

ORIGINAL ARTICLE

Non-Linear U-Shaped Trend Associations between HbA1c and All-Cause and Cardiovascular Mortality

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ABSTRACT

Background: Several well-designed prospective studies have assessed the association between glycated hemoglobin (HbA1c) and mortality risk in both the general population and diabetic patients. However, the results have been inconsistent.

Methods: We conducted a prospective study using data from NHANES 2003 - 2018, which included 38,072 adults. Cox proportional hazards regression and restricted cubic spline models were used to evaluate the linear and non-linear associations between HbA1c and both all-cause mortality and cause-specific mortality. To better detect non-linear relationships, we converted HbA1c from a continuous to a categorical variable. Kaplan-Meier survival curves and subgroup analyses were also performed.

Results: During an average follow-up period of 99.7 ± 53.6 months, 4,723 participants (12.4%) died. We observed a significant non-linear U-shaped association between baseline HbA1c levels and mortality. Compared with a moderate HbA1c level of 5.5%, the risk of all-cause and cause-specific mortality decreased for HbA1c values below 5.5%. However, mortality risk significantly increased for HbA1c levels above 5.5%. This indicates that individuals with either low or high HbA1c levels are at a higher risk of all-cause mortality. Additionally, we identified an L-shaped trend in cancer mortality.

Conclusions: We demonstrated a U-shaped association between baseline HbA1c levels and all-cause mortality in the general population. Individuals with both low and high HbA1c levels are at a greater risk of all-cause mortality. Future clinical trials on diabetes management should consider the consequences of lower HbA1c levels, especially across different populations.

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KEYWORDS

non-linear, associations, HbA1c, all-cause, cardiovascular mortality

INTRODUCTION

Glycated hemoglobin (HbA1c), a biomarker for monitoring long-term blood glucose control in diabetic patients, reflects the average blood glucose concentration over the preceding 8 - 12 weeks [1]. It is crucial for blood glucose management. Compared to fasting plasma glucose, HbA1c offers higher repeatability, is not affected by occasional fluctuations in blood sugar levels, and can be tested in a non-fasting state [2]. The Ameri-

can Diabetes Association and the World Health Organization have accepted HbA1c testing, with a threshold of $\geq 6.5\%$ as the diagnostic criterion for diabetes [3].

Previous cohort studies have shown a positive linear association between HbA1c values and future all-cause and cardiovascular mortality [4-7]. However, some studies have observed a J- or U-shaped correlation, indicating that both low and high HbA1c values could increase mortality [8,9]. In summary, current studies on this association have conflicting conclusions. These conflicts may be due to differences in study populations, causes of death, adjustments for important confounding factors, and statistical methods [10-12].

Due to varying results on the association of HbA1c with all-cause and cardiovascular mortality, evidence based on the general population is limited. Additionally, evidence on HbA1c target thresholds for managing the general population is sparse. Therefore, in this analysis, we aimed to assess the relationship between HbA1c, all-cause mortality, and cause-specific mortality in the general population.

MATERIALS AND METHODS

Study Population

The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC), is a large-scale, ongoing program that collects nationally representative data on the health conditions of U.S. civilians. Details of the survey design and data collection methods are publicly available online (<https://www.cdc.gov/nchs/nhanes/>).

In this study, we analyzed data from NHANES 2003 - 2018, which included 80,312 participants. We included only participants aged 20 or older who completed the questionnaire survey ($n = 44,790$). We excluded participants missing data on HbA1c information ($n = 3,982$) or mortality outcomes ($n = 127$). Participants missing information on critical covariates ($n = 2,609$) were excluded. Finally, 38,072 individuals were included in the study.

Measurement of HbA1c

During their visit to the ambulatory examination center, blood samples were collected from participants who had fasted for at least 8 hours, following a standardized protocol. These samples were tested within 24 hours. HbA1c levels were measured using high-performance liquid chromatography (HPLC). The reference range for HbA1c in our study, as defined by NGSP for adults without diabetes, is 4.0% to 5.6%.

Ascertainment of outcomes

We used the NHANES publicly available mortality data as of December 31, 2019, to determine the mortality status and causes of death in the follow-up population. The study outcomes included all-cause mortality, car-

diovascular disease (CVD) mortality (codes I00-I09, I11, I13, and I120-151), and cancer mortality (codes C00 - C97). Our follow-up period (in months) was measured from the date of examination to the date of death or the censor date (December 31, 2019), as described in a previous study.

Other covariates

We included demographic characteristics such as age, gender (male, female), race (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational background (below high school, high school or college, and above), and poverty income ratio (≤ 3 , > 3). Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared and categorizing participants into two weight-status groups: non-obese ($\text{BMI} < 30$) and obese ($\text{BMI} \geq 30$). Participants self-reported their smoking status (never smoked, currently smoke, or formerly smoked) and baseline disease history, including chronic kidney disease, cardiovascular disease (CVD), diabetes, and hypertension. Serum total cholesterol (TC, mg/dL), triglycerides, blood urea nitrogen, and uric acid levels were measured using standardized procedures. Hypertension was defined as systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 80 mmHg, use of antihypertensive medications, or self-reported history of hypertension. Diabetes was defined as fasting blood glucose (FBG) ≥ 126 mg/dL, self-reported diagnosis, hemoglobin A1c (HbA1c) $\geq 6.5\%$, or use of hypoglycemic drugs.

Statistical analysis

Participants were classified into HbA1c quartiles (Q1, Q2, Q3, Q4). Categorical variables are presented as numbers (percentages), and continuous variables with approximately normal distribution are described as mean (standard deviation). Continuous variables with skewed distribution are presented as median (interquartile range, IQR).

A multivariate Cox proportional hazard regression model was used to adjust for potential confounders and estimate the association between HbA1c and all-cause and cause-specific mortality. The lowest quartile (Q1) served as the reference group. The crude model made no adjustments. The adjusted model controlled for age, sex, race, and PIR. The fully adjusted model additionally controlled for education level, BMI, serum cotinine, serum cholesterol, serum triglycerides, blood urea nitrogen, uric acid, glomerular filtration rate, history of CKD, CVD, hyperlipidemia, hypertension, diabetes, and smoking status. The potential non-linear associations between HbA1c, all-cause mortality, and disease-specific mortality were evaluated using restricted cubic spline models fitted to Cox proportional hazard models. Two piecewise linear regression models were used to detect differences in the results. The cumulative Kaplan-Meier mortality curves during follow-up were plotted based on HbA1c quartiles.

Table 1. Baseline demographic and clinical parameters among participants by HbA1c quartiles.

Variables	Total (n = 38,072)	Q1 (n = 7,662)	Q2 (n = 9,707)	Q3 (n = 10,890)	Q4 (n = 9,813)	P
Gender, n (%)						
Female	19,608 (51.5)	4,296 (56.1)	5,019 (51.7)	5,484 (50.4)	4,809 (49)	< 0.001
Male	18,464 (48.5)	3,366 (43.9)	4,688 (48.3)	5,406 (49.6)	5,004 (51)	
Age, mean ± SD	49.7 ± 18.0	37.9 ± 15.5	44.6 ± 17.2	52.7 ± 17.0	60.5 ± 14.0	< 0.001
Race, n (%)						
Mexican american	6,230 (16.4)	1,154 (15.1)	1,592 (16.4)	1,744 (16)	1,740 (17.7)	< 0.001
Non-hispanic black	7,877 (20.7)	1,232 (16.1)	1,566 (16.1)	2,347 (21.6)	2,732 (27.8)	
Non-hispanic white	1,6945 (44.5)	4,004 (52.3)	4,746 (48.9)	4,712 (43.3)	3,483 (35.5)	
Other hispanic	3,353 (8.8)	615 (8)	797 (8.2)	1,020 (9.4)	921 (9.4)	
Other race	3,667 (9.6)	657 (8.6)	1,006 (10.4)	1,067 (9.8)	937 (9.5)	
PIR, n (%)						
< 3	22,010 (62.8)	4,186 (58.5)	5,515 (61)	6,258 (62.7)	6,051 (68)	< 0.001
≥ 3	13,059 (37.2)	2,971 (41.5)	3,525 (39)	3,716 (37.3)	2,847 (32)	
Education level, n (%)						
< High school	9,538 (25.1)	1,387 (18.1)	2,137 (22)	2,786 (25.6)	3,228 (32.9)	< 0.001
Graduated from high school	8,854 (23.3)	1,657 (21.6)	2,212 (22.8)	2,644 (24.3)	2,341 (23.9)	
College education or above	19,644 (51.6)	4,615 (60.2)	5,351 (55.1)	5,447 (50)	4,231 (43.1)	
NA	36 (0.1)	3 (0)	7 (0.1)	13 (0.1)	13 (0.1)	
BMI (kg/m ²), n (%)						
BMI < 30	23,375 (62.1)	5,744 (75.6)	6,701 (69.7)	6,574 (60.9)	4,356 (45.1)	< 0.001
BMI ≥ 30	14,281 (37.9)	1,849 (24.4)	2,918 (30.3)	4,216 (39.1)	5,298 (54.9)	
Serum cotinine (ng/mL)	0.0 (0.0, 9.3)	0.1 (0.0, 16.2)	0.0 (0.0, 16.8)	0.0 (0.0, 18.4)	0.0 (0.0, 1.2)	< 0.001
Triglycerides (mg/dL)	121.0 (80.0, 185.0)	100.0 (68.0, 157.0)	108.0 (74.0, 167.0)	123.0 (84.0, 186.0)	148.0 (101.0, 220.0)	< 0.001
Blood urea nitrogen (mmol/L)	4.8 ± 2.2	4.2 ± 1.8	4.6 ± 1.8	4.9 ± 2.0	5.6 ± 2.7	< 0.001
Total cholesterol (mg/dL)	194.4 ± 42.4	187.3 ± 39.9	194.7 ± 40.6	200.0 ± 41.3	193.3 ± 46.3	< 0.001
Uric acid (mg/dL)	5.4 ± 1.5	5.1 ± 1.4	5.3 ± 1.4	5.5 ± 1.4	5.8 ± 1.5	< 0.001
EPI-cr (mL/min)	93.8 ± 24.3	104.7 ± 22.1	98.3 ± 22.7	91.3 ± 23.1	83.8 ± 24.3	< 0.001
Follow-up time (month)	99.7 ± 53.6	112.2 ± 54.8	105.6 ± 54.4	96.9 ± 52.5	87.1 ± 50.0	< 0.001
Smoking status, n (%)						
Never	20,764 (54.6)	4,607 (60.1)	5,454 (56.2)	5,749 (52.8)	4,954 (50.5)	< 0.001
Former	9,429 (24.8)	1,401 (18.3)	2,140 (22.1)	2,778 (25.5)	3,110 (31.7)	
Now	7,860 (20.7)	1,653 (21.6)	2,109 (21.7)	2,354 (21.6)	1,744 (17.8)	
CKD, n (%)						
No	30,401 (79.9)	6,831 (89.2)	8,371 (86.2)	8,851 (81.3)	6,348 (64.7)	< 0.001
Yes	6,923 (18.2)	686 (9)	1,173 (12.1)	1,814 (16.7)	3,250 (33.1)	
NA	748 (2.0)	145 (1.9)	163 (1.7)	225 (2.1)	215 (2.2)	
CVD, n (%)						
No	33,722 (88.6)	7,314 (95.5)	9,029 (93)	9,681 (88.9)	7,698 (78.4)	< 0.001
Yes	4,350 (11.4)	348 (4.5)	678 (7)	1,209 (11.1)	2,115 (21.6)	

Table 1. Baseline demographic and clinical parameters among participants by HbA1c quartiles (continues).

Variables	Total (n = 38,072)	Q1 (n = 7,662)	Q2 (n = 9,707)	Q3 (n = 10,890)	Q4 (n = 9,813)	P
Diabetes, n (%)						
No	30,300 (79.6)	6,965 (90.9)	9,282 (95.6)	10,067 (92.4)	3,986 (40.6)	< 0.001
Yes	6,959 (18.3)	152 (2)	241 (2.5)	751 (6.9)	5,815 (59.3)	
NA	813 (2.1)	545 (7.1)	184 (1.9)	72 (0.7)	12 (0.1)	
Hyperlipidemia, n (%)						
No	10,840 (28.5)	3,399 (44.4)	3,351 (34.5)	2,682 (24.6)	1,408 (14.3)	< 0.001
Yes	27,231 (71.5)	4,263 (55.6)	6,356 (65.5)	8,208 (75.4)	8,404 (85.7)	
Hypertension, n (%)						
No	21,867 (57.4)	5,910 (77.1)	6,707 (69.1)	5,997 (55.1)	3,253 (33.1)	< 0.001
Yes	16,199 (42.5)	1,750 (22.8)	2,999 (30.9)	4,891 (44.9)	6,559 (66.8)	
NA	6 (0.0)	2 (0)	1 (0)	2 (0)	1 (0)	
CVD death, n (%)						
No	36,833 (96.7)	7,550 (98.5)	9,497 (97.8)	10,534 (96.7)	9,252 (94.3)	< 0.001
Yes	1,239 (3.3)	112 (1.5)	210 (2.2)	356 (3.3)	561 (5.7)	
Cancer death, n (%)						
No	37,011 (97.2)	7,542 (98.4)	9,480 (97.7)	10,579 (97.1)	9,410 (95.9)	< 0.001
Yes	1,061 (2.8)	120 (1.6)	227 (2.3)	311 (2.9)	403 (4.1)	
All-cause death, n (%)						
No	33,349 (87.6)	7,160 (93.4)	8,808 (90.7)	9,550 (87.7)	7,831 (79.8)	< 0.001
Yes	4,723 (12.4)	502 (6.6)	899 (9.3)	1,340 (12.3)	1,982 (20.2)	

BMI: body mass index, PIR: poverty income ratio, CKD: chronic kidney disease, CVD: chronic cardiovascular diseases.

All statistical analyses were performed using the R software package (<http://www.R-project.org>) and Empower Stats (<http://www.empowerstats.com>, X&Y Solutions, Inc., Boston, MA).

RESULTS

Participant characteristics

The baseline characteristics of participants grouped by HbA1c quartile are shown in Table 1. This study included 38,072 individuals with an average age of 49.7 ± 18 years. Of these participants, 48.5% were male. After an average follow-up of 99.7 ± 53.6 months, we observed 4,723 (12.4%) all-cause deaths, including 1,239 (3.3%) CAD deaths and 1,061 (2.8%) cancer deaths. Participants with higher HbA1c were more likely to be men, older, non-Hispanic white, have a lower PIR, a higher BMI, and be more likely to have hyperlipidemia, diabetes, and hypertension.

HbA1c with All-Cause and Cause-Specific Mortality

The relationships between HbA1c and all-cause and cause-specific mortality are shown in Table 2. In the fully adjusted model, we observed a positive association

between HbA1c and both all-cause mortality and cardiovascular disease mortality. However, no significant relationship was found between HbA1c and cancer mortality. We converted the HbA1c continuous variable into four quartiles (Q1: $\leq 5.1\%$; Q2: $5.1 - 5.4\%$; Q3: $5.4 - 5.8\%$; Q4: $\geq 5.8\%$), with Q3 ($5.4 - 5.8\%$) as the reference group. The third quartile (Q3: $5.4 - 5.8\%$) was explicitly chosen as the reference group for two primary reasons: First, our restricted cubic spline analysis identified a nadir of risk around 5.5%, which falls within this quartile. Second, using Q3 as the reference allows for a clear and clinically meaningful comparison, demonstrating the elevated mortality risk associated with both lower (Q1 - Q2) and higher (Q4) HbA1c levels, thereby highlighting the U-shaped relationship that is the central finding of our study. Compared with the middle quartile (Q3), the multivariable HRs (95% CIs) for the lowest quartile of HbA1c were 1.36 (1.21 - 1.52) for all-cause mortality, 1.31 (1.04 - 1.65) for cardiovascular mortality, and 1.4 (1.12 - 1.76) for cancer mortality.

The evaluation of non-linear relationships

Using the generalized additive model and penalty spline method, we found a U-shaped association between HbA1c and both all-cause and CVD mortality (Figure

Table 2. The association of selenium levels with all-cause mortality, cardiovascular mortality and cancer mortality.

HbA1c	Event (%)	Crude model		Adjusted model		Fully adjusted model	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause mortality							
HbA1c (%)	4,723 (12.4)	1.27 (1.25 - 1.29)	< 0.001	1.16 (1.13 - 1.19)	< 0.001	1.06 (1.03 - 1.1)	< 0.001
Quartiles (%)							
Q1 (≤ 5.1)	502 (6.6)	0.44 (0.4 - 0.49)	< 0.001	1.37 (1.23 - 1.53)	< 0.001	1.36 (1.21 - 1.52)	< 0.001
Q2 (5.1 - 5.4)	899 (9.3)	0.67 (0.62 - 0.73)	< 0.001	1.04 (0.96 - 1.14)	0.351	1.11 (1.01 - 1.21)	0.03
Q3 (5.4 - 5.8)	1,340 (12.3)	Ref		Ref		Ref	
Q4 (≥ 5.8)	1,982 (20.2)	1.88 (1.75 - 2.02)	< 0.001	1.35 (1.25 - 1.45)	< 0.001	1.07 (0.98 -1.16)	0.151
p for trend			< 0.001		0.002		< 0.001
CVD mortality							
HbA1c (%)	1,239 (3.3)	1.29 (1.26 - 1.33)	< 0.001	1.21 (1.16 - 1.27)	< 0.001	1.07 (1.01 - 1.14)	0.028
Quartiles (%)							
Q1 (≤ 5.1)	112 (1.5)	0.37 (0.3 - 0.46)		1.25 (1 - 1.56)	0.046	1.31 (1.04 - 1.65)	0.023
Q2 (5.1 - 5.4)	210 (2.2)	0.59 (0.5 - 0.7)	< 0.001	0.91 (0.76 - 1.08)	0.28	1 (0.83 - 1.02)	0.97
Q3 (5.4 - 5.8)	356 (3.3)	Ref		Ref		Ref	
Q4 (≥ 5.8)	561 (5.7)	2 (1.75 - 2.28)	< 0.001	1.42 (1.24 - 1.63)	< 0.001	1.01 (0.85 - 1.19)	0.94
p for trend			< 0.001		< 0.001		0.143
Cancer mortality							
HbA1c (%)	1,061 (2.8)	1.2 (1.16 - 1.25)	< 0.001	1.03 (0.97 - 1.1)	0.333	0.98 (0.9 - 1.06)	0.558
Quartiles (%)							
Q1 (≤ 5.1)	120 (1.6)	0.46 (0.37 - 0.57)	< 0.001	1.34 (1.08 - 1.67)	0.009	1.4 (1.12 - 1.76)	0.004
Q2 (5.1 - 5.4)	227 (2.3)	0.74 (0.62 - 0.87)	< 0.001	1.09 (0.92 - 1.31)	0.323	1.16 (0.97 - 1.4)	0.108
Q3 (5.4 - 5.8)	311 (2.9)	Ref		Ref		Ref	
Q4 (≥ 5.8)	403 (4.1)	1.64 (1.41 - 1.9)	< 0.001	1.16 (1 - 1.36)	0.055	1.16 (0.88 - 1.28)	0.522
p for trend			< 0.001		0.543		0.021

Crude model: not adjusted

Adjusted model: adjusted for gender, age, race and PIR.

Full-adjusted model: adjusted for gender, age, race, PIR, education level, BMI, serum cotinine, serum cholesterol, serum triglycerides, blood urea nitrogen, uric acid, glomerular filtration rate, disease history of CKD, CVD, hyperlipidemia, hypertension and diabetes, and smoking status.

1). We also observed an L-shaped association between HbA1c and cancer mortality. Furthermore, we compared the Cox proportional hazard model with the two-stage Cox proportional hazard model to investigate the non-linear relationship between HbA1c levels and all-cause and cause-specific mortality in the general population (p for log-likelihood ratio < 0.05). We determined that the inflection point for all-cause mortality and

cause-specific mortality was 5.5%. When HbA1c was $< 5.5\%$, an inverse relationship was observed with all-cause mortality, CVD mortality, and cancer mortality in the fully adjusted model (HR 0.52, 95% CI 0.43 - 0.63, $p < 0.01$; HR 0.5, 95% CI 0.33 - 0.73, $p < 0.01$; HR 0.56, 95% CI 0.38 - 0.83, $p < 0.01$) (Table 3). When HbA1c was $> 5.5\%$, we observed a positive association between HbA1c and both all-cause and CVD mortality.

Table 3. Threshold effect analysis of HbA1c level on all-cause, CVD mortality and cancer mortality in general population.

Outcome	HR (95%CI)	p for value
All-cause mortality		
Fitting by the standard linear model	1.13 (1.01 - 1.25)	0.03
Fitting by the two-piecewise linear model		
Inflection point	5.5%	
< 5.5	0.52 (0.43 - 0.63)	< 0.01
> 5.5	1.16 (1.13 - 1.2)	< 0.01
p for log-likelihood ratio		< 0.01
CVD mortality		
Fitting by the standard linear model	1.07 (1.01 - 1.14)	0.02
Fitting by the two-piecewise linear model		
Inflection point	5.5%	
< 5.5	0.5 (0.34 - 0.73)	< 0.01
> 5.5	1.16 (1.1 - 1.23)	< 0.01
p for Log-likelihood ratio		< 0.01
Cancer mortality		
Fitting by the standard linear model	0.98 (0.9 - 1.06)	0.55
Fitting by the two-piecewise linear model		
Inflection point	5.5%	
< 5.5	0.56 (0.38 - 0.83)	< 0.01
> 5.5	1.07 (0.99 - 1.15)	0.07
p for log-likelihood ratio		< 0.01

Two-piecewise linear regression model was adjusted for gender, age, race, PIR, education level, BMI, serum cotinine, serum cholesterol, serum triglycerides, blood urea nitrogen, uric acid, glomerular filtration rate, disease history of CKD, CVD, hyperlipidemia, hypertension and diabetes, and smoking status.

HR: hazard ratio, CI: confidence interval.

No significant association was found with cancer mortality, indicating an L-shaped trend for cancer mortality. As shown in Figure 2, Kaplan-Meier survival curves diverged by HbA1c levels. The highest risks for all-cause mortality, cardiovascular death, and cancer mortality were observed in the highest HbA1c quartile compared to the other groups.

DISCUSSION

In this study, we found that baseline HbA1c is a significant predictor of all-cause, CVD, and cancer mortality in the general population. Additionally, there are U-shaped associations between HbA1c and both all-cause and CVD mortality, and an L-shaped relationship between HbA1c and cancer mortality. The inflection point of these associations was HbA1c at 5.5%. In conclusion, controlling HbA1c around 5.5% can help reduce the risk of death in the general population.

Although previous studies have shown the association between baseline HbA1c and all-cause and disease-spe-

cific mortality in diabetes and other specific populations, such relationships in the general population are not well-established and conclusions are inconsistent. A large UK cohort study observed a U-shaped relationship between all-cause mortality and HbA1c in older patients with T2D treated with insulin, indicating that both low and high HbA1c levels increase the risk of all-cause mortality [13]. Data from a recent prospective cohort study also suggested a U-shaped association between HbA1c and all-cause mortality in an older population, but this association was not significant for CVD and cancer mortality [14]. In diabetic individuals with heart failure, the Cox regression model, after adjusting for all significant predictors, showed a U-shaped correlation between HbA1c and mortality, with the lowest risk of death when HbA1c ranged from 7.1% to 8.0% [15]. In a nationally representative cohort study, low HbA1c (< 4.0%) was linked to all-cause mortality in non-diabetic adults, with a higher risk when HbA1c was < 4.0% compared to 5.0% to 5.4% [8]. Similarly, we observed a higher risk for all-cause mortality and disease-specific mortality when HbA1c was below the threshold value.

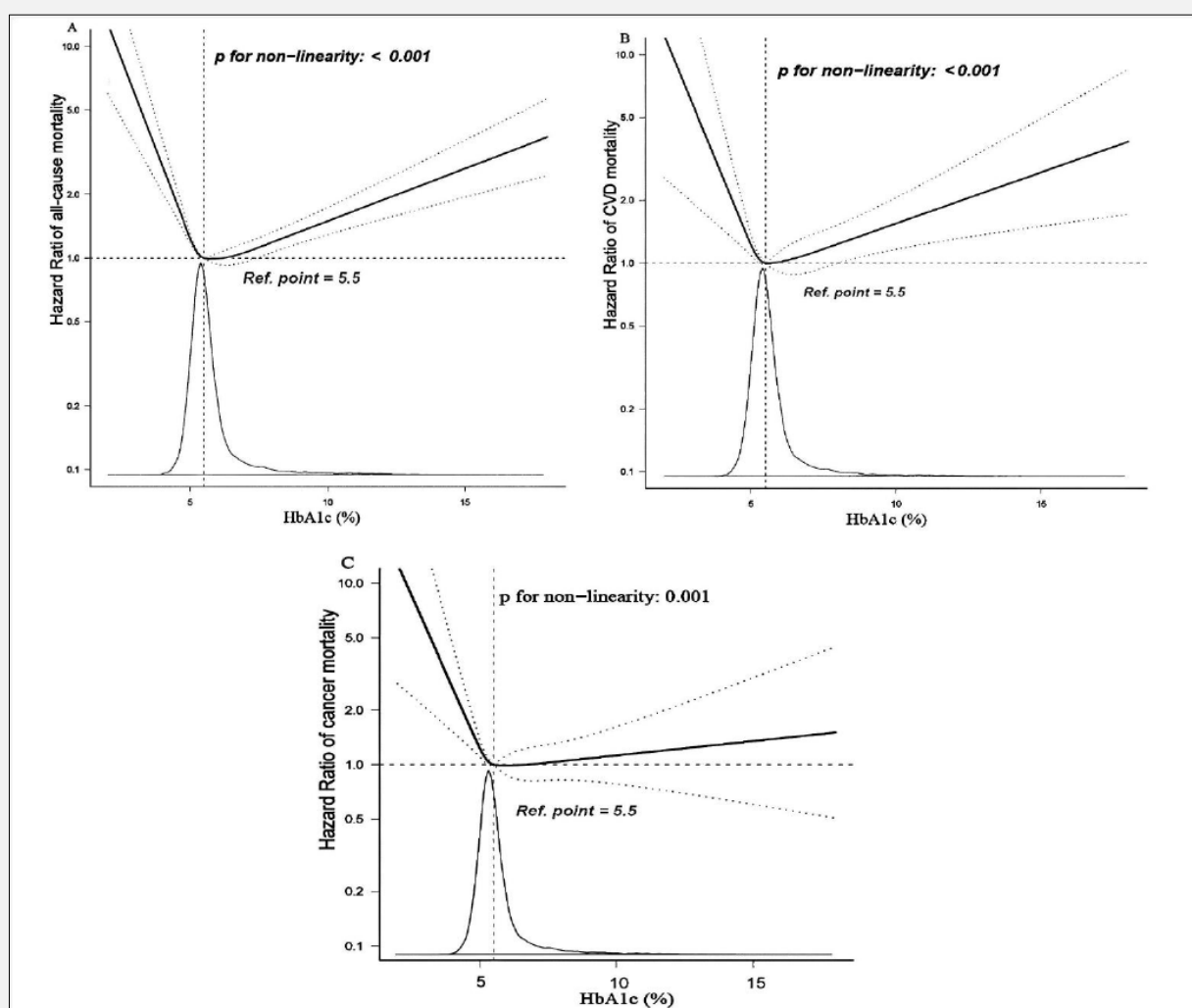


Figure 1. Risk of mortality basing on restricted cubic spline regression in general population. The data adjusted for age, sex, race, PIR, education level, BMI, serum cotinine, serum cholesterol, serum triglycerides, blood urea nitrogenuric acid, glomerular filtration rate, disease history of CKD, CVD, hyperlipidemia, hypertension and diabetes, and smoking status.

Unlike previous studies, we identified a lower threshold value of 5.5%. This discrepancy may be due to differences in population composition, as most participants in our study were non-diabetic (79.6%).

However, a previous study from Japan reported a significant linear relationship between HbA1c and both all-cause and CVD mortality in the general population [5]. Evidence from a population-based Australian study showed that HbA1c had a linear relationship with all-cause and CVD mortality, with an adjusted HR (95% CI) of 1.1 (1.0 - 1.2) for all-cause mortality (7). Both men and women with HbA1c levels $\geq 6.5\%$ had a significantly increased risk of death during follow-up compared to those with HbA1c levels of 5.4 - 5.6% among

Singaporean Chinese without a history of cancer, diabetes, or cardiovascular disease [16]. Another cohort study found that low HbA1c was associated with an increased risk of all-cause mortality, but found no significant relationship between HbA1c and CVD mortality [17]. The Sibutramine Cardiovascular Outcomes Trial showed that elevated HbA1c levels increased the risk of adverse cardiovascular outcomes and all-cause mortality in patients with diabetes. However, no evidence showed an increased risk of mortality when HbA1c was $\leq 6.4\%$ [18]. This study observed an inverse association between HbA1c and both all-cause and disease-specific mortality when HbA1c levels were below the threshold value. Additionally, a positive correlation was found be-

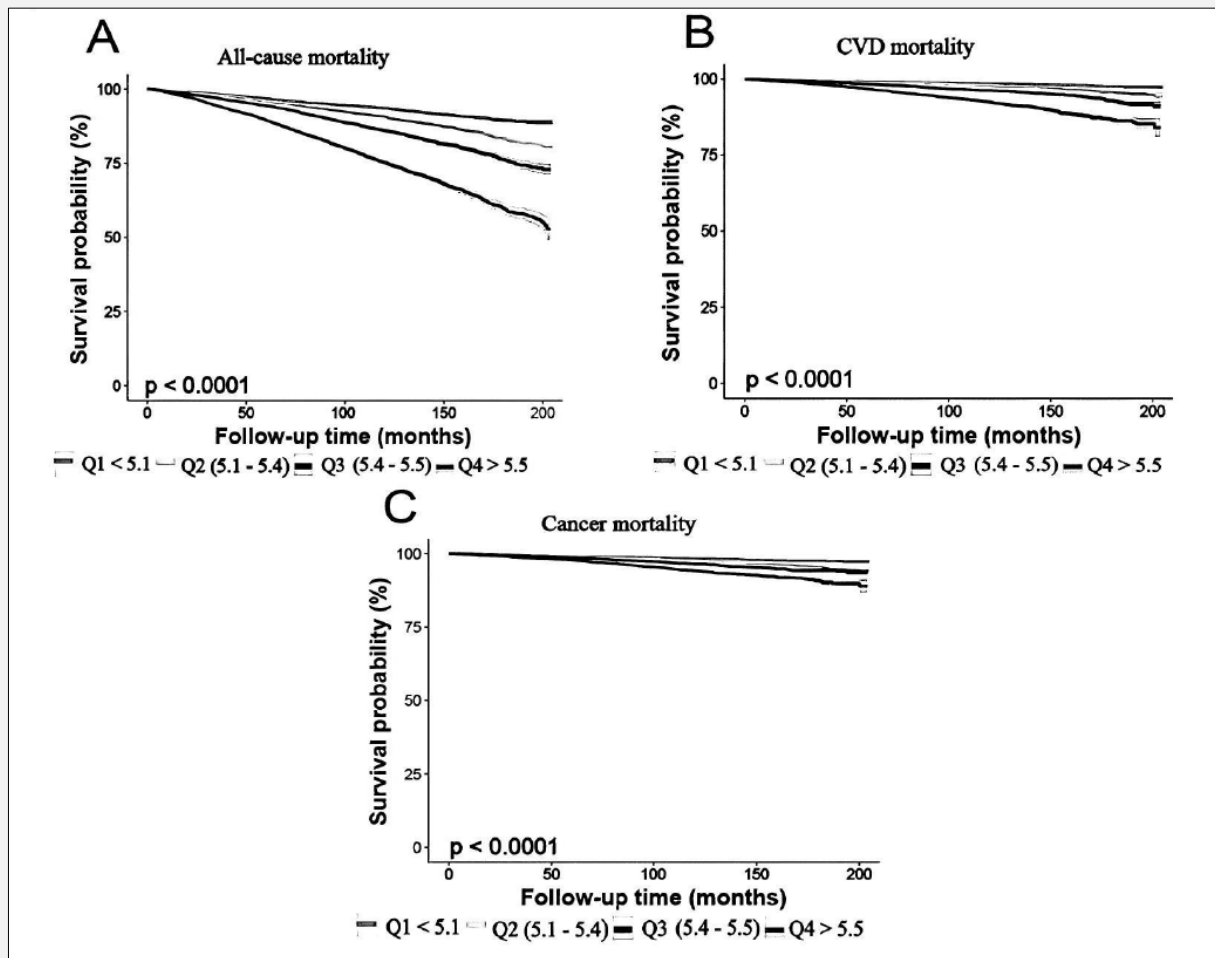


Figure 2. Kaplan-Meier survival curves of HbA1c with all cause (A) and cardiovascular (B) mortality and cancer mortality (C).

tween HbA1c and both all-cause and CVD mortality when HbA1c levels exceeded the inflection point. The discrepancies between these results may be attributed to differences in study populations, glycemic control, sample sizes, and adjustments for confounding covariates. The biological mechanisms linking high HbA1c levels to increased mortality have been thoroughly explained. Diabetes complications are the primary cause of death in diabetic patients. The theoretical mechanisms of diabetes complications due to high blood sugar include pathophysiologic derivatives like oxidants, high permeability, and glycation products, which harm tissues and cell signaling pathways (e.g., phospholipids or kinases) induced by glucose metabolism [19]. Hyperglycemia may be mediated by oxidative stress, triggering adverse reactions that accelerate cardiovascular events and worsen clinical outcomes [20,21]. Additionally, elevated HbA1c levels increase circulating insulin, insulin-

like growth factor 1 (IGF-1), and inflammatory cytokines, potentially accelerating cancer progression [22, 23]. However, the reason why low HbA1c levels are linked to higher all-cause mortality risk remains unknown. It is suggested that low HbA1c levels are linked to impaired red blood cell indicators and elevated liver function markers [24]. Moreover, these indicators, including red blood cell damage and abnormal liver function markers, are associated with inflammation and increased morbidity risk [25,26].

The strengths of this study include a long-term, population-based cohort with a large sample size and 15 years of follow-up. We used objective laboratory data on baseline HbA1c levels and updated means to avoid potential biases from recall and single baseline measurements. Additionally, our analysis was based on a representative sample of the general population, making our findings widely applicable.

Despite its strengths, the study had some limitations. We lacked comprehensive information on specific causes of death, assessing only cardiovascular and cancer-related deaths as endpoints. Although many confounding factors were adjusted for, residual confounding due to unmeasured variables (e.g., statin use affecting glucose control) cannot be ruled out. The study participants spanned a wide age range, so we adjusted for age and performed stratified analyses by age.

CONCLUSION

This study provides additional evidence for the U-shaped relationship between HbA1C and mortality, indicating that individuals with both low and high HbA1c levels have a higher risk of all-cause mortality. Future clinical trials on diabetes management should consider the implications of lower HbA1c levels, particularly across different populations.

Data availability statement:

The data for this study can be found on the official website of NHANES (www.cdc.gov/nchs/nhanes/).

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The authors declare no financial conflicts of interest.

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