomarkers (eg, inflammatory factors, indicators of oxidative stress) and validate the effect of a multidimensional intervention strategy based on LE8 on improving the prognosis of DN through randomized controlled trials.

Conclusion

This study is the first to demonstrate that the LE8 score functions as an independent protective factor for the risk of all-cause and cardiovascular mortality in patients with DN. The protective effect of the LE8 score demonstrates a linear dose-response pattern and is consistent across sociodemographic subgroups. These findings support the inclusion of the LE8 score in a comprehensive health assessment system for DN patients and provide a theoretical basis for individualized interventions (eg, health education for low-income populations and optimal sleep management). Future research is needed to explore the translation of LE8 scores into clinical practice, with the aim of achieving multidimensional precision management of cardiovascular health in patients with DN.

Data Sharing Statement

The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/).

Institutional Review Board Statement

The studies involving humans were approved by the National Center for Health Statistics Ethics Review Board. The participants provided their written informed consent to participate in this study. As NHANES is a publicly accessible database, the Changzhou Third People's Hospital Ethics Committee granted approval to waive ethical review and approved the study protocol (02A-A2024018).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this study.

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