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Glycated haemoglobin index is a new predictor for all-cause mortality and cardiovascular mortality in the adults

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Glycosylated haemoglobin index (HGI) has been shown to correlate with the prognosis of metabolic diseases, but the relationship with mortality remains unclear. This study included 18,285 US adults who participated in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018. During the median follow-up period of 115 months, a total of 2572 all-cause deaths and 671 cardiovascular disease (CVD) deaths occurred. The restricted cubic spline revealed a U-shaped correlation between HGI and all-cause and CVD mortality. After adjusting for all covariates, the optimal inflection point values in all-cause and CVD deaths were 0.17 and 0.02, respectively. In the left side of the inflection point, the risk of all-cause mortality and CVD mortality decreased by approximately 24% (HR 0.76, 95% CI 0.69, 0.84) and 25% (HR 0.75, 95% CI 0.60, 0.96) with the increase in HGI. Conversely, in the right of the inflection point, an increase of 1 unit in the HGI was linked with a 17% (HR 1.17, 95% CI 1.07, 1.27) and 31% (HR 1.31, 95% CI 1.15, 1.49) increase in all-cause and CVD mortality. Our study showed that HGI is an important tool for predicting the risk of all-cause mortality and CVD death in US adults and there is a U-shaped relationship between HGI and mortality.

Keywords Glycosylated haemoglobin index, All-cause mortality, Cardiovascular mortality, US adults, NHANES

Cardiovascular disease (CVD) poses a huge health and economic burden worldwide and remains the leading cause of death[1]. CVD was driven by a combination of genetic susceptibility and environmental risk factors, and early identification and intervention of risk factors is beneficial in delaying or reversing the onset and progression of CVD[2]. To date, the main treatments for patients with CVD are lifestyle and dietary interventions, pharmacological treatments, interventional and surgical procedures[3]. Despite significant advances in the treatment of CVD disease over the past decades, adverse events and deaths due to CVD remain high[4]. Therefore, early identification of predictors of CVD risk is important to prevent the development of CVD.

Glycated haemoglobin (HbA1c), a non-enzymatic reaction between haemoglobin and body sugar, represents the average blood glucose level in the past 2–3 months and has been used by the American Diabetes Association as a diagnostic indicator for diabetes mellitus[5]. However, more and more studies have confirmed that HbA1c is not only affected by blood glucose, but also has a complex inter-individual variation, which is related to genetic factors, red blood cell lifespan, ethnicity and other factors, and affects the judgement of the degree of blood glucose control[6]. Some studies have shown that even with comparable levels of glycaemic control, there are individual differences in actual HbA1c measurements in some patients[7].

In 2002, Hempe et al. first proposed the concept of the glycated haemoglobin variation index (HGI), which is defined as the difference between measured and predicted HbA1c, and quantifies the magnitude and direction of the difference between measured and predicted HbA1c in different individuals[8]. Previous studies have shown a correlation between HGI and cardiovascular metabolic indices, including obesity, lipids, uric acid, and insulin resistance[9–12]. However, whether HGI is associated with cardiovascular and all-cause mortality in the

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population remains unanswered. The aim of our study was to find out whether HGI has a prognostic value for the risk of all-cause mortality and the risk of CVD death in the general population.

Methods

Study population

Data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES) database (https://www.cdc.gov/nchs/nhanes/index.html), a cross-sectional study designed to assess the health status of the U.S. population. The NHANES database from 1999 to 2018 was selected as the study data. The study included 101,317 participants, and after screening, data from 18,285 participants aged ≥ 18 years were ultimately used (Fig. 1).

This survey was organised by the Centers for Disease Control and Prevention and the sample was representative through multistage complex sampling. All surveys were reviewed and approved by the Ethical Review Committee of the National Center for Health Statistics (NCHS) and all participants provided written informed consent. The current study was conducted in accordance with the Declaration of Helsinki and adheres to the STROBE reporting guidelines.

Definition of HGI

HbA1c was measured using high performance liquid chromatography. To account for changes in laboratory methods over time, we calibrated HbA1c levels using the equipercentile equating method by Selvin et al.[13]. This method uses a statistical correction to account for changes in both the mean and standard deviation of the distribution of HbA1c due to changes in laboratory methods and has been well accepted[14]. Blood collection was performed in the morning after fasting (at least 8 h or more but less than 24 h) to collect fasting plasma glucose (FPG). Due to the extensive time span from 1999 to 2018, changes in FPG testing methodologies were inevitable. To ensure the consistency of data testing across different cycles, we standardized and adjusted the FPG data according to the methodologies used by the CDC's NHANES laboratory (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/manuals.aspx?BeginYear=2019).

HbA1c and FPG levels in the laboratory data were obtained from the NHANES database and a linear regression to estimate the relation between the two variables. This resulted in the linear regression equation: Predicted HbA1c = 0.465* FPG + 2.92, $R^2 = 0.69$ (Fig. 2). The predicted HbA1c was calculated by substituting the FPG values of each patient into the regression equation. HGI was calculated using the formula[15]: HGI = measured HbA1c

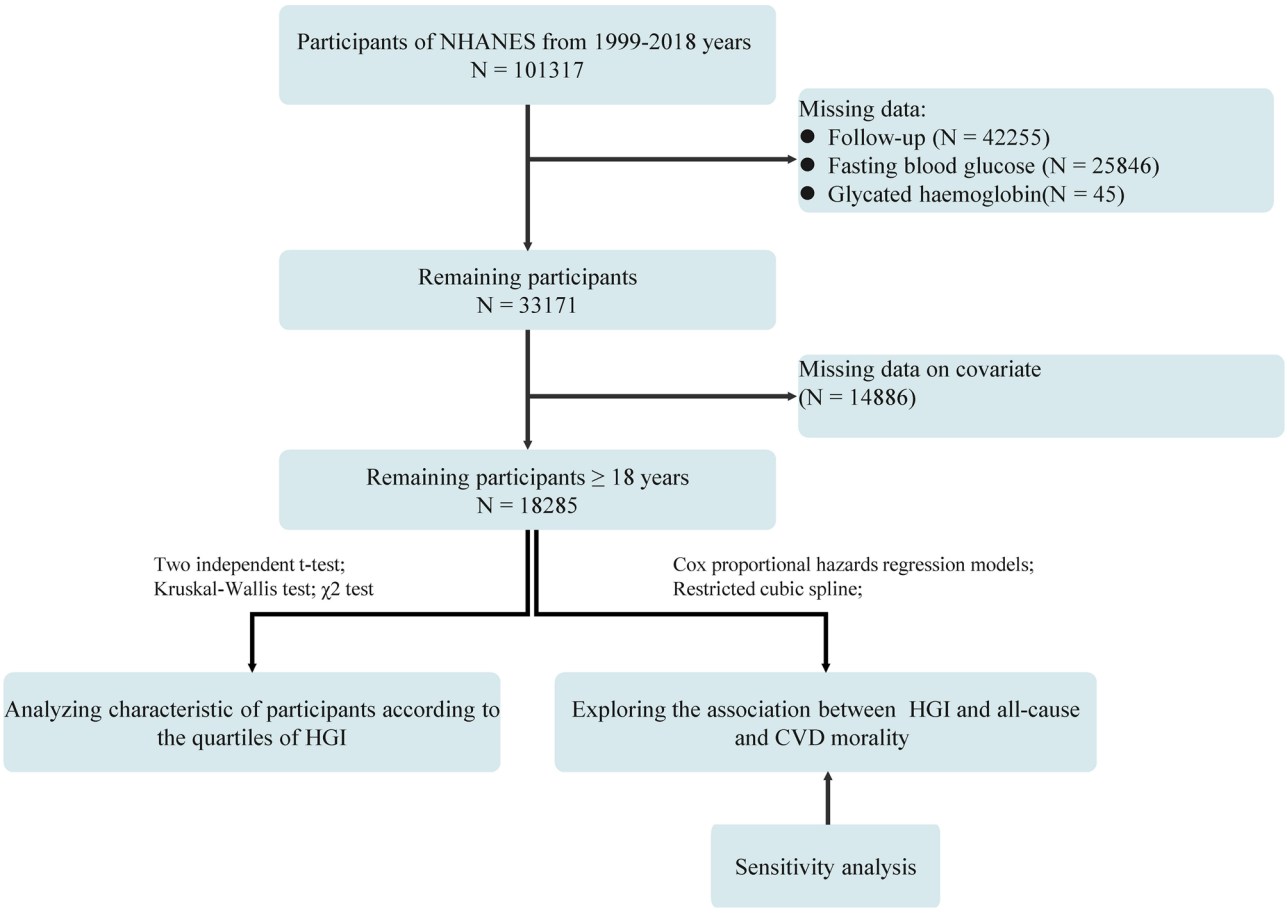

Figure 1. Study flowchart.

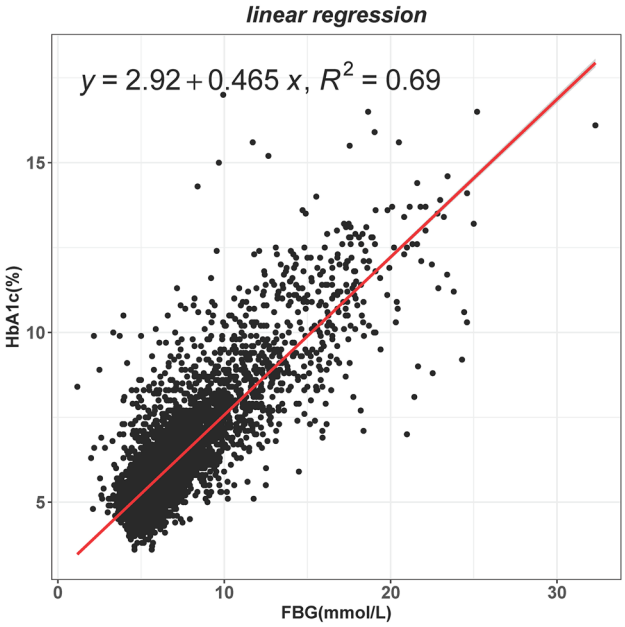

Figure 2. Linear relationship between glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG).

value—predicted HbA1c value. All participants were divided into four groups according to HGI quartiles: Q1 group (−5.66–−0.29), Q2 group (−0.29–−0.02), Q3 group (−0.02–0.24) and Q4 group (0.24–9.47).

Determination of mortality

The mortality information of NHANES participants was identified by the NHANES-linked National Death Index public access files. The International Statistical Classification of Diseases, 10th Revision (ICD-10) was used to determine specific deaths. Deaths from any cause are included in the all-cause mortality. CVD mortality (I00-I09, I11, I13, I20-I51) were defined according to the International Classification of Diseases, Tenth Clinical Revision (ICD-10) system codes and the NCHS classified heart diseases (054–064). Detailed definitions and categorisation can be found at: https://www.cdc.gov/nchs/data/datalinkage/underlying-and-multiple-cause-of-death-codes-508.pdf. We extracted potential leading causes of death from the mortality profile and the all-cause mortality and CVD mortality were used as endpoint events.

Data collection and covariate definition

To assess the impact of potential confounders, several important covariates were collected, including sociodemographic factors of age(years), sex (male and female), race (Mexican–American, non-Hispanic white, non-Hispanic black, and other races), education (less than high school college, high school or equivalent and college or above) and family poverty income ratio(PIR, ≤ 1, > 1 and ≤ 3, > 3), lifestyle factors of smoking status(Never, Now and Former), alcohol consumption(Never, Every day or nearly every day, 3 to 4 times a week, 1 to 2 times a week, Less than once a week), hypertension (Yes and No), diabetes (Yes and No), prediabetes (Yes and No), physical activity (Moderate activity, Vigorous activity and No), anthropometric measurements of body mass index (BMI, Kg/m^2), and laboratory data of aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), Serum creatinine(Scr, umol/L), blood urea nitrogen(BUN, mmol/L), total cholesterol (TC, mmol/L), triglyceride (TG, mmol/L), high density lipoprotein (HDL, mmol/L), Low-density lipoprotein(LDL, mmol/L), Uric acid (umol/L). Hypertension was defined as the self-report hypertension, or the mean systolic blood pressure ≥ 140 mmHg, or the mean diastolic blood pressure ≥ 90 mmHg. For those with three blood pressure measurements, the first systolic and diastolic readings were discarded and the average of the second and third readings was calculated as the mean blood pressure. If only two blood pressure measurements were taken, only the second reading was considered the average. If only one reading was obtained, it was used as the mean blood pressure. Blood collection was performed in the morning after fasting (at least 8 h or more but less than 24 h) to collect ALT, AST, Scr, BUN, TC, TG, HDL, LDL, Uric acid. Similarly, to minimize the measurement error in the fasting blood biochemistry tests, we standardized and adjusted the data for the different NHANES cycles from 1999 to 2018 according to the experimental methodologies established by the CDC. Considering the problem of covariance between covariates, we use the variance inflation factor (VIF) to estimate the possible covariance between variables, where VIF > 5 in the covariance analysis is considered to be the presence of multiple covariates[16]. As shown in Supplement Table 1, the multicollinearity analysis revealed that the VIF for TC exceeded the threshold of 5, indicating a significant level of multicollinearity with other covariates. To ensure the robustness and reliability of our statistical analysis, we excluded TC from the model.

In addition, we performed sensitivity analyses in three different subgroups of the population: those without hypertension, those with pre-existing CVD (comprising 1978 individuals), and those with treated diabetes. The diagnoses of CVD derived from self-reported physician diagnoses obtained during an individual interview using a standardized medical condition questionnaire. The participants were asked, "Has a doctor or other health expert ever informed you that you have Congestive Heart Failure (CHF)/Coronary Heart Disease (CHD)/angina pectoris/Myocardial Infarction (MI)/stroke?" A person was regarded as having CVD if he or she replied "yes" to any of the above questions. The treated diabetes was defined as "Do you currently take insulin?" Or "Do you currently take blood sugar-lowering diabetes medication?" The treated diabetes population was similarly derived from self-reported physician diagnoses. The participants were asked, "Are you now taking diabetic pills to lower your blood sugar?" or "Are you now taking insulin". An individual was defined as having treated diabetes if he or she replied "yes" to any of the above questions.

Statistical analyses

Data were extracted, combined and analyzed using R software (version 4.3.0) and Empower software (version 4.1). The continuous variables were tested by t-test or Kruskal–Wallis test, and categorical variables were tested by chi-square test. In the quartiles of HGI, the first quartile (Q1) and the fourth quartile (Q4) represent the lowest and highest levels, respectively. The Cox proportional hazards regression models were used to assess the risk ratios (HRs) and 95% CIs for the association of HGI with mortality, and three models were developed based on the covariates adjusted in the model: unadjusted model, minimally adjusted model (Sex, Age, Race), and fully adjusted model (Sex, Age, Race, Education, PIR, BMI, Drinking, Smoking, Hypertension, Diabetes, Prediabetes, Physical activity, TG, HDL, LDL, ALT, AST, BUN, Scr, Uric acid).

To investigate the relationship between HGI and all-cause and CVD mortality, we modelled Cox proportional hazards regression using restricted cubic spline (RCS) and smooth curve fitting (penalised spline method) based on the fully adjusted model. In nonlinear relationships, we estimated critical values through threshold effects, and then we used Cox proportional hazards models on both sides of the inflection point to investigate the relationship between HGI and mortality risk. Finally, three sensitivity analyses were conducted to test the robustness of our findings. Cox proportional hazards regression was performed in non-hypertensive and CVD populations to eliminate their confounding effects, respectively. In addition, analyses were also performed in the treated diabetic population to re-validate the association between HGI and mortality. Two-sided P-value < 0.05 were considered statistically significant.

Ethical approval and consent to participate

The data of NHANES is public databases. The patients involved in the database received ethical approval. Users can download relevant data for free for research and publication purposes.

Results

Participant's characteristics

A total of 18,285 participants were eventually enrolled, and the baseline characteristics of the four groups were shown in Table 1. The mean age of the subjects was 49 years, 8911 (48.19%) were male, and the median HGI was −0.02. Participants with a higher HGI were more likely to be older, obese, and female than those in the lowest quartile. Almost all of the clinical characteristics were statistically significant when compared among the four groups of participants ($p < 0.05$), except for the smoking status ($P > 0.05$).

Relationship between the HGI and mortality

The median follow-up period in our study was 115 months (range 1–249 months). A total of 2572 all-cause deaths and 671 CVD deaths occurred in the NHANES 1999–2018. Table 2 demonstrates the results of the Cox regression models between HGI and morality. After adjustment for all confounding factors, HGI was statistically positively associated with CVD mortality (HR = 1.22, 95% CI 1.10, 1.36). Furthermore, when the levels of HGI were divided into quartiles, although the Q2 group (HR = 0.86, 95% CI 0.77, 0.97) and Q3 group (HR = 0.87, 95% CI 0.78, 0.98) reduced all-cause mortality compared to the Q1 group, and the P value for trend was not statistically significant, the findings from the quartiles suggest that HGI may show a non-linear relationship with all-cause mortality. Importantly, it was found that the Q4 group (HR = 1.27, 95% CI 1.01, 1.53) significantly increased the CVD mortality compared with the lowest level of the Q1 group.

The nonlinear correlation between the HGI and mortality

Our results showed a nonlinear correlation between the HGI and all-cause and CVD mortality. Therefore, we used the restricted cubic spline test to assess the relationship between HGI and all-cause and CVD mortality. Figure 3 shows a U-shaped correlation between HGI and all-cause and CVD mortality. After adjusting for all covariates, the optimal inflection point values in all-cause and CVD deaths were 0.17 and 0.02, respectively (Table 3). In the left side of the inflection point, the risk of all-cause mortality and CVD mortality decreased by approximately 24% (HR 0.76, 95% CI 0.69, 0.84) and 25% (HR 0.75, 95% CI 0.60, 0.96) with the HGI increased (Table 3). Conversely, in the right of the inflection point, the risk of all-cause mortality and CVD mortality increased significantly. Specifically, an increase of 1 unit in the HGI was associated with a 17% increase in the risk of all-cause mortality (HR 1.17, 95% CI 1.07, 1.27) and a 31% increase in the risk of CVD mortality (HR 1.31, 95% CI 1.15, 1.49), respectively (Table 3).

HGI quartile	Overall	Q1 (−5.66–−0.29)	Q2 (−0.29–−0.02)	Q3 (−0.02–0.24)	Q4 (0.24–9.47)	*P*-value
N	18,285	4570	4550	4572	4593	
Age (Years)	49.00 (34.00–64.00)	43.00 (30.25–61.00)	44.00 (31.00–61.00)	50.00 (35.00–64.00)	57.00 (42.00–68.00)	< 0.01
BMI (kg/m2)	27.80 (24.26–32.21)	27.47 (24.11–31.60)	27.41 (24.05–31.49)	27.56 (24.00–32.13)	28.86 (25.00–33.76)	< 0.01
Sex (%)						< 0.01
Male	8911	2623 (57.40%)	2170 (47.69%)	2062 (45.10%)	2056 (44.76%)	
Female	9374	1947 (42.60%)	2380 (52.31%)	2510 (54.90%)	2537 (55.24%)	
Race (%)						< 0.01
Mexican American	3155	785 (17.18%)	884 (19.43%)	734 (16.05%)	752 (16.37%)	
Other hispanic	1429	338 (7.40%)	371 (8.15%)	369 (8.07%)	351 (7.64%)	
Non-hispanic white	8634	2503 (54.77%)	2337 (51.36%)	2196 (48.03%)	1598 (34.79%)	
Non-hispanic black	3515	600 (13.13%)	569 (12.51%)	866 (18.94%)	1480 (32.22%)	
Other race	1552	344 (7.53%)	389 (8.55%)	407 (8.90%)	412 (8.97%)	
Education (%)						< 0.01
Less than high school	4525	1035 (22.65%)	1037 (22.79%)	1148 (25.11%)	1305 (28.41%)	
High or equivalent	4226	1000 (21.88%)	1031 (22.66%)	1030 (22.53%)	1165 (25.36%)	
College or above	9534	2535 (55.47%)	2482 (54.55%)	2394 (52.36%)	2123 (46.22%)	
PIR (%)						< 0.01
≤ 1	3486	830 (18.16%)	871 (19.14%)	835 (18.26%)	950 (20.68%)	
> 1, ≤ 3	7642	1807 (39.54%)	1851 (40.68%)	1895 (41.45%)	2089 (45.48%)	
> 3	7157	1933 (42.30%)	1828 (40.18%)	1842 (40.29%)	1554 (33.83%)	
Hypertension (%)						< 0.01
No	11,938	3112 (68.10%)	3282 (72.13%)	3061 (66.95%)	2483 (54.06%)	
Yes	6347	1458 (31.90%)	1268 (27.87%)	1511 (33.05%)	2110 (45.94%)	
Smoking status (%)						0.05
Never	9818	2399 (52.49%)	2514 (55.25%)	2451 (53.61%)	2454 (53.43%)	
Now	3727	911 (19.93%)	925 (20.33%)	934 (20.43%)	957 (20.84%)	
Former	4740	1260 (27.57%)	1111 (24.42%)	1187 (25.96%)	1182 (25.73%)	
Drinking (%)						0.04
Never	5727	1152 (25.21%)	1262 (27.74%)	1472 (32.20%)	1841 (40.08%)	
Every day or nearly every day	3332	850 (18.60%)	856 (18.81%)	862 (18.85%)	764 (16.63%)	
3 to 4 times a week	2852	785 (17.18%)	770 (16.92%)	683 (14.94%)	614 (13.37%)	
1 to 2 times a week	4798	1365 (29.87%)	1262 (27.74%)	1182 (25.85%)	989 (21.53%)	
Less than once a week	1576	418 (9.15%)	400 (8.79%)	373 (8.16%)	385 (8.38%)	
Diabetes		796 (17.42%)	399 (8.77%)	444 (9.71%)	1494 (32.53%)	< 0.01
Prediabetes (%)	3133	1963 (42.95%)	1612 (35.43%)	1406 (30.75%)	2018 (43.94%)	< 0.01
Physical activity						< 0.01
No	9297	2142 (46.87%)	2198 (48.31%)	2368 (51.79%)	2589 (56.37%)	
Moderate activity	4611	1167 (25.54%)	1156 (25.41%)	1175 (25.70%)	1113 (24.23%)	
Vigorous activity	4377	1261 (27.59%)	1196 (26.29%)	1029 (22.51%)	891 (19.40%)	
FPG (mmol/L)	5.50 (5.11–6.05)	5.72 (5.33–6.38)	5.50 (5.10–5.91)	5.38 (5.05–5.82)	5.44 (5.00–6.29)	< 0.01
HbA1c (%)	5.50 (5.20–5.80)	5.10 (4.90–5.40)	5.30 (5.10–5.50)	5.50 (5.30–5.70)	5.90 (5.70–6.50)	< 0.01
LDL (mmol/L)	2.92 (2.35–3.57)	2.82 (2.28–3.41)	2.95 (2.38–3.54)	2.97 (2.40–3.62)	2.95 (2.30–3.62)	< 0.01
HDL (mmol/L)	1.32 (1.11–1.63)	1.29 (1.08–1.60)	1.34 (1.11–1.63)	1.34 (1.11–1.66)	1.32 (1.11–1.63)	< 0.01
TC (mmol/L)	4.94 (4.27–5.69)	4.81 (4.19–5.53)	4.97 (4.34–5.66)	5.02 (4.34–5.77)	4.99 (4.27–5.74)	< 0.01
TG (mmol/L)	1.20 (0.83–1.75)	1.20 (0.82–1.77)	1.21 (0.83–1.75)	1.17 (0.82–1.69)	1.22 (0.85–1.77)	0.01
AST (U/L)	22.00 (19.00–27.00)	23.00 (19.00–28.00)	22.00 (19.00–27.00)	22.00 (19.00–26.00)	22.00 (19.00–27.00)	< 0.01
ALT (U/L)	21.00 (16.00–28.00)	21.00 (16.00–30.00)	20.00 (16.00–28.00)	20.00 (16.00–27.00)	20.00 (16.00–27.00)	< 0.01
BUN (mmol/L)	4.28 (3.21–5.36)	4.28 (2.86–5.36)	4.28 (3.21–5.36)	4.28 (3.21–5.36)	4.28 (3.21–5.71)	< 0.01
Scr (umol/L)	73.37 (61.88–88.40)	76.02 (61.90–88.40)	71.60 (61.88–86.63)	71.60 (61.88–88.40)	75.14 (61.88–89.28)	< 0.01
Uric acid (umol/L)	321.20 (261.70–380.70)	327.10 (267.70–386.60)	315.20 (261.70–368.80)	315.20 (261.70–368.80)	321.20 (267.70–386.60)	< 0.01

Table 1. Baseline characteristics according to the HGI quartiles. Data were expressed as median with 25th and 75th percentile or n (%). BMI: Body Mass Index; PIR: Poverty Impact Ratio; FPG: Fasting Plasma Glucose; HbA1c: Glycosylated hemoglobin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total Cholesterol; TG: Triacylglycerol; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BUN: Blood urea nitrogen; Scr: Serum creatinine.

	Model 1	Model 2	Model 3
	HR (95% CI), *P*-value	HR (95% CI), *P*-value	HR (95% CI), *P*-value
All-cause mortality			
HGI	1.25 (1.17, 1.32) <0.01	1.08 (1.01, 1.16) 0.02	1.02 (0.96, 1.09) 0.48
Q1 (−5.656–−0.287)	1.0	1.0	1.0
Q2 (−0.287–−0.025)	0.86 (0.77, 0.97) 0.01	0.86 (0.77, 0.96) 0.01	0.86 (0.77, 0.97) 0.01
Q3 (−0.025–0.236)	1.03 (0.92, 1.15) 0.62	0.88 (0.78, 0.98) 0.02	0.87 (0.78, 0.98) 0.02
Q4 (0.236–9.468)	1.51 (1.36, 1.68) <0.01	1.12 (1.01, 1.25) 0.04	1.03 (0.92, 1.15) 0.64
P for trend	<0.01	0.02	0.48
CVD mortality			
HGI	1.45 (1.33, 1.59) <0.01	1.31 (1.18, 1.45) <0.01	1.22 (1.10, 1.36) <0.01
Q1 (−5.656–−0.287)	1.0	1.0	1.0
Q2 (−0.287–−0.025)	0.91 (0.71, 1.15) 0.42	0.92 (0.72, 1.17) 0.49	1.01 (0.79, 1.30) 0.91
Q3 (−0.025–0.236)	1.18 (0.94, 1.48) 0.15	1.00 (0.80, 1.26) 0.98	1.11 (0.88, 1.41) 0.38
Q4 (0.236–9.468)	2.02 (1.64, 2.50) <0.01	1.44 (1.16, 1.79) <0.01	1.27 (1.01, 1.53) 0.04
P for trend	<0.01	<0.01	0.02

Table 2. HRs (95% CIs) for mortality according to the HGI quartiles. Model 1 adjust for: None. Model 2 adjust for: Sex; Age; Race. Model 3 adjust for: Sex; Age; Race; Education; Poverty Impact Ratio; Body Mass Index; Drinking; Smoking; Hypertension; Diabetes; Prediabetes; Physical activity; Triacylglycerol; High-density lipoprotein; Low-density lipoprotein; Alanine aminotransferase; Aspartate transaminase; Blood urea nitrogen; Serum creatinine; Uric acid. Abbreviations: HGI: Hemoglobin glycation index, HR: Hazard ratio, CI: Confidence interval, CVD: Cardiovascular Disease.

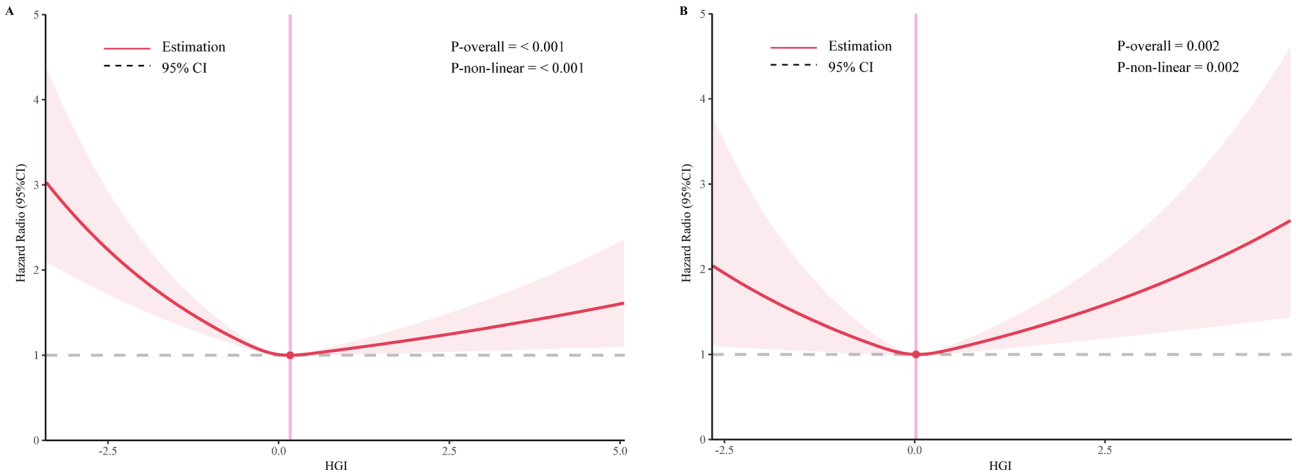

Figure 3. Restricted cubic spline curve for the association of HGI with all-cause mortality (**A**) and CVD mortality (**B**).

Curve fitting analysis of the relationship between HGI and mortality stratified by race

Because of individual differences between races, we stratified the analysis by race, curve fitted the nonlinear relationship between HGI and risk of mortality (Supplement Fig. 1), and developed Cox proportional hazards models for each racial segment (Supplement Table 2). The results showed that although there was no significant non-linear relationship between HGI and mortality in the Other Hispanic and Other Race groups, the *P* for interaction was > 0.05 (Supplement Table 2). This suggests that the effect of the non-linear relationship on the outcome variables was consistent across races.

Sensitivity analysis

To further substantiate the robustness of our findings, we performed sensitivity analyses in three different sub-groups of the population: those without hypertension (comprising 11,099 individuals), those with pre-existing

	Adjusted HR (95% CI)	*P*-value
All-cause mortality		
Inflection point	0.17	
HGI < 0.17	0.76 (0.69, 0.84)	< 0.01
HGI ≥ 0.17	1.17 (1.07, 1.27)	< 0.01
P for Log-likelihood ratio	< 0.01	
CVD mortality		
Inflection point	0.02	
HGI < 0.02	0.75 (0.60, 0.96)	0.01
HGI ≥ 0.02	1.31 (1.15, 1.49)	< 0.01
P for Log-likelihood ratio	< 0.01	

Table 3. Threshold effect analysis of HGI on all-cause and CVD mortality. Cox proportional hazards models were used to estimate HR and 95% CI. Adjusted for sex, age, race, education, Poverty Impact Ratio, Body Mass Index, Drinking, Smoking, Hypertension, Diabetes, Prediabetes, Physical activity, Triacylglycerol, High-density lipoprotein, Low-density lipoprotein, Alanine aminotransferase, Aspartate transaminase, Blood urea nitrogen, Serum creatinine, Uric acid. Abbreviations: HGI: Hemoglobin glycation index, HR: Hazard ratio, CI: Confidence interval, CVD: Cardiovascular Disease.

CVD (comprising 1978 individuals), and those with diabetes treated with hypoglycemic agents or insulin (comprising 1537 individuals). These subgroups were selected to assess threshold effects in different clinical conditions. All results were in general agreement with the main analysis (Table 4).

In addition, we also analyzed the relationship between HbA1c and mortality (Supplement Table 3). When HbA1c was included as a continuous variable in the Cox regression analysis, adjusted for all covariates, the results found that HbA1c was significantly associated with an increased risk of all-cause mortality (HR 1.11, 95% CI 1.07, 1.16) and CVD mortality (HR 1.19, 95% CI 1.11, 1.28). Categorizing HbA1c into quartiles, compared to the Q1 group, the highest Q4 group was associated with a significantly increased risk of all-cause mortality (HR 1.23, 95% CI 1.05, 1.44) and CVD mortality (HR 1.60, 95% CI 1.14, 2.26). This indicates a positive linear relationship between HbA1c levels and the risk of mortality. In contrast to HbA1c, a more significant positive association was observed between HGI and the risk of CVD mortality (HR 1.22, 95% CI 1.10 to 1.36). Notably, HGI demonstrated a U-shaped relationship with all-cause mortality and CVD mortality, differing from the linear association observed with HbA1c.

	Sensitivity-1	Sensitivity-2	Sensitivity-3
All-cause mortality			
Inflection point = 0.17			
HGI < 0.17	0.76 (0.67, 0.85) < 0.01	0.81 (0.72, 0.90) < 0.01	0.78 (0.71, 0.92) < 0.01
HGI ≥ 0.17	1.18 (1.07, 1.31) 0.01	1.11 (1.01, 1.23) 0.01	1.12 (1.02, 1.31) 0.03
P for Log-likelihood ratio	< 0.01	< 0.01	< 0.01
CVD mortality			
Inflection point = 0.02			
HGI < 0.02	0.56 (0.32, 0.92) 0.02	0.74 (0.49, 0.87) 0.01	0.87 (0.68, 0.94) 0.03
HGI ≥ 0.02	1.30 (1.08, 1.57) < 0.01	1.17 (1.03, 1.33) 0.01	1.27 (1.09, 1.47) < 0.01
P for Log-likelihood ratio	< 0.01	< 0.01	0.02

Table 4. Adjusted hazard ratios and 95% confidence intervals for HGI and mortality in different populations: a sensitivity analysis. (1) Sensitivity-1: including 11,099 subjects without hypertension, adjusted for sex, age, race, education, Poverty Impact Ratio, Body Mass Index, Drinking, Smoking, Diabetes, Prediabetes, Physical activity, Triacylglycerol, High-density lipoprotein, Low-density lipoprotein, Alanine aminotransferase, Aspartate transaminase, Blood urea nitrogen, Serum creatinine, Uric acid; (2) sensitivity-2: including 1978 subjects with CVD (Coronary heart disease, angina pectoris, myocardial infarction, heart failure, stroke), adjusted for sex, age, race, education, Poverty Impact Ratio, Body Mass Index, Drinking, Smoking, Hypertension, Diabetes, Prediabetes, Physical activity, Triacylglycerol, High-density lipoprotein, Low-density lipoprotein, Alanine aminotransferase, Aspartate transaminase, Blood urea nitrogen, Serum creatinine, Uric acid. (3) sensitivity-3: including 1537 diabetes with hypoglycemic drugs or insulin, adjusted for sex, age, race, education, Poverty Impact Ratio, Body Mass Index, Drinking, Smoking, Hypertension, Physical activity, Triacylglycerol, High-density lipoprotein, Low-density lipoprotein, Alanine aminotransferase, Aspartate transaminase, Blood urea nitrogen, Serum creatinine, Uric acid. Abbreviations: HGI: Hemoglobin glycation index; CVD: Cardiovascular Disease.

Discussion

Our study is the first comprehensive analysis of the relationship between HGI and mortality in this large-scale cohort of the US population. In this study, we found a U-shaped relationship between HGI and the risk of all-cause and cardiovascular mortality. The higher HGI was significantly associated with an increased risk of CVD and all-cause mortality. Overall, these findings suggest that HGI can be a valid predictor of CVD and all-cause mortality in clinical practice.

HbA1c is often considered as the standard method of assessing glycaemic control. Several previous studies have suggested that the risk of clinical complications in diabetic patients increases with an elevated HbA1c[17]. However, the results of the Action to Control Cardiovascular Risk in Patients with Diabetes (ACORRD) trial, a prospective, double-blind, controlled clinical study comparing intensive glucose lowering with standard glucose lowering in patients with diabetes, suggest that overly aggressive glucose-lowering therapy to keep HbA1c within the normal range may increase the risk of cardiovascular complications and death[18]. Similar results were obtained in another meta-analysis of multiple randomized clinical trials[19]. Thus, the use of HbA1c in isolation to predict the risk of adverse cardiovascular events in type 2 diabetes mellitus appears to be inadvisable and may be related to interindividual differences in HbA1c.

The concept of HGI was first introduced in 2002 by Hempe et al.[8]. Over the past few years, many studies have explored the clinical utility of HGI, which has been shown to be a good predictor of chronic diseases such as T2DM-related complications[20], metabolic syndrome[21], and hepatic steatosis[22]. There is limited research on the relationship between HGI and all-cause and cardiovascular mortality in adults. Previous studies have observed a U-shaped correlation between HGI and 5-year Major Adverse Cardiovascular Events (MACE) risk in type 2 diabetes[23]. Our study also found that a linear relationship may not accurately reflect the correlation between HGI and the risk of all-cause and CVD death. A U-shaped relationship between HGI and all-cause and cardiovascular death was found by RCS analysis. It showed that both low and high HGI were associated with a higher risk of death. These results may vary depending on factors such as age, sex, diabetes status and ethnic groups. Notably, at given serum glucose concentrations, the values of HbA1c vary significantly in different ethnic groups[24], but HGI can reflect individual differences in glucose metabolism and HbA1c[20]. Our study also suggests that HbA1c and HGI may have different predictive patterns for mortality risk, with HbA1c showing a linear positive relationship and HGI showing a more complex U-shaped relationship, which may indicate additional underlying biological mechanisms.

There are many associations between HGI and clinical situations[10,25]. In contrast to the linear relationship between HGI and vascular complications reported in previous studies[26–28], our study found a U-shaped association between HGI and mortality. Both low and high HGI patients had higher mortality in all-cause and CVD mortality. One possible explanation was stress hyperglycaemia[29], which may lead to high FPG, which in turn leads to low HGI, but more studies are needed to confirm this. In addition, the tests of FPG and HbA1c are inexpensive and convenient in the clinic. HGI can be conveniently calculated in adults undergoing physical examination. Early intervention in populations with cardiovascular-related risk factors can effectively reduce the incidence of mortality.

There are several possible mechanisms that could explain the association between HGI and mortality. First, hypoglycemia and postprandial hyperglycaemia are more prevalent in high HGI populations[20], and the resulting dysregulation of glucose homeostasis exacerbates vascular endothelial dysfunction and promotes atherosclerosis[30,31]. Hypoglycemia may also contribute to cardiovascular death by other mechanisms beyond atherosclerosis[32,33]. Second, the inflammatory response may also be one of the factors mediating the relationship between HGI and mortality, particularly CVD mortality. Current studies suggested that HGI may serve as a glucose metabolism phenotype, reflecting levels of inflammatory markers such as ultrasensitive C-reactive protein, erythrocyte sedimentation rate, complement C3, white blood cell counts and fibrinogen[10,34]. Elevated HGI may contribute to atherosclerosis through pro-inflammatory cell signalling and oxidative stress, which in turn may affect cardiovascular mortality[35]. Third, Lyu et al. found HGI was significantly related to telomere attrition, independent of HbA1c[36]. Whereas, telomere length has been shown to exhibit a U-shaped relationship with all-cause mortality[37]. It was also a potential correlation. In addition, some medications (steroids, statins, hormones, etc.) and diseases (asthma, anaemia, cancers, etc.), inflammation, iron metabolism and other factors may also have an effect on the levels of HGI, and the comprehensive and detailed mechanism still needs to be elaborated in further research.

One of the key strengths of our study was the utilisation of a large sample size, which allowed us to clearly reveal the association between HGI and the risk of all-cause mortality and cardiovascular death. These findings provide valuable biomarkers for mortality risk reduction, especially screening for cardiovascular death, and provide an important reference for future studies. However, our study also has some limitations. First, the exclusion of participants with incomplete covariate data may introduce selection bias, potentially affecting the generalizability of our findings. We have attempted to minimize this bias through rigorous statistical methods, yet the possibility of residual confounding remains a limitation of our study. Second, during the follow-up, there were some patients who were lost to follow-up, and there may have been confounding factors that led to residual confounding.Third, the calculation of the HGI was based on single measurements of FPG and HbA1c, which does not take into account the variability of HbA1c and does not reflect dynamic changes during long-term follow-up. Finally, our study was based on US participants. Therefore, further validation studies are needed when generalising our findings to other ethnic groups or other populations.

Conclusion

Our findings suggest that HGI is an important tool for predicting the risk of all-cause mortality and CVD death in US adults and that there is a U-shaped relationship between HGI and mortality.

Data availability

The data of National Health and Nutrition Examination Survey (NHANES) can be downloaded from the website: https://www.cdc.gov/nchs/nhanes/index.html.

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Conceptualization, J.Y.; Data curation, X.H., Y.H.; Funding acquisition, J.Y.; Investigation, X.H. and L.Z.; Methodology, J.Y., X.H., Y.H., L.Z.; Software, J.Y. and Y.H.; Supervision, L.Z.; Validation, Y.H., X.H.; Writing—original draft, Y.H. and X.H.; Writing—review & editing, J.Y., L.Z.

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