Cardiovascular Diabetology

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Can cardiovascular health and its modifiable healthy lifestyle offset the increased risk of all-cause and cardiovascular deaths associated with insulin resistance?

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Abstract

Background Insulin resistance(IR) is associated with an increased risk of all-cause and cardiovascular death, and modifiable healthy lifestyles play an active role in the improvement of IR and the reduction of all-cause and cardiovascular death. Whether cardiovascular health (CVH) and modifiable healthy lifestyles within it can attenuate or even offset the heightened perils of both all-cause and cardiovascular deaths associated with insulin resistance remains unclear.

Methods The study encompassed 14,172 healthy participants from the 2005–2018 NHANES programme. Insulin resistance was evaluated using the TyG index, TyG-WC, and TyG-WHtR, while CVH was assessed employing the LE8 score, in addition to the LE4 index redefined according to four health behaviours. Weighted multifactor Cox regression models were used to assess the association of IR and CVH with all-cause and cardiovascular mortality, and dose-response relationships were assessed using restricted cubic spline. Furthermore, subjects were grouped according to IR and CVH scores, and generalised linear models were used to estimate the weighted mortality and risk of death for each group and to calculate the absolute risk difference. Finally, the predicted probability of all-cause and cardiovascular mortality risk as a function of IR was computed, and the complex relationship between the three was visualised using two-dimensional grouped scatter plots and three-dimensional surface plots.

Results Among the 14,172 healthy participants included in the study, 1534 deaths occurred over a mean follow-up period of 7.6 years (382 of these deaths were due to cardiovascular causes). The weighted Cox regression analysis indicated that elevated TyG-WC and TyG-WHtR correlated with a greater likelihood of mortality from all causes and cardiovascular events, whereas cardiovascular health was inversely associated with these risks. Additional stratification revealed a notable reduction in the likelihood of mortality from all causes and cardiovascular events as cardiovascular health improved, irrespective of the presence of insulin resistance. Additionally, participants with high insulin resistance but moderate or high cardiovascular health did not have significantly increased risks compared with

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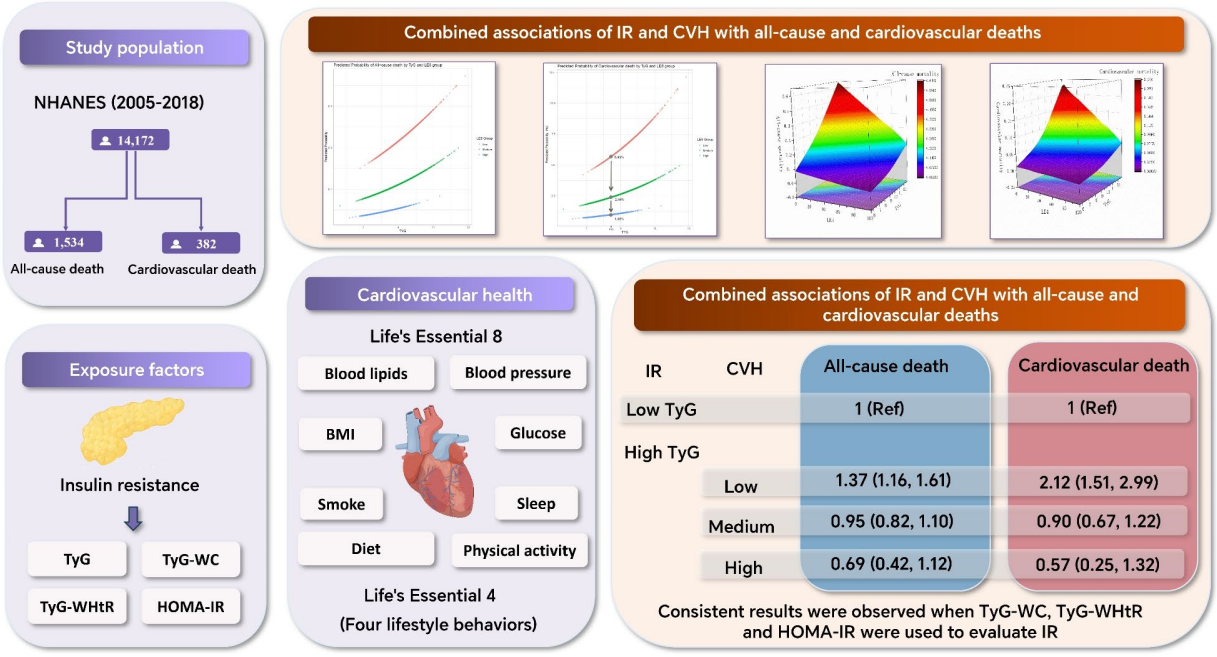
those with low insulin resistance. Stratified scatter plots and 3D surface plots revealed that cardiovascular health and modifiable healthy lifestyles significantly reduced the risk of insulin resistance-related death, with greater reductions observed at higher insulin resistance levels.

Conclusions In this cohort study, improving cardiovascular health and modifiable health behaviors significantly reduced the risk of insulin resistance-related all-cause and cardiovascular deaths. Maintaining cardiovascular health at moderate or high levels (LE8 ≥ 50) could offset the increased risks caused by insulin resistance.

Keywords Cardiovascular health, Insulin resistance, TyG index, TyG-WC, TyG-WHtR, All-cause death, Cardiovascular death

Graphical Abstract



Introduction

Cardiovascular disease (CVD) remains one of the primary causes of death on a global scale [1, 2]. Particularly concerning is the continuous increase in the CVD burden worldwide, driven significantly by modifiable factors, including cardiometabolic factors, lifestyle, and the social environment, which are significant drivers of this trend [2, 3]. However, there is currently inadequate awareness and promotion of ideal cardiovascular health (CVH) and modifiable risk factors, and effective and affordable prevention strategies, such as healthy lifestyles, remain overlooked by the public and health systems [4]. To meet the Sustainable Development Goal of decreasing premature deaths from noncommunicable diseases by a minimum of 30% by the year 2030 [5], there is an urgent need to examine the important risk factors contributing to CVD development and identify effective prevention strategies that can modify these risks.

Insulin resistance (IR) is characterized by decreased responsiveness to insulin [6] and is a typical feature of cardiometabolic syndrome that is closely related to the incidence and mortality of CVD [7–10]. Indeed, with the increasing global obesity rate, the occurrence and widespread presence of IR and associated CVD are rapidly increasing [11]. Despite the clinical significance of IR, it remains underexploited in clinical practice. Although the hyperinsulinemic-euglycemic clamp technique (HI-HG) is regarded as the gold standard, its complexity and invasiveness hinder widespread application [12]. Furthermore, while markers such as A1C, OGTT, or fasting glucose are often used as non-invasive alternatives to assess IR, they lack sensitivity and are typically only associated with IR in the later stages of disease [13]. This highlights the need to use other non-invasive and effective alternatives such as HOMA-IR to better assess early IR and its associated risks. Recently, introduced indices such as TyG, TyG-WC, and TyG-WHtR have demonstrated their simplicity and effectiveness as surrogate markers for assessing IR [14–17] and have shown greater efficacy than HI-HG and HOMA-IR in evaluating the risk of

diseases associated with IR [18, 19]. In addition, extensive observational studies have confirmed the strong link between the associations of TyG and related indices with CVD risk. Notably, compared to the TyG index alone, TyG-WC and TyG-WHtR simultaneously capture three interrelated metabolic abnormalities associated with mortality risk: central obesity quantified by WC/WHtR, and abnormalities in glucose and lipid metabolism represented by the TyG index. Therefore, they demonstrate superior performance in assessing disease risk [20–30].

Lifestyle modifications contribute significantly to alleviating IR and decreasing the risk of CVD [31–35]. A healthy lifestyle, including adequate sleep, quitting smoking, maintaining an optimal weight, engaging in regular exercise, and consuming a balanced diet, is linked to decreased cardiometabolic risk and CVD mortality among the broad population [2]. However, in healthcare settings, attention is frequently given to anthropometric measurements and serum markers while ignoring the assessment of modifiable healthy lifestyles [36, 37]. The American Heart Association introduced a novel framework for cardiovascular health in 2010, which considers various key factors, including healthy lifestyles such as physical activity, to quantify cardiovascular health and develop a cardiovascular health score [38]. In 2022, the score was revised to incorporate the improved Life's Essential 8 (LE8) metrics [39]. Current research findings indicate that an elevated LE8 score is correlated with a lower likelihood of cardiovascular and overall mortality [40–46]. However, it remains unclear whether CVH, assessed via LE8, and modifiable healthy lifestyles within it can offset the increased risk of all-cause and cardiovascular death associated with IR. The objective of this research was to assess the joint impact of IR, CVH and modifiable healthy lifestyles on all-cause and cardiovascular mortality in a prospective cohort to provide insights into the efficacy of lifestyle modifications in mitigating negative health consequences related to IR and improving long-term outcomes.

Methods

Study population

The subjects for this study were drawn from the National Health and Nutrition Examination Survey (NHANES), with pertinent data openly and freely available through the official NHANES website, reachable at https://www.cdc.gov/nchs/nhanes/index.htm. Extensive informatio n regarding the inception, components, and methodologies of the NHANES has been previously described in the literature. In summary, the NHANES operates as an ongoing, cross-sectional survey utilizing a sophisticated stratified probability sampling approach to engage with a representative subset of the US noninstitutionalized adult population every two years, with mobile examination centers conducting physical assessments and blood analyses. Written informed consent was obtained from all participants or their legal representatives, and approval was obtained from the ethical review board of the study center.

To increase the size of the sample, we amalgamate data from various two-year cycles of consecutive NHANES surveys. Given that information regarding sleep health was not available before 2005, we combined NHANES data obtained from seven cycles covering the period from 2005 to 2018 for our analysis. Out of the 70,190 adult participants included across these seven survey cycles, we discarded those with incomplete mortality data ($N = 28,168$), absent TyG index data ($N = 23,906$), and missing LE8 data ($N = 3944$). In the end, the study included 14,172 qualified adult participants. A detailed flowchart can be found in eFigure 1 in Supplement 1.

Definitions of CVH scores

The LE8 and LE4 scores were used to define CVH [39]. The LE8 score was calculated on the basis of a thorough assessment of four lifestyle behaviors—diet, smoking, exercise, and sleep—along with four cardiovascular-related health indicators—body mass index (BMI), blood pressure levels, and blood glucose and lipid levels. Furthermore, to prioritize the evaluation of modifiable healthy lifestyles and to account for potential collinearity among the four health factors and IR, a new score, referred to as LE4, was recalculated on the basis of the four health behaviors.

All four health behaviors were assessed through self-report questionnaires: (1) The diet score required 2-day dietary information (exclusion if only 1 day was available) and was scored according to the 2015 Healthy Eating Index; (2) the duration of weekly moderate to vigorous physical activity served as the foundation for calculating the physical activity score; (3) the nicotine exposure score considered participants' current and past smoking status, smoking cessation, and secondhand smoke exposure (with an additional 20-point deduction for living with other smokers); and (4) the sleep score was determined by participants' self-reported average nightly sleep duration.

The evaluation of the four health factors utilized anthropometric measurements and blood analysis data collected from a mobile examination center. These factors included the following: (1) BMI, derived from recorded height and weight, with scores assigned across five specified categories; and (2) blood glucose, which was assessed via measurements of fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) derived from blood samples. Diabetic individuals were scored according to HbA1c categories, whereas nondiabetic individuals received scores on the basis of both FBG and HbA1c

levels. (3) Blood lipid scoring was based on the assessment of non-high-density lipoprotein cholesterol (HDL-C) levels. (4) The blood pressure score was calculated on the basis of participants' blood pressure levels and their treatment status, which included a 20-point penalty for blood pressure measurements taken following antihypertensive treatment. Blood pressure levels were assessed based on at least two sets of measurement data. Trained professionals recorded systolic and diastolic blood pressures three consecutive times using a cuff after participants had been seated quietly for five minutes. To minimize variability, the average of the second and third measurements was used for analysis, excluding the first blood pressure reading.

Finally, the LE8 score was derived from the mean of the eight separate scores (with LE4 calculated using only the four health behavior scores). Additionally, following AHA recommendations, overall CVH was classified into three tiers (high: LE8 ≥ 80; moderate: 50 ≤ LE8 < 80; low: LE8 < 50). The detailed scoring procedures have been previously described [39].

Definition of IR

In this study, we utilized validated surrogate indices, including TyG, TyG-WC, and TyG-WHtR, to evaluate IR and additionally employed HOMA-IR in sensitivity analyses. The calculation formulas are as follows:

$$\begin{aligned}
\text{TyG} &= \ln[\text{TG(mg/dL)} \times \text{FBG(mg/dL)}/2]\ [14].\\
\text{TyG-WC} &= \ln[\text{TG(mg/dL)} \times \text{FBG(mg/dL)}/2]\\
&\quad \times \text{waist circumference (cm)}\ [17].\\
\text{TyG-WHtR} &= \ln[\text{TG(mg/dL)} \times \text{FBG(mg/dL)}/2]\\
&\quad \times \text{waist circumference } (cm)/\text{height (cm)}\ [21].\\
\text{HOMA-IR} &= \text{FBG}(mmol/L)\\
&\quad \times \text{fasting insulin (mIU/L)}/22.5.
\end{aligned}$$

Definition of outcomes

The primary aim of this study was to evaluate overall and cardiovascular mortality over the course of follow-up. Data on participant mortality were acquired by accessing the death registry maintained by the National Health Service Information Center, and for participants with missing mortality data we checked and excluded them prior to data analysis. Furthermore, details concerning the occurrence of mortality from any cause and cardiovascular origin were gathered through connections to death registries, with the cutoff date for mortality information set at December 31, 2019.

Covariates

In accordance with previous similar research [40], the covariates considered in this study included sex, age, race/ethnicity, education level, marital status, liver function (ALT and AST), renal function (creatinine), blood pressure (calculated as the average of several blood pressure readings taken from the patient), history of coronary heart disease (CHD) (yes or no), and the ratio of family income to poverty (PIR). CHD history was obtained through the question "Have you ever been told you had coronary heart disease?". To minimize the loss of sample size, all available data were analyzed. For categorical variables with missing data, we redefined new categories [47] and conducted additional sensitivity analysis by repeating the original data analysis after excluding individuals with missing data.

Statistical analysis

Considering the intricate multistage sampling structure, we took weights into account in our analysis. Moreover, to align the weights with the survey population, we recalculated the weights for the combined seven cycles of data on the basis of the NHANES analytical guidelines for combined data across cycles. Since all the analytical data included laboratory test results, we used the sample weights of the laboratory data for our analysis.

First, we differentiated between all-cause deaths and cardiovascular deaths and divided the participants into two categories according to mortality occurrence for comparative analysis. After weighted analysis, continuous variables were analyzed via the t test. With the $\chi 2$ test, comparisons were made for categorical variables expressed as counts (percentages). In addition, we additionally stratified 6 groups according to tyg and LE8 for differential comparisons. Taking into account the impact of multicollinearity among covariates on the results, we conducted a collinearity diagnosis (results of the collinearity screening are presented in eTables 13–17). Importantly, we did not find any significantly collinear covariates. To assess the associations between IR and both all-cause and cardiovascular deaths, four weighted Cox regression analysis models were constructed. Covariates were not included in the crude model, whereas demographic variables (age and sex) were adjusted for in Model 1. Model 2 further controlled for sociodemographic variables, including race, education, PIR, marital status, smoking habits, and alcohol consumption. In Model 3, additional adjustments were made for factors such as coronary heart disease history, blood pressure, liver function, and renal function. To assess the associations between CVH and mortality from any cause or cardiovascular origin, we also developed four weighted Cox regression analysis models. However, since the LE8 score includes nicotine exposure and blood pressure, smoking and blood pressure were not adjusted in Models 2 and 3. Using the Schoenfeld residual method, the proportional hazards assumption was verified, and Schoenfeld residual plots showing variable changes over time are presented in eFigures 2–3 in Supplement 1. In addition, based on

the model adjustment programme described above, we further performed weighted linear regression analyses to assess the association between IR and CVH. Finally, to further assess the nonlinear association between IR and CVH with both all-cause and cardiovascular deaths, we fitted their dose–response relationships via a 4-knot restricted cubic spline, including all variables in the analysis of Model 3. The likelihood ratio test was used to assess the significance of the nonlinear association.

To assess the combined impact of IR and CVH on mortality from any cause and cardiovascular origin, participants were stratified according to their IR levels and CVH scores. Given the lack of standardization for the cutoff value of TyG-related indices used to define IR, several previously published studies were referenced, and the median was used as the cutoff to categorize participants into two groups. The LE8 grouping was further categorized into high, medium, and low categories in accordance with prior definitions. Weighted mortality rates for each group were then estimated via generalized linear models, and the risk of death was assessed via weighted multifactorial Cox regression models. Additionally, to further assess the impact of CVH on the increased risk of death associated with IR, participants were categorized into six groups on the basis of their IR levels and CVH scores. Using participants with low LE8 and high TyG as the reference group, we calculated the absolute risk difference (RD) via generalized linear models [48, 49]. To illustrate the cumulative mortality rates over time for each group, Kaplan–Meier (KM) curves were plotted, and the log-rank test was applied to evaluate differences between groups. Finally, we compared the risk ratios of participants with high IR at different CVH levels, using participants with low IR as the reference, to assess whether CVH could offset the increased risk of mortality from any cause and cardiovascular origin associated with elevated IR.

To visually demonstrate the combined effects of CVH and IR on the occurrence of mortality from any cause or cardiovascular origin, we employed two-dimensional scatter plots and 3D surface plots to visualize these complex associations. Initially, we utilized the predict function from the "survival" package in R to calculate the predicted probabilities of all-cause and cardiovascular death risk associated with changes in IR. To control for the interference of covariates, we incorporated each covariate into the model using mean values (for continuous variables) or typical values (for categorical variables) to calculate the predicted probabilities [50]. We subsequently created two-dimensional scatter plots on the basis of the LE8 grouping and visualized them via the "ggplot2" package. Furthermore, we calculated the mortality rates corresponding to IR at P5, P50, and P95 to evaluate the advantages of enhancing CVH in decreasing mortality from any cause and cardiovascular origin across different IR levels. Additionally, we generated 3D surface plots to visualize the joint correlation between LE4, IR, and the risk of both all-cause mortality and cardiovascular mortality.

To further evaluate the potential influence of modifiable lifestyle factors within the CVH framework on IR and the associated risk of mortality from all causes and cardiovascular causes, several mediation analyses was conducted. Taking into account the effects of gender and age, we also performed subgroup mediation analyses by gender and age (< 50 and ≥ 50 years) subgroup. In these mediation analyses, all the variables from Model 3 were included for adjustment.

To ascertain the reliability of the results obtained, multiple sensitivity analyses were performed. First, we repeated the analysis using original data after excluding categorical variables with missing data. For continuous variables with missing values, we conducted multiple imputations [51] before repeating the analysis. Second, we further utilized HOMA-IR as an additional metric to assess IR for the purpose of conducting replicated analyses. Specifically, individuals with a HOMA-IR value exceeding 2.5, which is indicative of the presence of IR [52], were grouped under the category of "high HOMA-IR" as per the original classification. To ensure robustness, we performed four distinct sensitivity analyses, each incorporating this grouping. In addition, considering the potential impact of reverse causality caused by severe diseases, the exclusion criterion was applied to participants who passed away within a two-year period following the commencement of the follow-up phase of the study. Furthermore, given the significant differences in WC and WHtR between genders, we reanalyzed the data by dividing it into two separate sections based on sex, in order to prevent misclassification due to gender disparities in WC and WHtR. Finally, considering the possible influence of hypoglycemic, lipid-lowering, and antihypertensive therapies on the results, we adjusted the patients' treatment status into account and additionally excluded participants using insulin, taking into account the potential impact of insulin use on IR.

All analyses and graphical visualizations were conducted via R version 4.2.0, Origin 2024, and EmpowerStats 2.0. The results were considered statistically significant if the two-tailed P value was less than 0.05.

Results

Baseline characteristics of the participants

This study included 14,172 participants, with a median follow-up period of 7.6 years. During this period, 1534 participants died, including 382 from cardiovascular causes. The weighted characteristics of the baseline data are shown in Table 1. When stratified by death status,

Table 1 Baseline demographic, lifestyle, and laboratory characteristics of participants classified by the presence of different causes of death and incidence of death

	All-cause death			Cardiovascular death		
	No	Yes	*P*	No	Yes	*P*
Participants(n)	12,638	1534		13,790	382	
Age (years)	46.65 (0.25)	67.97 (0.53)	< 0.01	47.92 (0.26)	69.93 (0.75)	< 0.01
Sex, n (%)			< 0.01			< 0.01
Women	6803 (53.83%)	646 (42.11%)		7292 (52.88%)	157 (41.10%)	
Men	5835 (46.17%)	888 (57.89%)		6498 (47.12%)	225 (58.90%)	
Ethnic, n (%)			< 0.01			< 0.01
Mexican	2062 (16.32%)	123 (8.02%)		2155 (15.63%)	30 (7.85%)	
Other hispanic	1297 (10.26%)	70 (4.56%)		1353 (9.81%)	14 (3.66%)	
Non-hispanic white	5331 (42.18%)	1006 (65.58%)		6091 (44.17%)	246 (64.40%)	
Non-hispanic black	2585 (20.45%)	286 (18.64%)		2789 (20.22%)	82 (21.47%)	
Other race	1363 (10.78%)	49 (3.19%)		1402 (10.17%)	10 (2.62%)	
Education, n (%)			< 0.01			< 0.01
Below 9th grade	1135 (8.98%)	241 (15.71%)		1315 (9.54%)	61 (15.97%)	
9th to 11th grade	1654 (13.09%)	301 (19.62%)		1884 (13.66%)	71 (18.59%)	
High school graduation	2806 (22.20%)	426 (27.77%)		3120 (22.63%)	112 (29.32%)	
Some college or AA degree	3844 (30.42%)	345 (22.49%)		4109 (29.80%)	80 (20.94%)	
College graduate or above	3188 (25.23%)	218 (14.21%)		3348 (24.28%)	58 (15.18%)	
Missing	11 (0.09%)	3 (0.20%)		14 (0.10%)	0 (0.00%)	
CHD, n (%)			< 0.01			< 0.01
No	12,210 (96.61%)	1292 (84.22%)		13,196 (95.69%)	306 (80.10%)	
Yes	394 (3.12%)	216 (14.08%)		546 (3.96%)	64 (16.75%)	
Missing	34 (0.27%)	26 (1.69%)		48 (0.35%)	12 (3.14%)	
DM	2362 (19.07%)	651 (42.58%)	< 0.01	2836 (20.96%)	177 (46.34%)	< 0.01
Drinking status, n (%)			< 0.01			< 0.01
Non/small	1559 (12.34%)	219 (14.28%)		1717 (12.45%)	61 (15.97%)	
Former	1695 (13.41%)	527 (34.35%)		2086 (15.13%)	136 (35.60%)	
Mild	4127 (32.66%)	448 (29.20%)		4462 (32.36%)	113 (29.58%)	
Moderate	1894 (14.99%)	117 (7.63%)		1981 (14.37%)	30 (7.85%)	
Heavy	2317 (18.33%)	147 (9.58%)		2436 (17.66%)	28 (7.33%)	
Missing	1046 (8.28%)	76 (4.95%)		1108 (8.03%)	14 (3.66%)	
Smoking status, n (%)			< 0.01			< 0.01
Never	7200 (56.97%)	607 (39.57%)		7627 (55.31%)	180 (47.12%)	
Former	2989 (23.65%)	620 (40.42%)		3470 (25.16%)	139 (36.39%)	
Current	2444 (19.34%)	306 (19.95%)		2687 (19.49%)	63 (16.49%)	
Missing	5 (0.04%)	1 (0.07%)		6 (0.04%)	0 (0.00%)	
Marital status, n (%)			< 0.01			< 0.01
Married or cohabiting	6748 (53.39%)	732 (47.72%)		7309 (53.00%)	171 (44.76%)	
Single, widowed or separated	2465 (19.50%)	638 (41.59%)		2934 (21.28%)	169 (44.24%)	
Never married	3423 (27.08%)	164 (10.69%)		3545 (25.71%)	42 (10.99%)	
Missing	2 (0.02%)	0 (0.00%)		2 (0.01%)	0 (0.00%)	
PIR			< 0.01			< 0.01
Low income	3433 (29.58%)	517 (36.36%)		3834 (27.80%)	116 (30.37%)	
Low middle income	1523 (13.12%)	256 (18.00%)		1697 (12.31%)	82 (21.47%)	
Middle income	2900 (24.99%)	381 (26.79%)		3179 (23.05%)	102 (26.70%)	
High income	3750 (32.31%)	268 (18.85%)		3960 (28.72%)	58 (15.18%)	
Missing	1032 (8.17%)	112 (7.30%)		1120 (8.12%)	24 (6.28%)	
ALT (IU/L)	25.15 (0.19)	23.77 (0.63)	0.04	25.08 (0.18)	23.22 (1.62)	0.26
AST (IU/L)	24.79 (0.16)	28.09 (0.93)	< 0.01	25.02 (0.17)	26.85 (1.44)	0.20
Creatinine (umol/L)	76.35 (0.30)	97.81 (2.55)	< 0.01	77.63 (0.33)	100.22 (3.61)	< 0.01
SBP (mmHg)	120.60 (0.24)	130.98 (0.67)	< 0.01	121.21 (0.24)	132.73(1.38)	< 0.01
DBP (mmHg)	70.20 (0.21)	65.52 (0.46)	< 0.01	69.94 (0.21)	64.14 (0.74)	< 0.01

Table 1 (continued)

	All-cause death			Cardiovascular death		
	No	Yes	*P*	No	Yes	*P*
TG (mg/dL)	125.09 (1.22)	138.87 (3.06)	< 0.01	125.95 (1.19)	138.70 (5.39)	< 0.01
FBG (mg/dL)	99.27 (0.34)	113.57 (1.45)	< 0.01	100.15 (0.35)	113.51 (2.50)	< 0.01
Height (cm)	168.91 (0.12)	166.92 (0.34)	< 0.01	168.79 (0.12)	166.59 (0.64)	< 0.01
BMI (kg/m^2)	29.12 (0.10)	29.12 (0.22)	0.99	29.09 (0.10)	30.63 (0.49)	< 0.01
WC (cm)	99.29 (0.25)	103.34 (0.59)	< 0.01	99.48 (0.25)	105.95 (1.08)	< 0.01
FINS (mIU/L)	12.86 (0.17)	14.79 (0.59)	< 0.01	12.97 (0.16)	15.53 (1.31)	0.05
HOMA-IR	3.61 (0.06)	4.85 (0.27)	< 0.01	3.68 (0.06)	5.07 (0.63)	0.03
TyG	8.58 (0.01)	8.82 (0.02)	< 0.01	8.60 (0.01)	8.86 (0.04)	< 0.01
TyG-WC	856.52 (2.70)	915.61 (6.61)	< 0.01	859.50 (2.66)	941.08 (11.26)	< 0.01
TyG-WHtR	5.08 (0.02)	5.48 (0.04)	< 0.01	5.10 (0.02)	5.64 (0.07)	< 0.01
CVH scores						
LE8	68.90 (0.26)	59.76(0.51)	< 0.01	68.39 (0.27)	57.43 (0.86)	< 0.01
LE4	66.67 (0.35)	57.87(0.79)	< 0.01	66.12 (0.36)	58.30 (1.50)	< 0.01
Health behavior score						
Diet score	38.60 (0.47)	40.53 (1.19)	0.08	38.72 (0.48)	40.24 (1.67)	0.35
PA score	72.96 (0.62)	46.40 (1.57)	< 0.01	71.38 (0.61)	43.75 (3.16)	< 0.01
Smoke score	71.61 (0.61)	65.45 (1.53)	< 0.01	71.10 (0.62)	72.29 (2.74)	0.68
Sleep score	83.60 (0.36)	79.27 (0.90)	< 0.01	83.38 (0.35)	76.93 (1.88)	< 0.01
Health factor score						
BMI score	60.25 (0.49)	59.72 (1.07)	< 0.01	60.37 (0.46)	51.99 (2.25)	< 0.01
Blood lipids score	65.40 (0.40)	63.89 (0.85)	0.09	65.34 (0.39)	62.12 (1.79)	0.06
Glucose score	87.75 (0.27)	74.09 (1.01)	< 0.01	87.03 (0.28)	67.96 (1.80)	< 0.01
BP score	71.93 (0.44)	49.25 (0.93)	< 0.01	70.65 (0.43)	44.12 (2.00)	< 0.01

The values are expressed as the means (SDs), medians (quartile intervals) or n (%). CHD: Coronary heart disease; PIR: poverty income ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; FBG: fasting blood glucose; BMI: body mass index; WC: waist circumference; FINS: fasting insulin; HOMA-IR:; TyG: triglyceride glucose; TyG-WC: triglyceride glucose–waist circumference; TyG–WHtR: triglyceride–glucose–waist height ratio; CVH: cardiovascular health; LE8: life's essential 8; LE4: life's essential 4; PA: physical activity; BMI: body mass index; BP:blood pressure

significant differences were observed in multiple variables at baseline for both all-cause and cardiovascular deaths. Specifically, participants who died from any cause tended to be older, male, non-Hispanic White, have lower educational attainment, be single, divorced, or living alone, have coronary heart disease, have a history of alcohol consumption, have a smoking history, and belong to the low-to-middle income group. Additionally, compared with survivors, deceased participants had higher AST, creatinine, SBP, and IR-related indices (TyG, TyG-WC, and TyG-WHtR) but lower DBP and CVH scores (LE8, LE4, PA, sleep, BMI, glucose, smoking, and BP scores). For cardiovascular deaths, the results were similar to those for all-cause deaths, with the exception that no significant differences were found in AST levels or smoking scores between the deceased and survivor groups. When stratified participants into six groups by TyG and LE8 levels, revealing striking demographic and metabolic gradients (eTable 19). Specifically, individuals with high CVH (Groups 5–6) exhibited younger age, lower BMI, and better metabolic profiles (e.g., blood pressure, glucose, lipids) regardless of TyG levels. Furthermore, high LE8 attenuated IR burden in Group5 (high TyG) with 69% lower HOMA-IR and 25% lower TG versus Group1 ($p < 0.01$). These intriguing new findings collectively underscore the potential protective role of CVH in IR.

Association of IR with all-causes and cardiovascular death

The findings from the Cox regression analysis, which explored the relationship between IR, evaluated via TyG-related indicators, and the hazards of overall and cardiovascular mortality, are detailed in eTable 2 of Supplement 1. As anticipated, IR was significantly positively associated with the likelihood of all-cause and cardiovascular mortality. Although the gradual adjustment of covariates from the initial model to Model 3 weakened these associations, most of the significant connections persisted. In the ultimate model, the TyG index exhibited a notable correlation with an increased likelihood of cardiovascular-related fatalities (HR per SD: 1.14 (1.00, 1.30)), and a marginal correlation with all-cause mortality was exhibited (HR per SD: 1.05 (0.98, 1.12)). In contrast, even after accounting for numerous confounders, the connections between TyG-WC (HR per SD: all-cause: 1.10 (1.01, 1.19); cardiovascular death: 1.33 (1.12, 1.58)) and TyG-WHtR (HR per SD: all-cause: 1.10 (1.02, 1.19); cardiovascular death: 1.35 (1.14, 1.61)) and the risks of both all-cause and cardiovascular deaths continued to be significant.

Association of IR with CVH

We further performed weighted linear regression analyses to assess the association between IR and CVH. The results of the regression analysis indicate a strong inverse correlation between IR and CVH score (all $P < 0.001$), suggesting that higher TyG-related indices correspond to lower CVH scores. This association persists even after comprehensive adjustments (eTable 18). Specifically, in the fully adjusted model, for every increase of one standard deviation in TyG, TyG-WC, and TyG-WHtR, LE8 decreased by 6.33 (95% CI: – 6.59, – 6.07), 7.89 (95% CI: – 8.18, – 7.61), and 8.10 (95% CI: – 8.40, – 7.80), respectively. Additionally, LE4 showed a similar trend, decreasing by 2.72 (95% CI: – 3.14, – 2.31), 2.73 (95% CI: – 3.17, – 2.29), and 2.80 (95% CI: – 3.26, – 2.34), respectively. It is worth noting that TyG-WC and TyG-WHtR had stronger correlations with LE8/LE4 than TyG, highlighting the exacerbated IR-CVH link due to abdominal obesity.

Table 2 Weighted Cox regression analyses for the associations between LE8 and all-cause death or cardiovascular death

	HR per 1 de/increase (95% CI)			
	Crude model	**Model 1**	**Model 2**	**Model 3***
All-cause death				
LE 8 (Per 10)	0.68 (0.65,0.71)	0.75 (0.72,0.78)	0.81 (0.76, 0.85)	0.82 (0.78, 0.85)
LE 4 (Per 10)	0.83 (0.80, 0.86)	0.79 (0.76, 0.81)	0.83 (0.81, 0.86)	0.84 (0.81, 0.86)
CVH group				
Low CVH (LE 8 < 50)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium CVH (50 ≤ LE8 < 80)	0.46 (0.39, 0.54)	0.52 (0.46, 0.59)	0.63 (0.54, 0.72)	0.64 (0.55, 0.73)
High CVH (LE 8 ≥ 80)	0.14 (0.11, 0.18)	0.25 (0.20, 0.33)	0.38 (0.28, 0.50)	0.39 (0.30, 0.52)
P-trend	< 0.01	< 0.01	< 0.01	< 0.01
Cardiovascular death				
LE 8 (Per 10)	0.61 (0.57, 0.66)	0.66(0.60, 0.72)	0.70 (0.64, 0.78)	0.71(0.64, 0.79)
LE 4 (Per 10)	0.84 (0.78, 0.90)	0.79 (0.73, 0.86)	0.83 (0.77, 0.90)	0.84 (0.77, 0.91)
CVH group				
Low CVH (LE 8 < 50)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Medium CVH (50 ≤ LE8 < 80)	0.31 (0.24, 0.41)	0.34 (0.26, 0.45)	0.40 (0.30, 0.52)	0.41 (0.30, 0.55)
High CVH (LE 8 ≥ 80)	0.09 (0.05, 0.15)	0.16 (0.09, 0.29)	0.22 (0.11, 0.43)	0.24 (0.12, 0.46)
P-trend	< 0.01	< 0.01	< 0.01	< 0.01

All analyses take into account complex sample survey designs. Abbreviations as in Table 1

Crude model: adjusted for none

Model 1: adjusted for sex and age

Model 2: adjusted for sex, age, ethnicity, education, marital status, PIR, and drinking status

Model 3: adjusted for sex, age, ethnicity, education, marital status, PIR, drinking status, CHD, ALT, AST and creatinine

*Additional adjustment of SBP and DBP for LE4 in Model 3

Association of CVH with all-causes and cardiovascular death

The findings regarding the link between CVH, evaluated through LE8 and LE4, and mortality from all causes, as well as cardiovascular-related issues, are summarized in Table 2. In general, LE8 and a substantial inverse relationship were observed between LE4 and both overall and cardiovascular-related mortality. When accounting for various confounding factors, an increase of 10 points in LE8 was associated with an 18% reduction in overall mortality risk (HR: 0.82 (0.78, 0.85)) and a 29% decrease in cardiovascular mortality risk (HR: 0.71 (0.64, 0.79)). Similarly, each 10-point increase in LE4 corresponded to a 16% reduction in overall mortality risk (HR: 0.84 (0.81, 0.86)) and cardiovascular deaths (HR: 0.84 (0.77, 0.91)). When subgrouped for CVH, the results revealed a 36% (HR:0.64 (0.55, 0.64 (0.55, 0.73)) and 61% (HR:0.39 (0.30, 0.52)) reduction in the risk of all-cause mortality (HR:0.39 (0.30, 0.52)) and 59% (HR:0.41 (0.30, 0.55)) and 76% (HR:0.41 (0.30, 0.55)) reduction in the risk of cardiovascular mortality (HR:0.24 (0.12, 0.46)) for the mid-LE8 and high-LE8 groups, respectively, compared with the low-LE8 group; similarly, in modifiable health behaviors, the risk of cardiovascular deaths was lower for the mid-LE4 and high-LE4 groups than for the low-LE8 group (HR:0.24 (0.12, 0.46)); similarly, among modifiable health behaviors, t the moderate LE4 and high LE4 groups reduced the risk of all-cause mortality by 36% (HR:0.64 (0.55, 0.73)) and 61% (HR:0.39 (0.30, 0.52)), and the risk of cardiovascular mortality by 59% (HR. 0.41 (0.30, 0.55)) and 76% (HR:0.24 (0.12, 0.46)).

Dose–response relationships of IR and CVH with all-cause and cardiovascular deaths

Restricted cubic spline fitting of IR and CVH to dose–response relationships for all-cause and cardiovascular death. Overall, the results from RCS were similar to those from Cox regression, showing an increasing trend in both all-cause and cardiovascular mortality with increasing IR and a gradual decrease with increasing CVH scores (eFigure 4 in Supplement 1). Specifically, following the adjustment of all covariates in Model 3, a positive linear correlation between TyG and TyG-WC with cardiovascular deaths was observed, whereas LE8 and LE4 exhibited an inverse linear relationship with both all-cause and cardiovascular deaths (P-overall < 0.05, P-nonlinear > 0.05).

However, a nonlinear correlation with overall mortality was exhibited by TYG and TyG-WC, whereas a nonlinear correlation with both overall mortality and cardiovascular mortality was observed for TyG-WHtR (P-overall < 0.05, P-nonlinear < 0.05).

Combined associations of IR and CVH with all-cause and cardiovascular deaths

We attempted to conduct a joint analysis of IR and CVH with all-cause and cardiovascular deaths via a variety of methods. When participants were grouped on the basis of IR levels and CVH scores, we found that, regardless of the IR level, there was a notable decrease in the likelihood of overall and cardiovascular-related fatalities in the medium and high LE8 categories compared with the low LE8 category (eTables 2–3 in Supplement 1). Additionally, the calculated weighted mortality rates showed similar results, with a notable reduction in the number and rate of all-cause and cardiovascular deaths as LE8 increased from low to high.

Using participants with low TyG, TyG-WC, and TyG-WHtR as references, the results of multivariable regression analysis (Table 3) indicated that those with high TyG, TyG-WC and TyG-WHtR had increased risks of all-cause deaths of 37% (HR: 1.37 (1.16, 1.61)), 48% (HR: 1.48 (1.23, 1.77)), and 54% (HR: 1.54 (1.26, 1.87)), respectively, and increased risks of cardiovascular deaths of 121% (HR: 2.12 (1.51, 2.99)), 132% (HR: 2.32 (1.55, 3.49)), and 136% (HR: 2.36 (1.55, 3.58)), respectively, at low levels of CVH. In contrast, those with elevated levels of TyG, TyG-WC, and TyG-WHtR exhibited no substantial increase in overall or cardiovascular mortality when maintaining intermediate or greater CVH. Notably, in contrast to individuals with lower TyG-WC levels, those exhibiting higher TyG-WC who maintained higher levels of CVH had a significant 72% reduction in cardiovascular death risk (HR: 0.28 (0.08, 0.93)). These findings underscore that maintaining moderate or higher levels of CVH offsets the increased risks of all-cause and cardiovascular deaths associated with elevated IR.

Furthermore, participants were divided into six categories on the basis of their IR levels and CVH scores to calculate absolute rate differences (ARD) (eTables 4–5 in Supplement 1). The findings indicated that, in comparison with subjects exhibiting low LE8 and high TyG (Group 1), those with high LE8 and low TyG (Group 6) had reduced rates of all-cause and cardiovascular deaths by 13.94% (ARD(%): -13.94 (-16.39 to -11.49)) and 4.82% (ARD(%): -4.82 (-6.13 to -3.51)), respectively. Similarly, compared with participants with low LE8 and high TyG-WC (Group 1), those with high LE8 and low TyG-WC (Group 6) had lower death rates by 13.63% (ARD(%): -13.63 (-17.22 to -10.4)) and 4.62% (ARD(%): -4.62 (-5.91 to -3.33)), respectively. Similarly, in comparison with participants who presented low LE8 and high TyG-WHtR (Group 1), those with high LE8 and low TyG-WHtR (Group 6) presented 13.63% (ARD(%): (-16.15 to -11.25)) and 4.54% (ARD(%): -4.54 (-5.83 to -3.25)) lower death rates, respectively. Notably, compared with participants with low LE8 and high TyG (Group 1), those with low LE8 and low TyG (Group 2) had an increased all-cause death rate of 6.63% (ARD(%): 6.63 (1.40–11.86)), whereas there were no significant differences in death rates between Groups 1 and 2 in other analyses. The same results were observed when the K–M curves were plotted according to the above groupings (eFigure 5 in Supplement 1).

The combined impact of IR and CVH on all-cause and cardiovascular deaths is visualized in Fig. 1 (two-dimensional grouped scatter plot) and Fig. 2 (3D surface plot). The two-dimensional grouped scatter plot reveals that when LE8 is low, both all-cause and cardiovascular mortality rates rise rapidly with increasing IR levels. However, as the LE8 category progresses from low to high, this increase in mortality gradually slows. The all-cause and cardiovascular mortality rates associated with IR at P5, P50, and P95 are presented in eTables 6–8 in Supplement 1. The results suggest that elevated IR levels correspond to a greater decrease in IR-related all-cause and cardiovascular deaths as CVH increases from low to high. Specifically, when TyG is at P5, the risk of cardiovascular death decreases by 4.06% (from 4.90 to 0.84%), and the all-cause mortality rate decreases by 13.14% (from 17.25 to 4.11%). At TyG P50, the risk of cardiovascular death decreased by 4.83% (from 5.83 to 1.00%), and the all-cause mortality rate decreased by 15.27% (from 20.22 to 4.95%). At TyG P95, the decrease in cardiovascular death risk was 5.95% (from 7.21 to 1.26%), with an 18.19% reduction in all-cause mortality (from 24.41 to 6.22%). Consistent results were observed for IR, as assessed by TyG-WC and TyG-WHtR. The 3D surface plot shows similar findings, with swift increases in overall and cardiovascular mortality rates with increasing IR when LE4 is low. However, as the LE4 score gradually increases, the mortality increases. Collectively, these findings underscore that adopting a healthy lifestyle, which leads to an increased CVH score, can significantly decrease the risk of all-cause and cardiovascular deaths associated with elevated IR.

Mediation analysis

A mediation analysis was conducted via CVH, which was assessed on the basis of four modifiable lifestyle factors. The results (eFigure 6 in Supplement 1) indicate that IR acts as a partial mediator in the relationship between a healthy lifestyle and both all-cause mortality and cardiovascular mortality. Specifically, 12.01% ($P < 0.01$) of the reduced cardiovascular mortality risk associated with a healthy lifestyle can be explained by a decrease in TyG.

Table 3 Incidence and hazard ratios for all-cause and cardiovascular deaths among participants with high TyG, TyG-WC, and TyG-WHtR at different levels of CVH compared with participants with low TyG, TyG-WC and TyG-WHtR

Exposure	No of deaths/No.	Weighted death (%)	HR (95% CI)
All-cause death			
TyG			
Low TyG	651/7458	2,832,287 (6.07)	1 (Ref)
High TyG			
Low CVH	264/1353	1,137,580 (16.06)	1.37 (1.16, 1.61)
Medium CVH	591/4819	2,712,650 (9.36)	0.95 (0.82, 1.10)
High CVH	28/542	160,316 (4.65)	0.69 (0.42, 1.12)
TyG-WC			
Low TyG-WC	543/6893	2,450,057 (5.70)	1 (Ref)
High TyG-WC			
Low CVH	276/1460	1,191,819 (15.81)	1.48 (1.23, 1.77)
Medium CVH	560/5111	2,540,878 (8.09)	0.90 (0.77, 1.06)
High CVH	18/322	101,320 (4.48)	0.58 (0.32, 1.05)
TyG-WHtR			
Low TyG-WHtR	506/6599	2,329,607 (5.41)	1 (Ref)
High TyG-WHtR			
Low CVH	280/1483	1,199,433 (15.88)	1.54 (1.26, 1.87)
Medium CVH	581/5321	2,626,683 (8.38)	0.98 (0.83, 1.15)
High CVH	21/367	102,240 (4.71)	0.67 (0.38, 1.18)
Cardiovascular death			
TyG			
Low TyG	154/7458	643914 (1.380)	1 (Ref)
High TyG			
Low CVH	82/1353	371,166 (5.24)	2.12 (1.51, 2.99)
Medium CVH	139/4819	594,117 (2.05)	0.90 (0.67, 1.22)
High CVH	7/542	31,373 (0.91)	0.57 (0.25, 1.32)
TyG-WC			
Low TyG-WC	120/6893	515,801 (1.20)	1 (Ref)
High TyG-WC			
Low CVH	84/1460	384,458 (5.10)	2.32 (1.55, 3.49)
Medium CVH	134/5111	568,478 (1.81)	0.91 (0.63, 1.31)
High CVH	3/322	11,082 (0.49)	0.28 (0.08, 0.93)
TyG-WHtR			
Low TyG-WHtR	116/6599	495,203 (1.15)	1 (Ref)
High TyG-WHtR			
Low CVH	82/1483	379,166 (5.02)	2.36 (1.55, 3.58)
Medium CVH	138/5321	586,145 (1.87)	0.99 (0.69, 1.41)
High CVH	4/367	15,846 (0.73)	0.49 (0.18, 1.34)

Abbreviations as in Table 1

Adjusted model: adjusted for sex, age, ethnic, education, PIR, Drinking status, CHD, ALT, AST and creatinine

The predicted probabilities of all-cause and cardiovascular death risks were calculated via the predict function across varying levels of IR. The plot displays the predicted all-cause and cardiovascular death rates corresponding to IR within different CVH groups (based on LE8 scores)

A three-dimensional matrix was constructed to visualize the associations of IR and CVH (based on LE4 scores) with all-cause and cardiovascular death. The plot shows the predicted all-cause and cardiovascular death rates corresponding to IR and LE4 at different levels

Similarly, a 5.08% ($P<0.01$) decrease in all-cause mortality was mediated by a reduction in TyG levels. In contrast, when IR assessed by TyG-WC and TyG-WHtR was used in the mediation analysis, TyG-WC and TyG-WHtR mediated 10.84% ($P=0.02$) and 11.65% ($P<0.01$) of the association between CVH and cardiovascular mortality, respectively, whereas its mediating effect between CVH and all-cause mortality was not significant. In addition, considering that different components of CVH may contribute differently to the outcome, we conducted additional mediation analyses to evaluate the role of four modifiable healthy lifestyle factors as independent components within the CVH on the IR-mortality pathway. The results indicated that IR partially mediated the associations between exercise (3.14% for all-cause mortality and 6.68% for cardiovascular mortality), smoking (5.59%

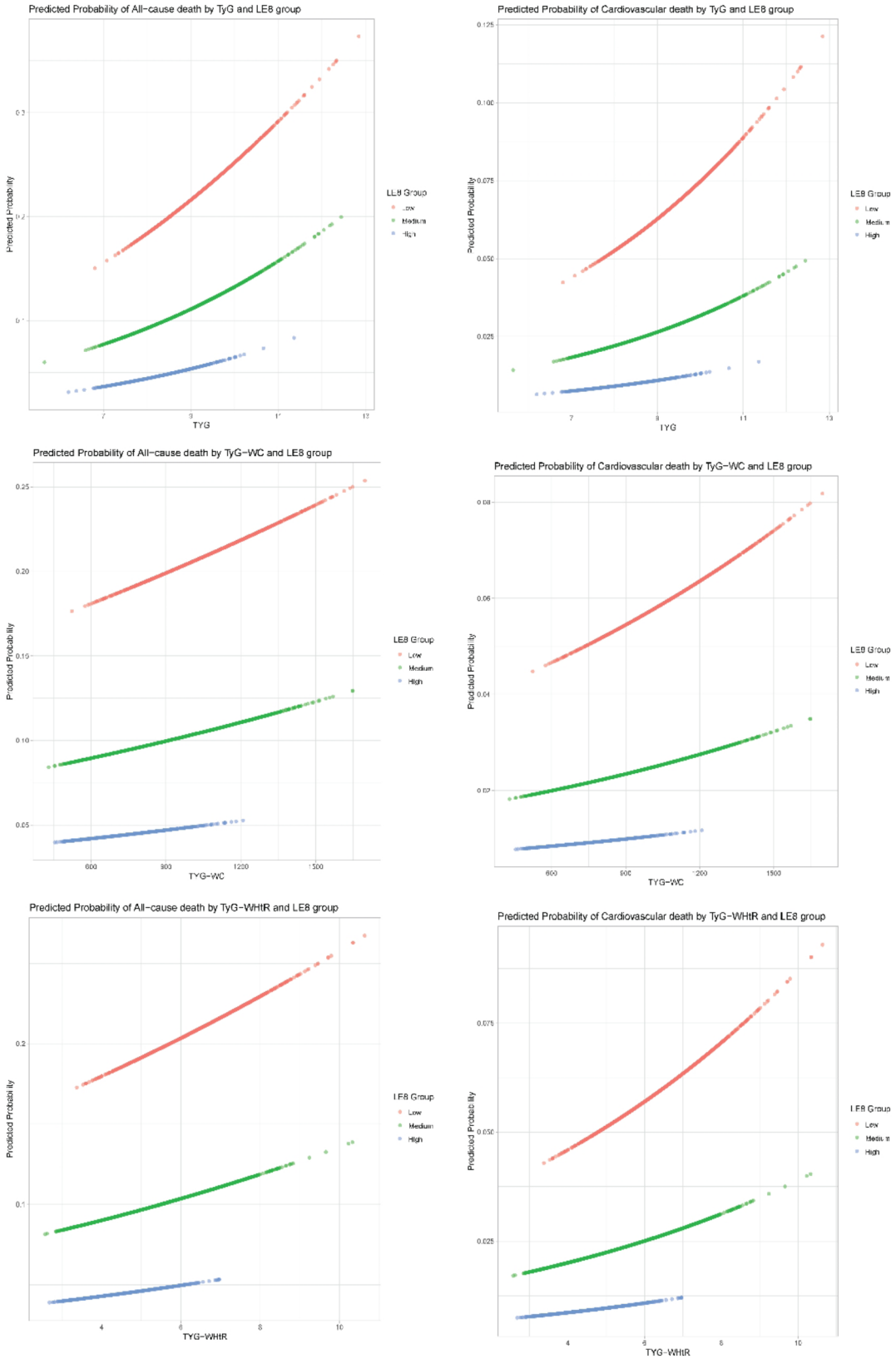


Fig. 1 Two-dimensional grouped scatter plot showing the combined effects of IR and LE8 on all-cause and cardiovascular death

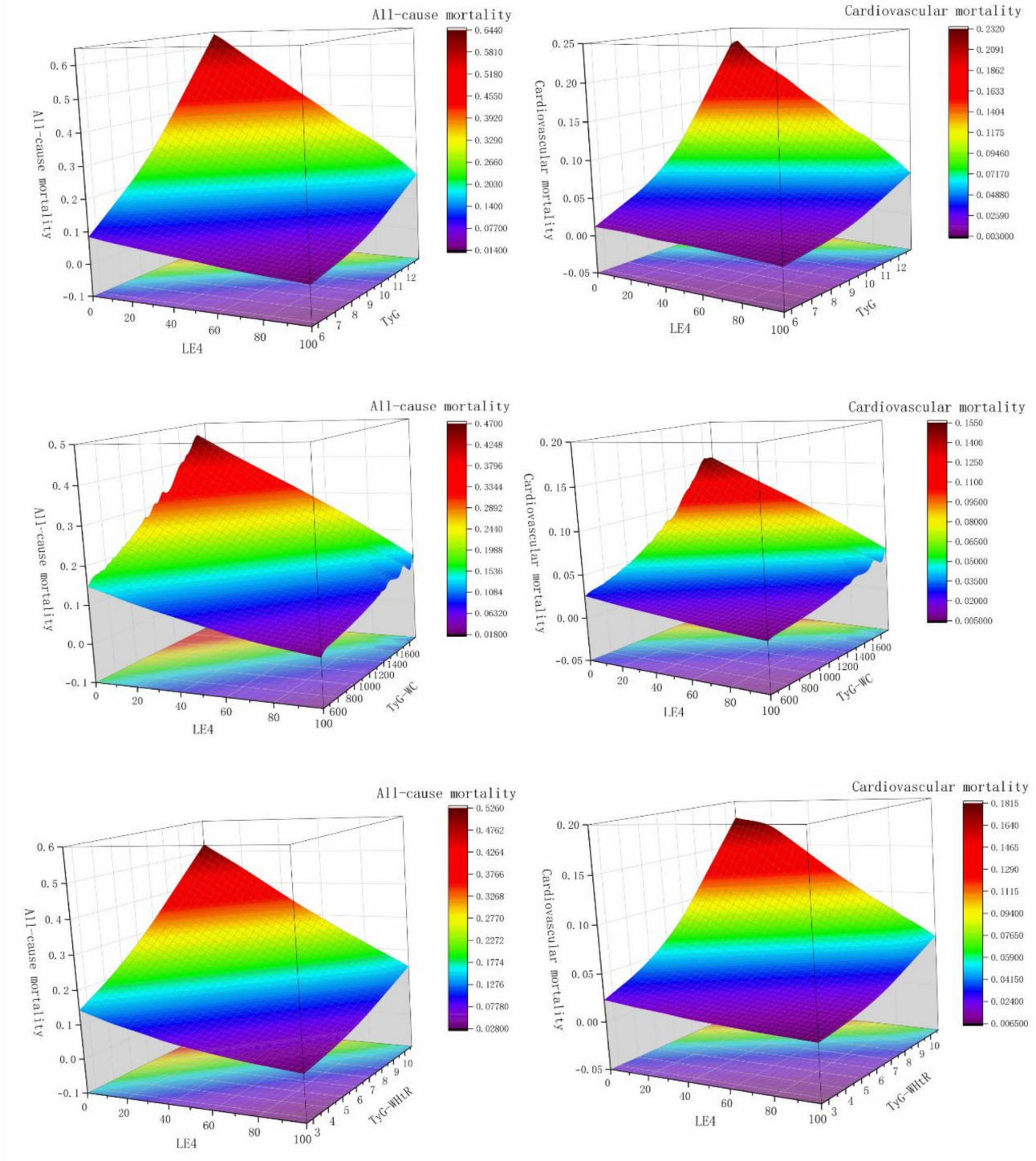


Fig. 2 3D surface plot illustrating the combined effects of IR and LE4 on all-cause and cardiovascular death

for all-cause mortality), and sleep (5.59% for all-cause mortality and 4.59% for cardiovascular mortality) with mortality. In contrast, smoking only showed a modest mediation effect in all-cause deaths (proportion mediated: 5.59%), while diet did not exert a mediating effect through IR ($P > 0.05$). Subgroup analyses stratified by sex and median age (cutoff: 50 years) revealed distinct patterns in the mediation effects of TyG-related indices on cardiovascular health (CVH) and mortality (eFigure 8–9). In the gender-stratified analysis, the mediating effect of TyG was stronger in women than in men: TyG accounted for 6.39% of the association between CVH

and all-cause mortality in women, whereas it accounted for 4.51% in men. This gender dimorphism was even more pronounced in cardiovascular mortality, where TyG mediated 22.74% of the correlation between CVH and cardiovascular death in women, while no significant mediating effect was observed in men ($p < 0.05$). In contrast, both TyG-WC and TyG-WHtR demonstrated significant mediating effects in both genders. Age-stratified analysis further identified distinct mediating effects: in the CVH-all-cause mortality association, the mediating role of TyG was higher in participants younger than 50 years old (with a mediating proportion of 7.49%) compared to those older than 50 years old (with a mediating proportion of 5.30%). Similar age-dependent trends were observed for TyG-WC and TyG-WHtR, although their mediating proportions in the two age groups were not statistically significant ($P > 0.05$). These findings underscore that a portion of the effect of a healthy lifestyle on all-cause and cardiovascular mortality is partially achieved by reducing IR.

Sensitivity analysis

The findings from the sensitivity analysis can be found in eTables 9–11 in Supplement 1. When participants with missing data were excluded, multiple imputations were applied to missing data, IR was assessed via HOMA-IR, individuals who had passed away within a two-year follow-up were excluded, re-grouping was done according to gender-specific cutoff values, adjustments were made for pharmacological therapies and participants using insulin were excluded, consistent trends emerged. Overall, these results imply that sustaining a moderate or higher level of CVH may counteract the heightened risk of both all-cause and cardiovascular mortality linked to increased IR.

Discussion

In this longitudinal observational study, we investigated the combined associations of CVH and IR with the risk of all-cause and cardiovascular mortality for the first time. The results revealed that CVH, assessed via the LE8, and modifiable healthy lifestyle factors were significantly associated with a reduced risk of all-cause and cardiovascular mortality. Conversely, IR, evaluated on the basis of TyG-related parameters, was associated with a greater likelihood of all-cause and cardiovascular death. These findings underscore that improving CVH and its modifiable healthy lifestyle factors could notably decrease the IR-related risks of all-cause and cardiovascular mortality. The results of the mediation analysis further indicated that the impact of modifiable healthy lifestyle factors within CVH on the risk of all-cause and cardiovascular death was partly achieved by reducing IR. Importantly, we discovered that maintaining a moderate or high level of CVH could offset the increased risks of all-cause and cardiovascular mortality associated with IR. The observations from this study provide new insights into strategies for optimizing healthy lifestyles to increase the incidence of CVH and reduce IR-related mortality risk.

Extensive research evidence suggests that IR is linked to a greater likelihood of overall and cardiovascular mortality, irrespective of conventional risk factors [7–10]. In recent years, the potential of lifestyle modifications to offset the adverse effects of IR has emerged as a compelling research area [53, 54]. Reliable evidence indicates that maintaining a healthy lifestyle can markedly lower the risk of IR-related diseases [55, 56]. The link between IR and the risk of mortality highlights the necessity of recognizing lifestyle factors that can be modified. The LE8 developed by the American Heart Association provides a comprehensive approach to evaluating lifestyle behaviors that contribute to CVH and has been shown to correlate with reduced risks of all-cause and cardiovascular mortality [40–46]. Thus, investigating the impact of CVH on mortality outcomes within the realm of heightened IR is important for public health benefits.

Previous extensive research has focused on the separate relationships of IR and CVH with all-cause and cardiovascular mortality. In the present study, we used the widely validated TyG and its related indices (TyG-WC and TyG-WHtR) to assess IR. Following the control of various confounding variables, our findings indicated that TyG was significantly associated with an increased risk of cardiovascular mortality but not all-cause mortality. Interestingly, the RCS indicated a nonlinear relationship between all-cause mortality and the TyG score. Indeed, previous research on the association between mortality outcomes and TyG has yielded inconsistent results across different countries, regions, and populations [21, 28, 57–61]. Furthermore, a meta-analytic review failed to establish a definitive link between mortality outcomes and TyG [62]. In contrast, both TyG-WC and TyG-WHtR were notably linked to the risk of all-cause and cardiovascular mortality, which is consistent with previous studies by Dang et al.[21] and Li et al. [28]. Additionally, in the present study, the RCS results revealed a J-shaped association between all-cause mortality and TyG-WC and TyG-WHtR, which aligns with the findings of Li et al. [28]. These discrepancies in results may be attributed to the fact that TyG focuses solely on glycolipid imbalance, whereas TyG-WC and TyG-WHtR synergistically capture metabolic dysfunction and visceral fat/central obesity, which are significantly associated with mortality risks [63]. With respect to cardiovascular mortality, our results indicated a linear association between cardiovascular death and TyG-WC, whereas the TyG-WHtR exhibited a nonlinear relationship. Although these findings differ from those of previous studies [21, 28], the curve fitting

results emphasized that both the TyG-WC and TyG-WHtR indices were linked to a greater likelihood of cardiovascular mortality, which increased with increasing TyG-WC and TyG-WHtR values. Regarding the impact of CVH, assessed via LE8, on mortality outcomes, previous findings [40–46] have consistently shown that CVH is linked to a lower likelihood of all-cause and cardiovascular mortality. An inverse linear relationship between CVH, as assessed by LE8 and its modifiable lifestyle factors, and the risk of all-cause and cardiovascular mortality was also revealed in our study.

Furthermore, to our knowledge, this study is the first comprehensive investigation into the combined effects of IR, CVH and modifiable healthy lifestyle factors on all-cause and cardiovascular mortality. Randomized clinical trials evaluating the impact of lifestyle interventions on IR-related disease risk are scarce, and similar studies have yielded mixed results. Evidence from the PREDIMED-plus trial [64] and the TIMET study [65] suggests that lifestyle interventions can effectively reduce cardiovascular risk factors in individuals with metabolic syndrome. Additionally, a 30-year cluster randomized trial in Da Qing, China [66], demonstrated that lifestyle interventions could lower all-cause and cardiovascular mortality rates among individuals with compromised glucose metabolism. Conversely, studies such as Look AHEAD [67] and the Diabetes Prevention Program [68] did not show such protective effects of lifestyle. Observational studies have focused primarily on populations with diabetes and metabolic syndrome and have assessed the impact of lifestyle behaviors, including dietary habits, alcohol consumption, smoking, and physical activity [69–72]. Limited research has been conducted in populations with IR, and only one study reported an association between CVH, assessed via LE8, and reduced mortality risk in patients with IR [73]. There is scant evidence regarding the combined effects of IR and healthy lifestyles on all-cause and cardiovascular mortality risks. Hellgren MI et al.'s study [74] indicated that moderate-to-vigorous exercise eliminated the impact of IR on nondiabetic CVD in male individuals. Furthermore, a prospective cohort study [75] showed that lifestyle could reduce all-cause mortality risk in patients with type 1 diabetes by altering IR. In the current study, we comprehensively analyzed the joint association of CVH and IR with all-cause and cardiovascular mortality risks through LE8 and its four modifiable lifestyle factors (LE4). We further validated whether CVH improves mortality risk by reducing IR via mediation analysis. Profoundly, we found that CVH and its modifiable healthy lifestyle factors can significantly reduce the risk of all-cause and cardiovascular deaths associated with IR. Moreover, the protective effect of CVH on mortality is partially achieved by improving IR. The findings underscore that maintaining a moderate or high level of CVH can offset the increased mortality risk linked to IR. It's worth mentioning that our research indicates a more pronounced reduction in mortality risk when individuals with higher IR levels improve their CVH. Additionally, mediation analysis results based on gender and age groupings reveal that the proportion of IR-mediated CVH to all-cause and cardiovascular deaths is higher among women and younger populations compared to men and older participants. This suggests that women and younger individuals with higher IR may benefit more from improving their CVH. From a public health prevention perspective, we recommend that individuals with significant insulin resistance actively strive to improve their CVH to lower the elevated mortality risk associated with IR, potentially yielding more significant results for women and younger participants. This could be a highly effective strategy for reducing IR-related deaths globally. Given the increasing global incidence of IR and the associated disease risks, our results highlight the importance of timely lifestyle modifications to mitigate IR-related all-cause and cardiovascular mortality risks.

Although the exact pathways by which the combined effects of CVH and IR influence all-cause and cardiovascular mortality are not fully understood, several studies have indicated that certain modifiable lifestyle factors within CVH can significantly improve IR and IR-related metabolic characteristics, thereby reducing the risk of death. First, IR is defined by decreased insulin responsiveness, with the core mechanism being an impairment in insulin signaling that leads to compromised glucose metabolism [6]. Modifiable lifestyle factors, such as increased physical activity and a balanced diet, can increase insulin sensitivity, thereby improving glucose metabolism [31, 76, 77]. Additionally, weight management and healthy dietary patterns have been shown to lower IR levels [78–80]. Second, smoking cessation and improvements in sleep adequacy may also play a role in improving IR through multiple pathways [81–83]. It is profound that these lifestyle factors have also been found to improve metabolic characteristics (such as blood pressure and blood lipids) associated with IR and risk of death [84–91]. Thus, a healthy lifestyle may reduce the risk of death by improving IR and IR-related metabolic characteristics. In the present study, our mediation analysis similarly indicated that IR mediates the associations between CVH and both all-cause mortality and cardiovascular mortality. The differences in gender and age observed in mediation analysis may be partially explained by age-related metabolic plasticity and the role of sex hormones.

Compared to older populations, younger individuals demonstrate superior metabolic plasticity, particularly during the development of insulin resistance [92–94].

Lifestyle interventions may have a more pronounced effect on reversing IR in young developing individuals. Hence, the impact of lifestyle on mortality among younger participants may be more significantly mediated through the improvement of IR, as opposed to older participants. Gender differences are primarily attributed to sex hormones. As is widely known, estrogen can enhance insulin sensitivity and ameliorate insulin resistance [95]. Improvements in lifestyle factors such as diet, exercise, and sleep are closely linked to estrogen secretion, especially during the menopausal transition [96, 97]. This suggests that improvements in lifestyle among women may partly contribute to the amelioration of IR through promoting estrogen secretion. Therefore, compared to men, the impact of CVH on mortality among women may be mediated more through the pathway of improving IR. However, further research is needed to elucidate the complex interplay between lifestyle, IR, and mortality risk, with particular attention to age and gender differences.

Strengths and limitations

To our knowledge, this is the first cohort study to evaluate the combined effects of CVH and IR on all-cause and cardiovascular mortality. Multiple validated surrogate markers have been used to assess IR, which not only provides a comprehensive understanding of IR but also enhances the reliability of the results and reduces potential biases associated with a single assessment method. Furthermore, through visual representations such as two-dimensional curves and three-dimensional surface plots, we uncovered the associations between CVH, IR, and the risk of death, offering new insights into the complex interactions among these factors. The strengths of our study also lie in the large and representative weighted sample size, adjustments for various potential confounders, and a unified assessment of multiple lifestyles, ensuring the broad applicability and scientific rigor of the findings.

However, the current study has some limitations. First, lifestyle factor data were collected through questionnaires, and participants may have underestimated or overestimated their health behaviors. Second, we did not use the gold standard to assess IR, which may have resulted in an inadequate reflection of participants' actual IR status. Nevertheless, the use of multiple validated IR assessment indicators to comprehensively evaluate IR from different perspectives has strengthened the reliability of IR assessment. Third, despite considering various possible confounding factors, the potential for confounding by unmeasured variables cannot be discounted, including genetic susceptibility, psychological state, and possible reverse causation. Fourth, while composite LE8 and LE4 scores provide a holistic view of cardiovascular health, they may obscure differential contributions of individual components to mortality risk. For instance, behaviors like smoking cessation and physical activity might exert stronger effects than dietary patterns or sleep health. Although we conducted exploratory mediation analyses to disentangle component-specific effects through insulin resistance, these findings should be interpreted cautiously due to potential collider bias and measurement variability across components. Fifthly, our study is limited by the lack of longitudinal data on the duration and stability of CVH components. Some individuals who have recently adopted healthy behaviors may still exhibit higher IR due to delayed metabolic adaptation, which could potentially attenuate the observed protective effects of CVH. Additionally, reverse causality remains a possibility—baseline IR may change over time with CVH, and our study design cannot definitively exclude this bidirectional relationship. Future studies should incorporate continuous CVH/IR measurements over a period of time to allow for an analysis that considers behavioral changes along the temporal trajectory. Sixthly, due to the limitations inherent in study design, we were unable to assess whether the same individual would exhibit a lower risk of death after improving their CVH, and future interventional studies are needed to elucidate this conclusion. Seventh, due to the lack of population-specific reference intervals for TyG, the results of this study should be interpreted with caution, and the establishment of a unified TyG standardised interval should be considered in the future to validate our result. Eighth, as the population included in our current study consisted mainly of younger participants (mean age 50.1 years), the generalisability to older people needs to be interpreted with caution, especially given the role of older patients as a major population of cardiovascular deaths. Finally, this study is limited in its assessment of the influence of baseline lifestyle on the risk of death, while participants' lifestyles may have arisen throughout the prolonged observation period, which may have interfered with the results.

Conclusions

In this cohort study, our findings indicate that higher levels of CVH, assessed via LE8, and its modifiable healthy behaviors significantly mitigate the heightened risk of all-cause and cardiovascular mortality associated with IR. Maintaining CVH at moderate or higher levels (CVH ≥ 50) can offset the risk of all-cause and cardiovascular death resulting from increased IR. The results underscore that although individuals with elevated IR face a continuously increased risk of all-cause and cardiovascular mortality, enhancing CVH through healthy behaviors (including a balanced diet, smoking cessation, adequate sleep, and increased physical activity) can

significantly mitigate this risk. CVH represents a positive health attribute, calling for both public and healthcare professionals to prioritize the beneficial role of healthy lifestyles and take proactive measures to improve the adverse health outcomes associated with IR.

Abbreviations

CVH	Cumulative atherogenic index of plasma
IR	Insulin resistance
LE8	Life's essential 8
LE4	Life's essential 4
CVD	Cardiovascular disease
TyG	Triglyceride glucose
TyG-WC	Triglyceride glucose–waist circumference
TyG–WHtR	Triglyceride–glucose–waist height ratio
HOMA-IR	Homeostasis model assessment of insulin resistance
HI-GI	Hyperinsulinemic-euglycemic clamp
NHANES	National Health and Nutrition Examination Survey
FPG	Fasting plasma glucose
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
BMI	Body Mass Index
CHD	Coronary heart disease
PIR	Poverty income ratio
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
PA	Physical activity
BMI	Body mass index
RCS	Restricted cubic spline
RD	Risk difference
K-M	Kaplan–Meier
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

L.J.were responsible for conceptualization, methodology, supervision, and project administration and Q.J. wrote the main manuscript text, Q.J., L.J., X.S., Z.H., Z.Y. and Y.S. wrote the reviewing and editing, Q.J. and L.J. developed the software，Q.J., F.L., H.J. and F.J. conducted formal analysis and validation, Q.J., Z.H. and Z.Y. curated the data.All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

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