Evaluating the Life's Crucial 9 score as a predictor of all-cause and cardiovascular mortality in a diabetic and prediabetic population: insights from NHANES 2005–2018

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Abstract

Introduction: The aim of the study was to investigate the association between the Life's Crucial 9 (LC9) score and all-cause and cardiovascular mortality in individuals with diabetes or prediabetes.

Material and methods: This prospective cohort study included 11,564 adults with diabetes/prediabetes from NHANES 2005–2018. The LC9 score (0–100) comprised four health behaviors, four health factors, and a depression component (PHQ-9). Weighted Cox proportional hazards models, Kaplan–Meier curves, and restricted cubic splines were used. Incremental predictive performance was assessed by C-index, time-dependent AUC, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Multiple imputation was performed for sensitivity analysis.

Results: Higher LC9 scores were associated with lower all-cause and cardiovascular mortality. In fully adjusted models, compared with the lowest quartile (Q1), the highest quartile (Q4) yielded HRs of 0.434 (95% CI: 0.317–0.594) for all-cause mortality and 0.449 (95% CI: 0.365–0.552) for cardiovascular mortality (both p for trend < 0.0001), with no significant evidence of nonlinearity. Adding LC9 significantly improved the C-index (all-cause: from 0.806 to 0.815; cardiovascular: from 0.833 to 0.847), with NRIs of 34.7% and 42.3%, and IDIs of 0.70% and 0.61%, respectively. Time-dependent AUCs were consistently improved across follow-up. Stronger associations were observed in younger participants and those without a family history of cardiovascular disease.

Conclusions: Higher LC9 scores are associated with lower risks of all-cause and cardiovascular mortality in U.S. adults with diabetes/prediabetes. Adding LC9 to the baseline model provided additional prognostic information, with discrimination and reclassification analyses suggesting potential improvement in risk stratification.

Key words: mortality, NHANES, cardiovascular, Life's Crucial 9, diabetes and prediabetes.

Introduction

Diabetes mellitus is a major global health issue and is classified into several types, including type 1 diabetes, type 2 diabetes, gestational diabe-

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tes, and other specific types of diabetes [1]. According to the International Diabetes Federation, the number of individuals aged 20-79 years living with diabetes is projected to reach 629 million by 2045 [2]. Diabetes is a significant risk factor for cardiovascular disease (CVD), and the prevalence of CVD is higher among adults with diabetes than among individuals without diabetes. The risk of CVD increases progressively with rising fasting glucose levels, even before glucose levels reach the diagnostic threshold for diabetes [3, 4]. Moreover, CVD is one of the leading causes of death in patients with diabetes, accounting for approximately half of all diabetes-related deaths.

CVD is a multifactorial disease [5]. Although preventive strategies targeting established risk factors have been developed to reduce its incidence and mortality, CVD remains one of the leading causes of death in most countries worldwide [6, 7]. A recent systematic review reported that coronary heart disease, heart failure, and stroke affect 21.2%, 14.9%, and 7.6% of adults with type 2 diabetes (T2D), respectively [8]. Therefore, identifying additional relevant factors for mortality risk assessment and risk stratification in individuals with diabetes and prediabetes is of considerable importance [9].

Depression affects more than 300 million people worldwide [10] and has been identified as a novel risk factor for coronary heart disease [11]. Depression is also associated with other CVD risk factors, and individuals with depression often exhibit unhealthy lifestyle behaviors, such as sedentary behavior, alcohol consumption, and smoking. These factors may contribute to a higher burden of chronic conditions, including diabetes, hypertension, and stroke [12–14]. In 2010, the American Heart Association (AHA) introduced Life's Simple 7 (LS7), which defined ideal cardiovascular health (CVH) based on seven modifiable lifestyle and biological risk factors [15]. The AHA subsequently released an updated algorithm for assessing CVH, the Life's Essential 8 (LE8) score, which incorporates sleep health, assessed by sleep duration, into the original LS7 framework and refines the scoring system [16].

However, neither LS7 nor LE8 explicitly incorporates mental health into CVH assessment. Recent perspectives have emphasized the important role of mental health in CVD prevention, prompting the development of a new metric, Life's Crucial 9 (LC9), which integrates mental health into the LE8 framework [17]. However, the relationship between the LC9 score and mortality in individuals with diabetes or prediabetes remains unclear.

This study therefore aims to investigate these associations, specifically for cardiovascular and all-cause mortality.

Material and methods

Study population

This prospective cohort study utilized baseline data from the seven cycles of the National Health and Nutrition Examination Survey (NHANES) conducted in the United States between 2005 and 2018. Further details regarding the NHANES survey design and methodology can be found in the NHANES Program and Operations Manual. The original NHANES surveys received ethical approval from the National Center for Health Statistics Research Ethics Review Board, and all participants gave written informed consent. As this study constitutes a secondary analysis of anonymized NHANES data, no additional ethical approval was required. All research methods complied with relevant guidelines and regulations.

The study population was drawn from participants in the NHANES study between 2005 and 2018. A total of 67,364 participants were initially included. We excluded 26,868 participants aged < 18 years and 20,591 participants who did not meet the study criteria for diabetes or prediabetes, leaving 19,905 eligible participants. Among these eligible participants, the proportion of missing data across individual LC9 components ranged from 24.1% to 29.7% (Supplementary Table SI). A further 8,341 participants were excluded because of mortality-linkage ineligibility or incomplete LC9-related or covariate data required to construct the analytic dataset. The final analytic cohort comprised 11,564 participants (Figure 1). Supplementary Table SII compares selected characteristics between included and excluded participants. Differences in several baseline characteristics between the two groups suggest the possibility of selection bias related to analytic-cohort inclusion, although these differences did not uniformly indicate a healthier profile among included participants.

Life's Crucial 9 measurement

The LC9 score includes four health behaviors (diet, physical activity, tobacco/nicotine exposure, and sleep health), four health factors (body mass index [BMI], blood lipids, blood glucose, and blood pressure), and a depression component. The scoring criteria for each LE8 component have been described in previous literature [16]. Briefly, each of the nine components was assigned a score ranging from 0 to 100, and the overall LC9 score was calculated as the arithmetic mean of the nine component scores:

$$LC9 \text{ score} = \frac{\sum_{i=1}^{9} S_i}{9},$$

where S_i represents the score (0–100) for each of the nine LC9 components,, including diet, physical activity, tobacco/nicotine exposure, sleep health,

BMI, blood lipids, blood glucose, blood pressure, and depression. Higher LC9 scores indicate better overall cardiovascular and mental health status.

The diet component was assessed using the 2015 Healthy Eating Index [18], derived from the average of two 24-hour dietary recalls, consistent with previous NHANES-based LE8 research [19]. Healthy Eating Index scores were calculated using a simple scoring algorithm and official SAS code provided by the National Cancer Institute [20]. Physical activity, tobacco/nicotine exposure, sleep duration, medical history, and medication use were assessed using standardized self-report questionnaires. Height, weight, and blood pressure were measured during physical examinations. BMI was calculated as weight in kilograms divided by height in meters squared. Blood samples were sent to a central laboratory for measurement of lipid profiles, fasting blood glucose, and hemoglobin A1c (HbA1c). The depression component was derived from the Patient Health Questionnaire-9 (PHQ-9), a validated depression screening tool [21]. PHQ-9 raw scores range from 0 to 27, with higher raw scores indicating more severe depressive symptoms. For the LC9 depression component, PHQ-9 scores were converted to a 0–100 score according to predefined categories, with higher depression component scores indicating fewer depressive symptoms and better mental health. LC9 was categorized into quartiles to facilitate interpretation of exposure gradients and to ensure adequate sample size within each group. Because no clinically established cut-off values currently exist for LC9, data-driven categorization was adopted. This approach is consistent with previous studies evaluating Life's Essential 8 and related cardiovascular health metrics in NHANES and other cohort datasets.

Assessment of diabetes, prediabetes

Using available NHANES data, diabetes was defined as meeting any of the following criteria [22]: (1) self-reported physician diagnosis of diabetes; (2) current use of antihyperglycemic medications or insulin; (3) random plasma glucose level ≥ 11.1 mmol/l; (4) glycated hemoglobin (HbA1c) level ≥ 6.5%; (5) fasting plasma glucose level ≥ 7.0 mmol/l; or (6) 2-hour plasma glucose level ≥ 11.1 mmol/l during an oral glucose tolerance test (OGTT). In this study, diabetes and prediabetes status were used to define the study population, whereas cardiovascular mortality and all-cause mortality were the primary outcomes.

Prediabetes was defined according to the World Health Organization (WHO) criteria as a state of intermediate hyperglycemia, including impaired fasting glucose (IFG), defined as fasting plasma glucose (FPG) of 6.1–6.9 mmol/l (110–125 mg/dl), and/or impaired glucose tolerance (IGT), defined as 2-hour plasma glucose of 7.8–11.0 mmol/l (140–200 mg/dl) after a 75-g oral glucose load [23].

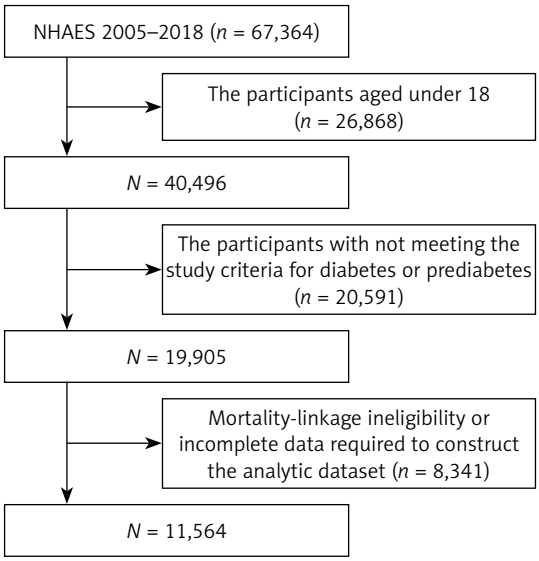

Figure 1. Flowchart

Mortality assessment

Mortality status and cause of death were ascertained using the NHANES public-use linked mortality files, with follow-up available through December 31, 2019. NHANES participant records were linked to the National Death Index (NDI) by the National Center for Health Statistics (NCHS) using a probabilistic matching algorithm. Follow-up time was calculated from the date of the NHANES interview to the date of death or December 31, 2019, whichever came first. The underlying cause of death was identified according to the International Classification of Diseases, 10th Revision (ICD-10). Cardiovascular mortality was defined as death due to heart diseases, including ICD-10 codes I00–I09, I11, I13, and I20–I51, or cerebrovascular diseases, including ICD-10 codes I60–I69 [24]. All-cause mortality was defined as death from any cause during follow-up.

Potential confounding factors

Demographic and socioeconomic factors were considered as potential confounders, including sex, age, race/ethnicity, education level, marital status, and poverty-income ratio (PIR). Sex was categorized as male or female. Race/ethnicity was categorized as Mexican American, Other Hispanic, non-Hispanic White, non-Hispanic Black, or other race. Education level was categorized as less than high school, high school or equivalent, or more than high school. Marital status was categorized as married or living with a partner, divorced, separated, or widowed, or never married. PIR was categorized as < 1.3, 1.3–3.5, or ≥ 3.5. Additional

covariates included alcohol consumption, medication use, family history of diabetes, and family history of CVD. Family history of CVD was defined as a close biological relative with heart attack or angina before age 50 years. Medication use included antidiabetic drugs, antihypertensive drugs, and antihyperlipidemic drugs.

Statistical analysis

To account for the complex multistage probability sampling design of NHANES, all analyses, including Cox proportional hazards regression models, Kaplan–Meier survival analyses, log-rank tests, and restricted cubic spline (RCS) models, incorporated the NHANES sampling weights (WTMEC2YR divided by 7), primary sampling units (SDMVPSU), and stratification variables (SDMVSTRA) to account for the complex survey design. Continuous variables are presented as weighted means with standard deviations (SEs), and categorical variables are presented as weighted percentages. Differences in baseline characteristics across LC9 score quartiles were compared using weighted linear regression models for continuous variables and weighted χ^2 tests for categorical variables.

Multivariable Cox proportional hazards regression models were fitted to examine the associations of the LC9 score with all-cause mortality and cardiovascular mortality among individuals with diabetes and prediabetes. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. LC9 score quartiles were treated as categorical variables, with the lowest quartile (Q1) used as the reference group.

Three models were constructed. Model 1 was unadjusted. Model 2 was adjusted for age, sex, race/ethnicity, and education level. Model 3 was further adjusted for alcohol consumption, marital status, PIR, family history of diabetes, family history of CVD, antidiabetic drug use, antihypertensive drug use, and antihyperlipidemic drug use. Smoking status and BMI were not additionally included as separate covariates in the main models because tobacco/nicotine exposure and BMI are components of the LC9 score, and additional adjustment for these variables may introduce overadjustment or collinearity.

Kaplan–Meier survival curves were generated to compare all-cause and cardiovascular survival across LC9 score quartiles, and log-rank tests were used to assess differences in survival distributions. RCS models were used to evaluate the dose-response relationship and potential nonlinearity between the LC9 score and mortality outcomes.

To examine whether the associations of the LC9 score with cardiovascular mortality and all-cause mortality differed across subgroups, stratified analyses were conducted by age, sex, race/ethnicity, alcohol consumption, PIR, family history of diabetes, and family history of CVD. In this study, the primary analyses were based on the final analytic cohort and reported the primary results accordingly. Furthermore, we used the Multiple Imputation by Chained Equations (MICE) method as a sensitivity analysis to address missing data and evaluate the robustness of our findings. Additional details on the MICE approach are available in the supplementary materials. In addition, we evaluated the incremental predictive performance of LC9 beyond the baseline model by assessing discrimination and reclassification metrics, including Harrell's C-index, time-dependent AUCs, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). All analyses were performed using R version 4.4.2. Two-sided p-values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the study participants across LC9 score quartiles are presented in Table I. The final analytic cohort included 11,564 individuals with diabetes or prediabetes. Overall, the mean age was 54.33 years, 51.35% of participants were male, and 68.99% were non-Hispanic White.

Participants with higher LC9 scores tended to be younger and were more likely to be male, non-Hispanic White, married or living with a partner, have a higher poverty-income ratio (PIR), and have more than a high school education. In contrast, participants in lower LC9 quartiles were more likely to have a family history of diabetes or CVD and to use antidiabetic, antihypertensive, or antihyperlipidemic medications.

The mean LC9 score increased progressively across quartiles, from 47.72 in Q1 to 80.49 in Q4. Similar increasing trends were observed for all LC9 components, including diet, physical activity, tobacco exposure, sleep health, BMI, non-high-density lipoprotein cholesterol, blood glucose, blood pressure, and the PHQ-9-derived depression component. These findings indicate that participants with higher LC9 scores had more favorable overall cardiovascular and mental health profiles.

Associations between LC9 scores and cardiovascular/all-cause mortality in diabetes and prediabetes

The associations between LC9 score quartiles and cardiovascular and all-cause mortality are shown in Table II. Across all three Cox proportional hazards models, higher LC9 score quartiles were

Table I. Baseline characteristics of participants across LC9 score quartiles, NHANES 2005–2018

Variables	LC9					*P*-value
	Total	Q1 [13.89, 55.556]	Q2 (55.556, 65]	Q3 (65, 73.333]	Q4 (73.333, 100]	
Age [years], weighted mean (SE)	54.33 (0.25)	55.76 (0.34)	56.20 (0.36)	54.29 (0.42)	51.76 (0.50)	**< 0.001**
Sex, *n* (%)						**< 0.001**
Female	48.65	54.36	47.48	46.54	46.93	
Male	51.35	45.64	52.52	53.46	53.07	
Race/ethnicity, *n* (%)						**< 0.001**
Mexican American	7.89	7.15	8.68	8.00	7.72	
Non-Hispanic Black	11.51	15.95	12.68	10.78	7.75	
Non-Hispanic White	68.99	67.21	67.59	69.98	70.74	
Other Hispanic	4.74	4.40	4.95	4.92	4.69	
Other race, including multi-racial	6.87	5.29	6.09	6.32	9.11	
Marital status, *n* (%)						**< 0.001**
Divorced/separated/widowed	22.20	29.11	24.54	22.24	15.03	
Married/living with a partner	66.73	59.04	66.06	66.86	72.96	
Never married	11.08	11.85	9.40	10.89	12.01	
PIR, *n* (%)						**< 0.001**
< 1.3	19.42	30.04	20.20	16.95	12.67	
1.3–3.5	37.90	42.58	41.33	35.01	33.78	
≥ 3.5	42.68	27.38	38.47	48.03	53.55	
Alcohol, *n* (%)						**< 0.001**
Former	17.26	25.47	18.16	16.27	11.10	
Heavy	16.43	18.79	17.84	17.73	12.49	
Mild	40.17	31.12	39.52	39.60	47.96	
Moderate	15.02	14.97	14.33	15.20	15.48	
Never	11.12	9.65	10.15	11.20	12.96	
Education level, *n* (%)						**< 0.001**
≥ College	58.15	44.36	52.86	62.32	69.68	
Completed high school	25.05	30.56	27.14	24.58	19.54	
< High school diploma	16.80	25.08	20.00	13.10	10.78	
Mean LC9 score (weighted mean (SE))	65.65 (0.25)	47.72 (0.19)	60.80 (0.07)	69.12 (0.06)	80.49 (0.15)	**< 0.0001**
Mean HEI-2015 diet score (weighted mean (SE))	39.26 (0.54)	23.55 (0.63)	32.43 (0.68)	41.53 (0.87)	54.97 (1.01)	**< 0.0001**
Mean physical activity score (weighted mean (SE))	67.13 (0.65)	33.62 (1.22)	59.02 (1.11)	77.30 (1.03)	91.21 (0.62)	**< 0.0001**
Mean tobacco exposure score (weighted mean (SE))	71.04 (0.60)	49.90 (1.14)	66.43 (0.96)	75.77 (1.04)	87.14 (0.69)	**< 0.0001**
Mean sleep health score (weighted mean (SE))	82.44 (0.38)	68.57 (0.73)	81.25 (0.62)	86.24 (0.66)	90.93 (0.40)	**< 0.0001**
Mean body mass index score (weighted mean (SE))	51.11 (0.47)	30.86 (0.73)	44.48 (0.74)	51.83 (0.78)	71.29 (0.74)	**< 0.0001**
Mean blood lipid score (weighted mean (SE))	59.07 (0.49)	45.18 (0.74)	54.92 (0.83)	60.08 (0.83)	72.19 (0.79)	**< 0.0001**
Mean blood glucose score (weighted mean (SE))	69.41 (0.39)	53.14 (0.68)	64.92 (0.65)	72.31 (0.64)	83.13 (0.57)	**< 0.0001**
Mean blood pressure score (weighted mean (SE))	60.65 (0.44)	45.36 (0.81)	53.39 (0.87)	62.71 (0.69)	76.56 (0.64)	**< 0.0001**
Mean psychological health score (weighted mean (SE))	90.77 (0.27)	79.31 (0.74)	90.39 (0.49)	94.34 (0.49)	96.97 (0.28)	**< 0.0001**

Table I. Cont.

Variables	LC9					*P*-value
	Total	Q1 [13.89, 55.556]	Q2 (55.556, 65]	Q3 (65, 73.333]	Q4 (73.333, 100]	
Family history of diabetes, *n* (%)						**< 0.0001**
No	52.25	41.36	50.31	51.96	62.30	
Yes	47.75	58.64	49.69	48.04	37.70	
Family history of CVD, *n* (%)						**< 0.0001**
No	83.42	76.82	83.92	85.92	89.26	
Yes	15.43	23.18	16.08	14.08	10.74	
Antidiabetic, *n* (%)						**< 0.0001**
No	81.01	64.57	78.08	84.96	92.94	
Yes	18.92	35.43	21.92	15.04	7.06	
Antihypertensive, *n* (%)						**< 0.0001**
No	56.96	41.45	49.39	59.30	73.19	
Yes	42.97	58.55	50.61	40.70	26.81	
Antihyperlipidemic, *n* (%)						**< 0.0001**
No	68.83	61.28	65.79	70.24	76.08	
Yes	31.10	38.72	34.21	29.76	23.92	

LC9 – Life's Crucial 9, HEI-2015 – Healthy Eating Index-2015, PIR – poverty-income ratio, CVD – cardiovascular disease. Bold values indicate p < 0.05.

Table II. Associations of LC9 score quartiles with cardiovascular and all-cause mortality

Variable	Model 1 HR (95% CI)	*P*-value	Model 2 HR (95% CI)	*P*-value	Model 3 HR (95% CI)	*P*-value
Cardiovascular mortality						
LC9						
Q1	Ref		Ref		Ref	
Q2	0.720 (0.619, 0.837)	< 0.001	0.641 (0.550, 0.746)	< 0.0001	0.725 (0.621, 0.845)	< 0.0001
Q3	0.587 (0.494, 0.697)	< 0.0001	0.561 (0.471, 0.669)	< 0.0001	0.675 (0.567, 0.804)	< 0.0001
Q4	0.334 (0.273, 0.409)	< 0.0001	0.342 (0.277, 0.421)	< 0.0001	0.449 (0.365, 0.552)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
All-cause mortality						
LC9						
Q1	Ref		Ref		Ref	
Q2	0.649 (0.513, 0.821)	< 0.0001	0.558 (0.446, 0.698)	< 0.0001	0.627 (0.499, 0.788)	< 0.0001
Q3	0.531 (0.403, 0.699)	< 0.0001	0.488 (0.362, 0.659)	< 0.0001	0.606 (0.456, 0.807)	< 0.0001
Q4	0.315 (0.235, 0.421)	< 0.0001	0.309 (0.228, 0.419)	< 0.0001	0.434 (0.317, 0.594)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001

Model 1 (crude model): no covariates were adjusted for. Model 2: adjusted for age, sex, ethnicity, and education. Model 3: adjusted for age, sex, ethnicity, education, alcohol use, marital status, poverty income ratio (PIR), family history of diabetes, family history of cardiovascular disease (CVD), antidiabetic drugs, antihypertensive drugs, and antihyperlipidemic drugs. LC9 – Life's Crucial 9, CI – confidence interval, HR – hazard ratio.

consistently associated with lower risks of both cardiovascular mortality and all-cause mortality.

For cardiovascular mortality, compared with participants in the lowest LC9 quartile (Q1), those in the highest quartile (Q4) had a significantly lower risk in the fully adjusted model (Model 3: hazard ratio [HR] = 0.449, 95% confidence interval [CI]: 0.365–0.552; $p < 0.0001$). Similar inverse associations were observed for Q2 and Q3, with fully adjusted HRs of 0.725 (95% CI: 0.621–0.845; $p < 0.0001$) and 0.675 (95% CI: 0.567–0.804; $p < 0.0001$), respectively. The trend across LC9 quartiles was statistically significant in all models.

For all-cause mortality, higher LC9 score quartiles were also associated with lower mortality risk. In the fully adjusted model, compared with

Q1, the HRs were 0.627 (95% CI: 0.499–0.788; $p < 0.0001$) for Q2, 0.606 (95% CI: 0.456–0.807; $p < 0.0001$) for Q3, and 0.434 (95% CI: 0.317–0.594; $p < 0.0001$) for Q4. A significant trend was also observed across LC9 quartiles for all-cause mortality.

Kaplan–Meier survival analysis

Kaplan–Meier survival curves stratified by LC9 score quartiles are shown in Figure 2. Survival probabilities differed across LC9 quartiles for both all-cause mortality and cardiovascular mortality. Participants in lower LC9 quartiles showed lower survival probabilities during follow-up, whereas those in higher LC9 quartiles had more favorable survival patterns. These findings were consistent with the Cox regression results, suggesting inverse associations between LC9 scores and mortality outcomes.

Restricted cubic spline (RCS) analysis

RCS analyses were used to evaluate the dose–response relationship between LC9 scores and mortality outcomes (Figure 3). The results demonstrated an overall inverse association between LC9 score and both all-cause and cardiovascular mortality.

The association was approximately linear across the observed range of LC9 scores, and formal tests for nonlinearity were not statistically significant for either outcome (all-cause mortality: p for nonlinearity = 0.1125; cardiovascular mortality: p for nonlinearity = 0.2937). These findings are consistent with the dose–response patterns observed in the quartile-based Cox regression analyses.

Stratified analyses

Subgroup analyses of the association between LC9 scores and cardiovascular mortality are shown in Table III A. The inverse association between LC9 scores and cardiovascular mortality was generally observed across most subgroups. Significant interactions were found for age and family history of CVD. The association appeared stronger among participants younger than 60 years than among those older than 60 years. In addition, the inverse association was more evident among participants without a family history of CVD, whereas the association was not statistically significant among those with a family history of CVD.

Subgroup analyses for all-cause mortality are shown in Table III B. Higher LC9 scores were also associated with lower all-cause mortality across most subgroups. Significant interactions were observed for age and family history of CVD. Similar to the findings for cardiovascular mortality, the association was stronger among participants younger than 60 years and among those without a family history of CVD. No significant interactions were observed by sex, race/ethnicity, or family history of diabetes.

Missing data and sensitivity analyses

The missing data patterns for the study variables are summarized in Supplementary Table SI.

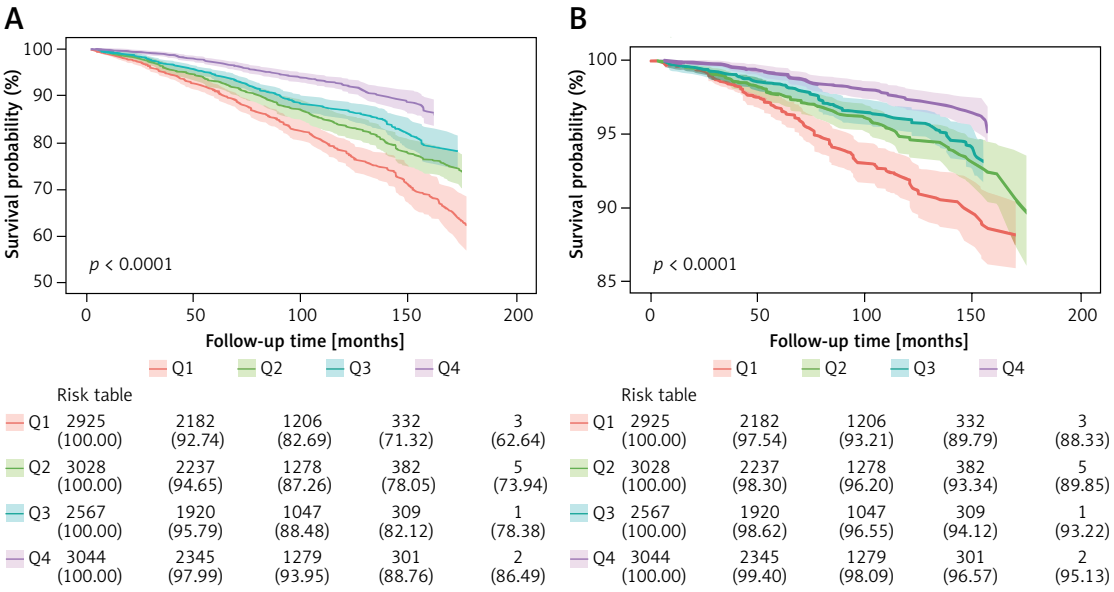

Figure 2. Kaplan–Meier survival curves according to LC9 score quartiles among individuals with diabetes or prediabetes. **A** – All-cause mortality. **B** – Cardiovascular mortality. Q1 represents the lowest LC9 score quartile, and Q4 represents the highest LC9 score quartile. Shaded areas indicate 95% confidence intervals. Risk tables show the number of participants at risk at each follow-up time point. Differences in survival distributions were assessed using log-rank tests

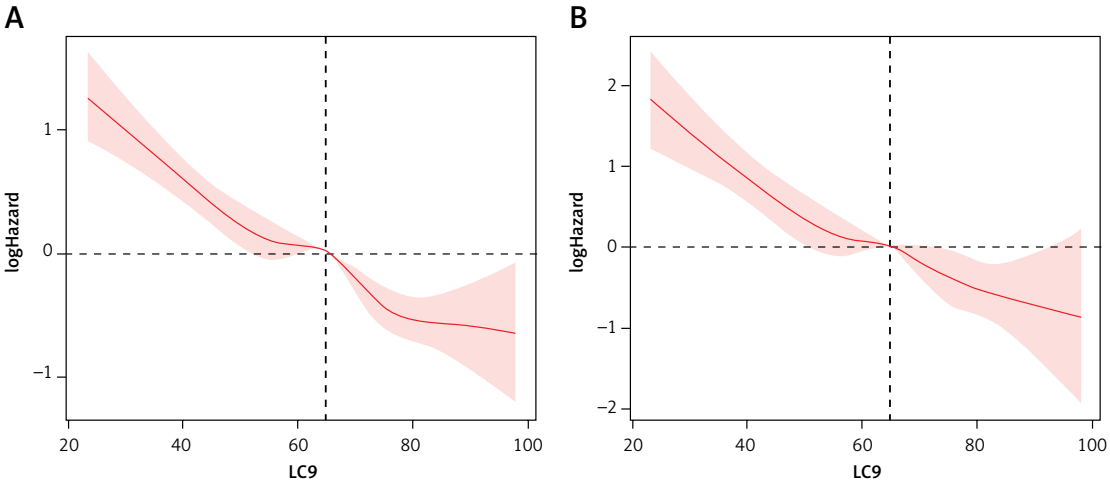

Figure 3. Restricted cubic spline analyses of the associations between LC9 scores and mortality outcomes among individuals with diabetes or prediabetes. **A** – All-cause mortality. **B** – Cardiovascular mortality. The solid red lines represent estimated log hazard ratios, and the shaded areas represent 95% confidence intervals. The horizontal dashed line indicates a log hazard ratio of 0, and the vertical dashed line indicates the reference LC9 score. *P*-values for nonlinearity were 0.1125 for all-cause mortality and 0.2937 for cardiovascular mortality

Supplementary Table SII compares the baseline characteristics between included and excluded participants. Supplementary Table SIII compares the main results of the primary analysis with those of multiple imputation (MI). In the fully adjusted model following multiple imputation, participants in the highest quartile of LC9 scores had a hazard ratio of 0.467 for cardiovascular mortality and a hazard ratio of 0.478 for all-cause mortality. Supplementary Table SIV presents the full imputation results for the association between the LC9 score and mortality; these findings are consistent with the main analysis and further support the robustness of the negative association between the LC9 score and mortality outcomes.

Incremental predictive performance of LC9

To further evaluate the incremental predictive performance of LC9, we assessed its incremental predictive performance beyond the baseline model. For all-cause mortality, the addition of LC9 significantly improved model discrimination, with the C-index increasing from 0.806 (95% CI: 0.796–0.817) in the baseline model to 0.815 (95% CI: 0.805–0.825) in the LC9-augmented model ($p < 0.001$). The NRI was 34.7% (95% CI: 28.7–40.8%), and the IDI was 0.70% (95% CI: 0.34–1.17%). For cardiovascular mortality, similar improvements were observed. The C-index increased from 0.833 (95% CI: 0.818–0.851) to 0.847 (95% CI: 0.833–0.862) after adding LC9 ($p < 0.001$). Correspondingly, the NRI was 42.3% (95% CI: 28.7–56.2%), and the IDI was 0.61% (95% CI: 0.15–1.33%) (as shown in Table IV).

Time-dependent AUC analyses showed consistent improvement in predictive performance across follow-up durations (Figure 4). For all-cause mortality, the LC9-augmented model yielded higher AUCs at 1 year (0.817 vs. 0.808), 3 years (0.815 vs. 0.805), 5 years (0.822 vs. 0.812), and 10 years (0.840 vs. 0.832). For cardiovascular mortality, corresponding AUCs were 0.844 vs. 0.822 at 1 year, 0.833 vs. 0.812 at 3 years, 0.860 vs. 0.843 at 5 years, and 0.868 vs. 0.855 at 10 years, suggesting consistent improvement in risk stratification over time.

Discussion

In this prospective cohort study of adults with diabetes or prediabetes from NHANES 2005–2018, higher LC9 scores were associated with lower risks of cardiovascular mortality and all-cause mortality. These associations persisted after adjustment for demographic and socioeconomic factors and selected clinical covariates. However, because this was an observational study, the findings should be interpreted as associations rather than causal effects. Although missing data were present for several LC9 components, sensitivity analyses using multiple imputation showed similar inverse associations, supporting the robustness of the main findings.

Our findings demonstrate a significant association between LC9 scores and cardiovascular mortality in diabetes and prediabetes, with no significant evidence of nonlinearity between LC9 scores and all-cause mortality showing an inverse association. Lower LC9 scores were associated with steeper increases in cardiovascular and all-cause mortality. These associations remained significant after adjusting for multiple covariates. Subgroup analyses suggested that the association between LC9 and mortality may differ by age and family history of heart disease. However, it should be

Table III. A – Subgroup analyses of the association between LC9 score and cardiovascular mortality. **B** – Subgroup analyses of the association between LC9 score and all-cause mortality

A

Parameter	HR (95% CI)	*P*-value	*P* for interaction
Ethnicity			0.149
Mexican American	0.958 (0.944,0.972)	< 0.0001	
Non-Hispanic Black	0.978 (0.965,0.990)	< 0.001	
Non-Hispanic White	0.989 (0.937,1.045)	0.693	
Other Hispanic	0.966 (0.913,1.021)	0.214	
Other race, including multi-racial	0.995 (0.961,1.030)	0.760	
Sex			0.153
Female	0.971 (0.959,0.982)	< 0.0001	
Male	0.981 (0.965,0.998)	0.032	
Age			< 0.001
< 60	0.947 (0.922,0.973)	< 0.001	
≥ 60	0.992 (0.981,1.003)	0.156	
Family history of diabetes			0.696
No	0.976 (0.961,0.990)	0.001	
Yes	0.967 (0.954,0.980)	< 0.0001	
Family history of CVD			0.046
No	0.972 (0.960,0.983)	< 0.0001	
Yes	0.991 (0.970,1.014)	0.435	

B

Parameter	HR (95% CI)	*P*-value	*P* for interaction
Ethnicity			0.260
Mexican American	0.977 (0.966,0.988)	< 0.0001	
Non-Hispanic Black	0.974 (0.964,0.983)	< 0.0001	
Non-Hispanic White	0.983 (0.957,1.010)	0.207	
Other Hispanic	0.969 (0.936,1.002)	0.068	
Other race, including multi-racial	0.993 (0.968,1.019)	0.610	
Sex			0.705
Female	0.978 (0.968,0.988)	< 0.0001	
Male	0.972 (0.961,0.984)	< 0.0001	
Age			0.002
< 60	0.964 (0.948,0.979)	< 0.0001	
≥ 60	0.987 (0.979,0.995)	0.002	
Family history of diabetes			0.163
No	0.969 (0.959,0.980)	< 0.0001	
Yes	0.981 (0.971,0.991)	< 0.0001	
Family history of CVD			0.042
No	0.971 (0.962,0.980)	< 0.0001	
Yes	0.989 (0.975,1.004)	0.137	

noted that these analyses were exploratory and were not adjusted for multiple comparisons. The substantial overlap of confidence intervals across subgroups indicates that the evidence for effect modification is limited. The possibility that these findings represent chance observations cannot be excluded. Further validation in independent cohorts with larger sample sizes and prespecified subgroup hypotheses is warranted to confirm these patterns.

To date, few studies have explored the relationship between LC9 scores and cardiovascular

Table IV. Discrimination and reclassification improvement for LC9 added to the baseline model

Model	C-index (95% CI)	*P*-value	NRI (95% CI)	IDI (95% CI)
All-cause mortality				
Baseline model	0.806 (0.796–0.817)	Reference	Reference	Reference
+ LC9	0.815 (0.805–0.825)	< 0.001	34.7% (28.7–40.8%)	0.70% (0.34–1.17%)
Cardiovascular mortality				
Baseline model	0.833 (0.818–0.851)	Reference	Reference	Reference
+ LC9	0.847 (0.833–0.862)	< 0.001	42.3% (28.7–56.2%)	0.61% (0.15–1.33%)

The baseline model was adjusted for age, sex, marital status, alcohol consumption, education level, and poverty-income ratio. LC9 – Life's Crucial 9, IDI – integrated discrimination improvement, NRI – net reclassification improvement, Ref – reference.

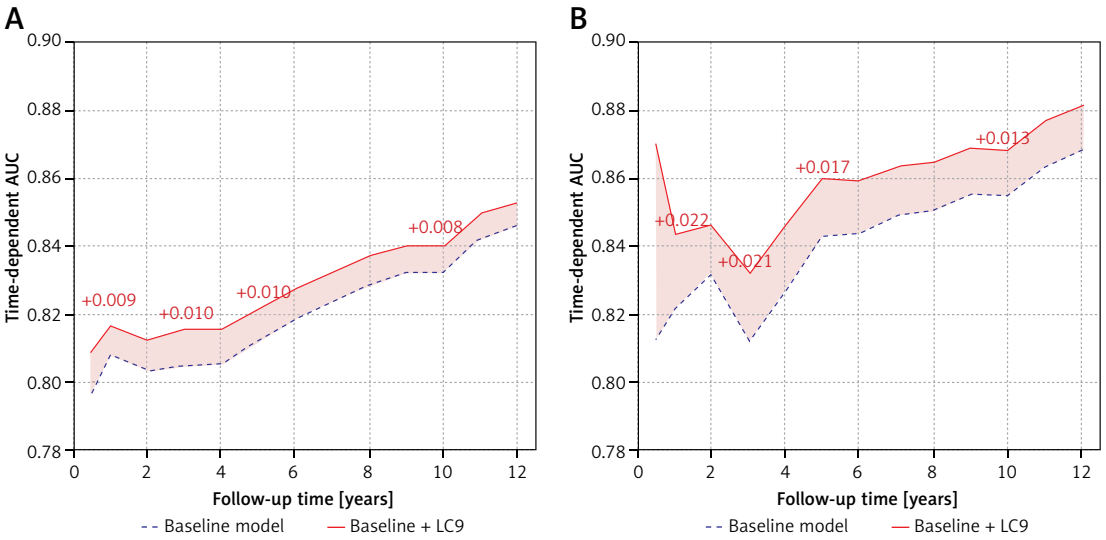

Figure 4. Time-dependent AUC for all-cause and cardiovascular mortality based on models with and without LC9. **A** – All-cause mortality. **B** – CVD-specific mortality. The baseline model was adjusted for age, sex, marital status, alcohol consumption, education level, and poverty-income ratio. Solid and dashed lines represent the baseline + LC9 model and the baseline model, respectively. Shaded areas indicate the improvement in AUC upon adding LC9. Numerical values denote the absolute increase in AUC at specific follow-up time points (1, 3, 5, and 10 years)

disease [17]. Data on the potential impact of LC9 scores on health outcomes in diabetic populations are limited. Since the introduction of the AHA's LE8 framework [16], multiple large prospective studies have confirmed its strong inverse association with all-cause and cardiovascular mortality in the general U.S. population [19, 25]. More recent evidence suggests that this protective association may be particularly pronounced among individuals with diabetes. These patients derive greater absolute risk reduction from higher cardiovascular health scores compared with those without diabetes [26]. One study reported that a 10-point increase in LE8 scores was associated with an 18% lower risk of macrovascular disease and a 15% lower risk of microvascular complications in T2D individuals after adjusting for confounders [27]. Another study showed that the impact of optimal CVH on diabetes was more pronounced in normoglycemic participants than in those with prediabetes ($p < 0.0001$) [28]. Collectively, higher LE8 and LC9 scores are consistently associated with reduced risks of cardiovascular events, microvascular complications, and mortality in individuals across the glycemic spectrum [25–29]. Our findings extend this evidence by showing that higher LC9 scores were associated with lower mortality and that adding LC9 to the baseline model modestly improved predictive performance. This domain has been frequently disregarded in traditional cardiovascular risk assessment, and our results are corroborated by emerging studies on LC9 in other clinical populations [30, 31]. In terms of predictive performance, the addition of LC9 to the baseline model yielded a net reclassification improvement of 34.7% for all-cause mortality and 42.3% for cardiovascular mortality. The positive NRI estimates indicated a net improvement in reclassification after LC9 was added to the baseline model. Adding LC9 to the baseline model modestly improved predictive performance (C-index increase of 0.009–0.014), suggesting that LC9 provided additional prognostic information beyond the baseline model used in this study.

In stratified analyses, the protective association of LC9 scores with cardiovascular mortality was more pronounced in individuals without a family history of heart disease. This pattern

may reflect that families share environmental and behavioral risk factors, including dietary patterns, physical activity habits, and smoking exposure. These factors are partially captured by LC9 components such as diet, physical activity, tobacco and nicotine exposure, and sleep duration. Several studies across disease contexts have shown that the benefits of a favorable lifestyle are at least as strong as, and often additive to, the risk conferred by family history [32]. Conversely, individuals with a family history of heart disease may carry unmeasured hereditary risk factors. These factors are not fully modifiable through the lifestyle and behavioral domains assessed by LC9. Gene-environment interaction studies in hypertension have demonstrated that adherence to healthy lifestyles can substantially mitigate the risk attributable to genetic variants. These findings suggest that the interplay between family history and cardiovascular health metrics warrants further investigation [33]. Future studies incorporating genetic data, repeated measures of LC9 components, and longer follow-up are needed. Such work would clarify whether the differential association by family history reflects residual confounding, genuine effect modification, or chance, particularly since our exploratory subgroup analyses cannot distinguish among these possibilities. Dietary-specific two-day recall weights were not used for the HEI-2015 component, which may have affected population-representative estimates involving diet.

Age-related differences in the association between LC9 scores and cardiovascular mortality were also observed in our study. Aging is a well-established non-modifiable risk factor for cardiovascular disease. Its relationship with mortality is mediated through cumulative exposure to metabolic, hemodynamic, and inflammatory stressors. Physical activity, diet, blood glucose, blood lipids, and blood pressure are among the LC9 components. These represent modifiable pathways through which cardiovascular risk may be reduced across all age groups. A recent study demonstrated that biological aging, measured via clinical biomarkers, partially mediates the association between LE8 and mortality among individuals with diabetes and/or hypertension [34]. This finding suggests that cardiovascular health metrics may exert their protective effects partly through slowing biological aging processes. Recent evidence from a large prospective cohort study demonstrated that higher levels of leisure time physical activity, including moderate-intensity activities, were associated with a lower risk of all-cause mortality among older adults, with evidence of a dose-response relationship [35]. This observation is consistent with the protective role of higher LC9 scores across age groups in our study. The relationship between cardiovascular health and aging appears bidirectional. Healthier behaviors attenuate age-related cardiovascular decline, while age-related changes in turn may influence health behaviors. Further studies with biomarker data are needed to determine whether the observed associations are mediated by biological aging processes, as has been suggested for LE8 in prior work [34].

Key strengths of this study include the use of a large U.S. sample of adults with diabetes or prediabetes from NHANES (2005–2018), prospective mortality follow-up with a large sample size and long-term outcome ascertainment, adjustment for multiple potential confounders, and sensitivity analyses using multiple imputation that confirmed the robustness of the findings.

As a prospective cohort study, causal inference cannot be drawn. Self-reported components (diet, physical activity, tobacco, sleep, depressive symptoms) may introduce recall bias. LC9 was measured only at baseline, precluding assessment of changes over time. Residual confounding remains possible. The LC9 uses equal weights for comparability, but optimal weighting, especially for depression, remains unknown. The exploratory subgroup analyses should be interpreted cautiously given the absence of adjustment for multiple testing. Additionally, the LC9 framework itself is relatively new, and findings from this single NHANES cohort require validation in independent populations with diverse geographic and ethnic backgrounds. Therefore, findings may not be generalizable beyond U.S. adults.

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Ethical approval

This secondary analysis used eidentified, publicly available NHANES data; no additional institutional ethical approval was required.

Conflict of interest

The authors declare no conflict of interest.

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