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The ketogenic diet has the potential to decrease all-cause mortality without a concomitant increase in cardiovascular-related mortality

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The impact of the ketogenic diet (KD) on overall mortality and cardiovascular disease (CVD) mortality remains inconclusive.This study enrolled a total of 43,776 adults from the National Health and Nutrition Examination Survey (NHANES) conducted between 2001 and 2018 to investigate the potential association between dietary ketogenic ratio (DKR) and both all-cause mortality as well as cardiovascular disease(CVD) mortality.Three models were established, and Cox proportional hazards regression analysis was employed to examine the correlation. Furthermore, a restricted cubic spline function was utilized to assess the non-linear relationship. In addition, subgroup analysis and sensitivity analysis were performed.In the adjusted Cox proportional hazards regression model, a significant inverse association was observed between DKR and all-cause mortality (HR = 0.76, 95% CI = 0.63–0.9, *P* = 0.003). However, no significant association with cardiovascular mortality was found (HR = 1.13; CI = 0.79–1.6; *P* = 0.504). Additionally, a restricted cubic spline(RCS) analysis demonstrated a linear relationship between DKR and all-cause mortality risk. In the adult population of the United States, adherence to a KD exhibits potential in reducing all-cause mortality risk while not posing an increased threat of CVD-related fatalities.

Keywords Ketogenic diet , Mortality , NHANES, Cohort study

The ketogenic diet(KD) is characterized by an extremely low carbohydrate intake, high fat consumption, and moderate protein intake. In recent years, it has garnered attention due to its potential benefits in weight loss, epilepsy management, and impact on metabolic diseases[1,2]. This dietary approach induces a shift from carbohydrate metabolism to fat metabolism within the body, resulting in the production of ketones such as acetoacetate and β-hydroxybuty-rate. This metabolic switch is believed to offer various health advantages including improved insulin sensitivity, reduced inflammation, and enhanced cognitive function[3–5]. Although the KD has been utilized for decades in treating childhood epilepsy, its application in other health conditions remains a topic of intense debate and further exploration, particularly regarding its effects on overall mortality rate and cardiovascular disease(CVD) risk.

CVD risk is a significant contributor to global morbidity and mortality, with dietary factors playing a pivotal role in its pathogenesis. Recent research has elucidated the intricate and nuanced relationship between the KD and CVD risk. On one hand, reducing carbohydrate intake and enhancing insulin sensitivity may confer beneficial effects on CVD risk factors such as blood pressure and lipid levels[6,7]. Conversely, the high-fat content of the KD, particularly saturated fat, may exert detrimental effects on lipid metabolism, trigger inflammatory responses, and augment CVD risk[8,9]. These contradictory findings underscore the imperative for further investigation into the long-term implications of the KD on mortality rates and CVD risk.

Based on the research background, the objective of this study is to utilize comprehensive information from the National Health and Nutrition Examination Survey (NHANES) data spanning 2001–2018 in the United States. This dataset encompasses dietary intake, anthropometric measurements, laboratory testing, and health

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outcomes, enabling an exploration into the impact of a KD on all-cause mortality and CVD mortality risk[10]. The NHANES dataset represents a large-scale nationally representative survey conducted on the U.S. population, providing invaluable resources for investigating long-term effects of various dietary patterns on health, including the KD.

This study aims to rigorously examine and meticulously analyze the long-term effects of a KD on mortality rates and CVD risk while gaining deeper insights into its impact on health. Ultimately, these findings aim to contribute towards developing scientifically accurate dietary guidelines and public health strategies that can extend lifespan and reduce chronic disease burden. Furthermore, these findings may offer significant implications for chronic disease management as well as promoting healthy aging processes.

Methods

Study design and participants

This cohort study utilized data from the nine national health and nutrition examination survey (NHANES) cycles conducted between 2001 and 2018, which included at least one dietary recall assessment (https://www.cdc.gov/nchs/NHANES/index). NHANES is a cross-sectional study initiated in 1999 by the National Center for Health Statistics (NCHS), aiming to evaluate the health and nutritional status of the non-institutional civilian population in the United States. To supplement this study, we linked the NHANES database from 2001 to 2018 with the NHANES Public Use Associated Mortality Archive, providing mortality follow-up data until December 31, 2019 (https://www.cdc.gov/nchs/data-linkage/ mortality.htm).The selection process of the study population is depicted in Fig. 1. A total of 91,351 participants were initially included in the retrospective cohort study. However, individuals below the age of 20 ($N=41,150$), those with missing CVD data ($N=491$), missing dietary data ($N=5619$), missing follow-up data ($N=79$), and those with missing covariate data ($N=236$) were excluded from the analysis. Consequently, complete information on 43,776 adults was ultimately considered for the final analysis. All participants provided written informed consent, and the trial protocol of this study has been approved by the Ethics Review Committee at the National Center for Health Statistics.

Dietary intake data

Dietary intake data were collected through two 24-hour retrospective NHANES surveys conducted by trained dietary investigators. The initial survey was administered face-to-face, followed by a subsequent telephone survey within three to 10 days. In the follow-up survey, participants were requested to recall and report the types and quantities of various foods and beverages consumed in the preceding 24 h, with dietary intake estimated based on the average of these two recalls[11]. Energy and nutrient intakes for all food items were calculated using the Food and Nutrition database in dietary studies[12].

The dietary ketogenic ratio(DKR)

To evaluate dietary patterns for achieving nutritional ketosis, we calculated the Dietary Ketogenic Ratio (DKR) based on the proportion of macronutrients in the diet with ketogenic and antiketogenic properties. The DKR for macronutrients was determined using the equation developed by Withrow[13]. Essentially, this calculation involves dividing (0.9×grams of fat + 0.46×grams of protein) by (0.1×grams of fat + 0.58 × grams of protein + grams of net carbohydrates), resulting in values ranging from 0 to 9. A higher DKR value indicates a greater likelihood of inducing nutritional ketosis.

Outcome variables

In this study, we evaluated all-cause mortality as the primary outcome measure, with secondary outcomes including mortality related to CVD. Information regarding vital status of participants was acquired from publicly accessible mortality data files. To establish a connection between death records in the National Death Index and continuous NHANES data, both probabilistic and deterministic approaches were employed by the National Center for Health Statistics. The success rate for establishing linkages surpassed 99%[14]. The observation period began at baseline (defined as the date of NHANES participation) and ended either upon occurrence of death or on December 31st, 2019.

Covariates

Information regarding sociodemographic and lifestyle characteristics was obtained from demographics and questionnaire data. This included information on age(Youth group,≤40 years; Middle-aged group, 40–60 years and Elderly group, ≥60 years), gender, Race/ethnicity (Mexican American、Non-Hispanic White、Non-Hispanic Black、Other Hispanic、Other Race), educational level(Less than High school、High school/GED, More than high school), family income to poverty ratio (PIR), marital status(Married, Widowed, Divorced, Separated, Never married, Living with partner), smoking status, and BMI (<18.5 kg/m^2,18.5–24 kg/m^2, 24–28 kg/m^2, ≥28 kg/m^2). Participants were categorized as smokers if they responded affirmatively to the query, "Have you smoked at least 100 cigarettes in your entire life?" Conversely, those who answered negatively were classified as non-smokers. Standing height (centimeter, cm) and weight (kilogram, kg) were measured at the mobile examination center. The Body Mass Index (BMI, kg/cm^2) was calculated by dividing the weight by the square of standing height.

Participants were considered to have a history of cardiovascular disease if they had been diagnosed by a medical professional with congestive heart failure(CHF), coronary heart disease(CHD), angina/angina pectoris, and myocardial infarction(MI). The presence of hypertension, stroke, and cancer/malignancy was determined through questionnaire responses. The definition of hypertension encompassed self-reported hypertension, systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, or documented use of

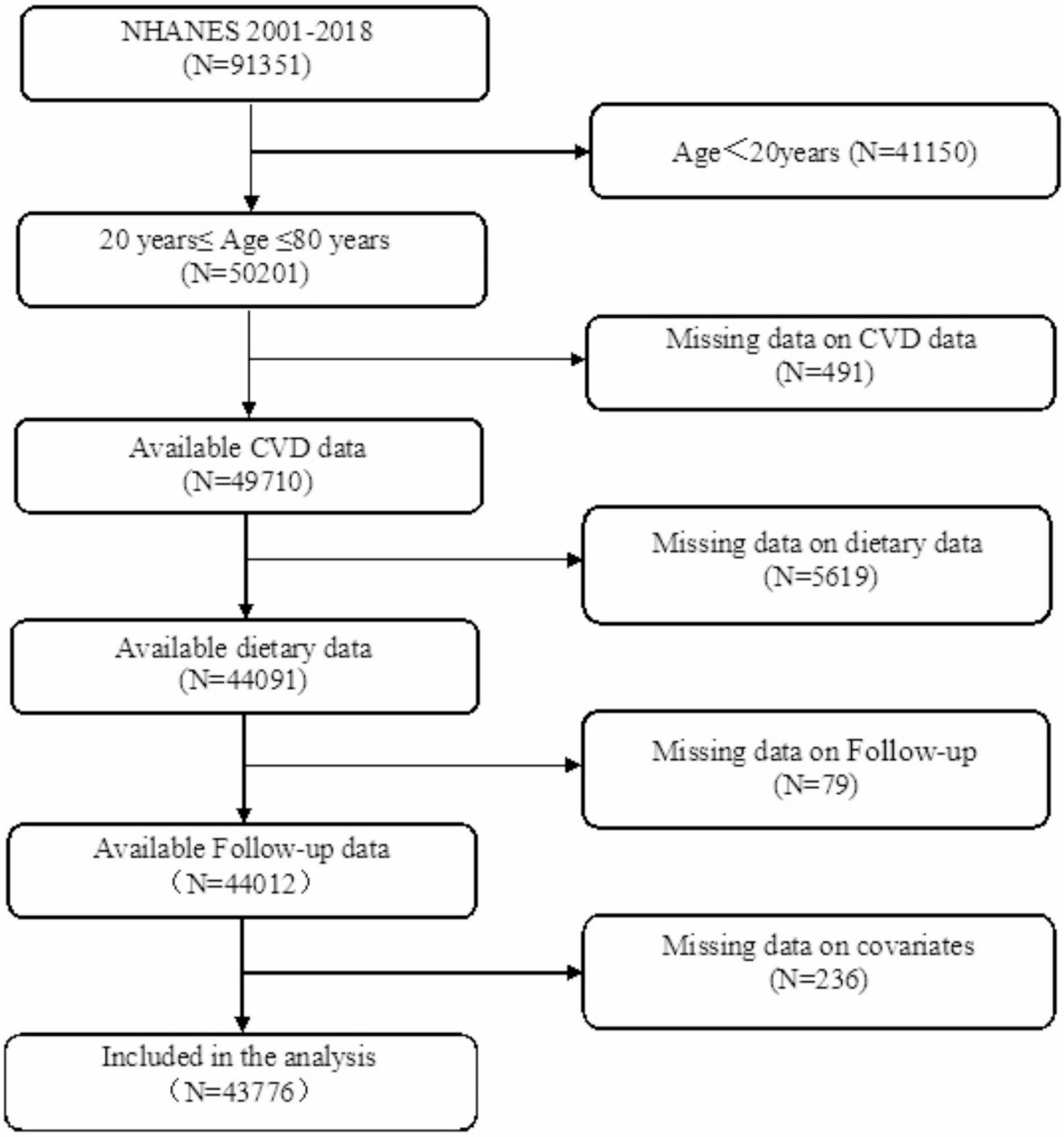

Fig. 1. Flow diagram of the study participant selection. NHANES, National Health and Nutrition Examination Survey; CVD, cardiovascular diseases.

antihypertensive medication.Diabetes was defined as HbA1c ≥ 6.5% or self-reported use of glucose-lowering medications.

Multiple imputation techniques were employed to handle missing values in covariates, with the percentage of missing values being less than 10%. These covariates included PIR (missing 7.8%), BMI (missing 1.5%), hypertension (missing 0.2%), and no variables exhibited missing values exceeding 10%.

Statistical analysis

The participants were categorized into two groups based on their survival status.

The baseline characteristics were subjected to descriptive analysis, with continuous variables presented as mean ± standard deviation (SD) or median (interquartile range), while categorical variables were reported as counts and percentages.Between-group comparisons were conducted using appropriate statistical tests: the Student's t-test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed variables, and the chi-square test for categorical variables.

The associations between DKR and all-cause and cardiovascular mortality were evaluated using multivariate Cox proportional hazard models, yielding hazard ratios (HRs) along with their corresponding 95% confidence intervals (CIs).The quartiles of DKR were utilized to calculate HRs, with Q1 serving as the reference group in Model A, which incorporated unadjusted covariates. Model B was adjusted for age, education level, race, marital status, and PIR. In Model C, additional covariates including BMI, diabetes mellitus, CHF, CHD, angina pectoris, MI, stroke history, and cancer diagnosis were included.

To investigate the dose-response relationship between DKR and all-cause and CVD mortality, we utilized multivariable adjusted restricted cubic splines (RCS) in model C to explore potential non-linear associations.

The statistical significance was determined at a two-tailed p-value of less than 0.05. All data were analyzed using SPSS 27 software. The data were generated by GraphPad Prism 9.4 and R version 3.6.

Results

Baseline characteristics of the participants

The baseline characteristics of the participants are presented in Table 1. Among the final cohort of 43,776 participants, the mean age was 49.4 ± 18.1 years, with a female representation of 2,532 (48.3%). Following a median follow-up period of 9.1 years, all-cause mortality was observed in 6,054 participants (13.8%), while cardiovascular mortality occurred in 1,533 individuals (3.5%). Table 1 presents the baseline characteristics of both the survival and death groups; statistically significant differences were found across all variables ($P < 0.05$). In comparison to the death group, the survival group exhibited a higher proportion of females and younger individuals who identified as Mexican American and were married with higher levels of education and household income; they also had lower rates of smoking and BMI values. Additionally, compared to the death group, the survival group demonstrated lower prevalence rates for comorbidities such as diabetes mellitus, CVD, stroke, and cancer.

DKR and all-cause mortality

In this study, we developed three Cox regression models to investigate the association between DKR and all-cause mortality (refer to Table 2). The unadjusted model A did not demonstrate a statistically significant relationship between DKR and the risk of all-cause mortality(HR = 1.10, 95%CI = 0.93–1.3, $P = 0.255$). However, after adjusting for multiple variables in the multivariate analysis, we observed a significant inverse association between DKR and the risk of all-cause mortality. Specifically, as DKR increased, there was a substantial decrease in mortality risk. This finding remained consistent in both model B (HR = 0.80, 95%CI = 0.67–0.9, $P = 0.015$) and model C (HR = 0.76, 95%CI = 0.63–0.9, $P = 0.003$). Notably, in model C where adjustments were made for all variables considered relevant to our study population's characteristics and confounding factors alike; each standard deviation increase in DKR resulted in a noteworthy 24% reduction in the risk of death.Furthermore when comparing patients within different quartiles after adjusting for multiple variables using multivariate analysis, it was found that patients within lower quartiles exhibited lower hazard ratios compared to those within higher quartiles.This trend consistently persisted both in model B (HR = 0.90; 95% CI = 0.83 -0.96; $P = 0.003$) as well as being replicated by similar results obtained from model C (HR = 0.86; CI = 0.80–0.93; $P < 0.001$).In the adjusted C model accounting for all covariates, our RCS analysis revealed a linear correlation between DKR and all-cause mortality. Notably, the dose-response relationship exhibited a significant inverse trend, indicating a progressive reduction in all-cause mortality with increasing DKR (refer to Fig. 2).

DKR and CVD mortality

We constructed three COX regression models to evaluate the association between DKR and the risk of CVD mortality. However, none of the three models demonstrated a statistically significant association between DKR and CVD mortality risk (Model A: HR = 1.31; CI = 0.94–1.8; $P = 0.113$, Model B: HR = 1.32; CI = 0.93–1.8; $P = 0.124$, or Model C: HR = 1.13; CI = 0.79–1.6; $P = 0.504$). Furthermore, no significant change in cardiovascular disease death risk was observed when comparing the lowest quartile of DKR with each subsequent quartile increase. In the Q4 group, the HRs of three COX models were as follows: model A (HR = 1.17; CI = 1.01–1.34; $P = 0.033$), model B (HR = 0.97; CI = 0.84–1.12; $P = 0.706$), and model C (HR = 0.95; CI = 0.83–1.10; $P = 0.524$). Similarly, in the adjusted C model that accounted for all covariates, our restricted cubic spline analysis revealed no discernible association between DKR and CVD mortality (refer to Fig. 3).

Stratified and sensitivity analyses

In Model C, after adjusting for confounding factors, we conducted stratified analyses to determine the association between DKR and the risk of all-cause mortality as well as CVD mortality.The specific findings are presented in Table 3; Fig. 4. The results from the subgroup analyses were generally consistent with the overall outcomes, indicating that high DKR was linked to a reduced risk of all-cause mortality but not CVD mortality across different subgroups. In terms of subgroup analyses for all-cause mortality, no significant interactions were observed between DKR and male sex, age < 60 years, BMI < 24 kg/m^2, smoking status, hypertension or diabetes. However, significant interactions were found among female participants, those aged ≥ 60 years old, individuals with BMI ≥ 24 kg/m^2, non-smokers as well as non-hypertensive and non-diabetic patients. Notably, a more pronounced effect of DKR on the risk of all-cause mortality was noted within specific subgroups including women participants aged ≥ 60 years old with BMI ≥ 24 kg/m^2 who were also non-smokers as well as

Characteristic	Mortality status no. (%)		*p*-value
	Deceased, *N* = 6,054	Survival, *N* = 37,722	
Gender			< 0.001
Male	3,388 (56.0%)	17,758 (47.1%)	
Female	2,666 (44.0%)	19,964 (52.9%)	
Age, y			< 0.001
< 40	251 (4.1%)	14,908 (39.5%)	
40–60	947 (15.6%)	13,121 (34.8%)	
≥ 60	4,856 (80.2%)	9,693 (25.7%)	
Race/ethnicity			< 0.001
Mexican American	639 (10.6%)	6,634 (17.6%)	
Other hispanic	247 (4.1%)	3,373 (8.9%)	
Non-hispanic white	3,757 (62.1%)	15,899 (42.1%)	
Non-hispanic black	1,217 (20.1%)	8,062 (21.4%)	
Other race	194 (3.2%)	3,754 (10.0%)	
Education level			< 0.001
Less than high school	2,279 (37.6%)	8,871 (23.5%)	
High school/GED	1,543 (25.5%)	8,667 (23.0%)	
More than high school	2,232 (36.9%)	20,184 (53.5%)	
Marital status			< 0.001
Married	2,906 (48.0%)	20,078 (53.2%)	
Widowed	1,624 (26.8%)	1,986 (5.3%)	
Divorced	715 (11.8%)	3,853 (10.2%)	
Never married	448 (7.4%)	7,292 (19.3%)	
Separated	176 (2.9%)	1,269 (3.4%)	
Living with partner	185 (3.1%)	3,244 (8.6%)	
PIR			< 0.001
< 1.5	2,388 (39.4%)	12,332 (32.7%)	
1.5–2.5	1,533 (25.3%)	7,755 (20.6%)	
≥ 2.5	2,133 (35.2%)	17,635 (46.7%)	
BMI, kg/m^2			< 0.001
< 24	1,417 (23.4%)	8,427 (22.3%)	
24–28	1,810 (29.9%)	10,279 (27.2%)	
≥ 28	2,827 (46.7%)	19,016 (50.4%)	
Smoking status			< 0.001
Yes	3,656 (60.4%)	16,281 (43.2%)	
No	2,398 (39.6%)	21,441 (56.8%)	
Hypertension			< 0.001
Yes	3,615 (59.7%)	11,703 (31.0%)	
No	2,439 (40.3%)	26,019 (69.0%)	
Diabetes			< 0.001
Yes	1,458 (24.1%)	3,851 (10.2%)	
No	4,596 (75.9%)	33,871 (89.8%)	
CVD			
CHF			< 0.001
Yes	720 (11.9%)	657 (1.7%)	
No	5,334 (88.1%)	37,065 (98.3%)	
CHD			< 0.001
Yes	778 (12.9%)	1,013 (2.7%)	
No	5,276 (87.1%)	36,709 (97.3%)	
Angina			< 0.001
Yes	499 (8.2%)	700 (1.9%)	
No	5,555 (91.8%)	37,022 (98.1%)	
MI			< 0.001
Yes	818 (13.5%)	1,004 (2.7%)	

Continued

Characteristic	Mortality status no. (%)		*p*-value
	Deceased, *N* = 6,054	Survival, *N* = 37,722	
No	5,236 (86.5%)	36,718 (97.3%)	
Smoking status			< 0.001
Yes	708 (11.7%)	927 (2.5%)	
No	5,346 (88.3%)	36,795 (97.5%)	
Cancer			< 0.001
Yes	1,393 (23.0%)	2,754 (7.3%)	
No	4,661 (77.0%)	34,968 (92.7%)	
Energy(kcal)			< 0.001
Median (IQR)	1,672 (1,248, 2,239)	1,980 (1,462, 2,658)	
Protein (gm)			< 0.001
Median (IQR)	63 (46, 87)	75 (53, 102)	
Carbohydrate (gm)			< 0.001
Median (IQR)	205 (150, 274)	240 (172, 324)	
Total fat (gm)			< 0.001
Median (IQR)	61 (42, 88)	73 (49, 105)	
Dietary fiber (gm)			< 0.001
Median (IQR)	13 (9, 19)	15 (10, 22)	
Total folate (mcg)			< 0.001
Median (IQR)	313 (215, 452)	347 (234, 501)	
DKR			0.045
Q1	1,563 (25.8%)	9,374 (24.9%)	
Q2	1,540 (25.4%)	9,414 (25.0%)	
Q3	1,498 (24.7%)	9,443 (25.0%)	
Q4	1,453 (24.0%)	9,491 (25.2%)	

Table 1. Patient demographics and baseline characteristics. Abbreviations: PIR, Ratio of family income to poverty; BMI, Body Mass Index; CVD, Cardiovascular disease; CHF, Congestive heart failurer; CHD, Coronary heart disease; MI, Myocardial infarction; DKR, Dietary ketogenic ratio; IQR, Interquartile range.

Variables	Q1		Q2		Q3		Q4		DKR	
	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value
All-cause mortality										
Model A	Ref.	-	1.03(0.96, 1.10)	0.468	1.05(0.97, 1.12)	0.222	1.05(0.98, 1.13)	0.159	1.10(0.93,1.3)	0.255
Model B	Ref.	-	0.93(0.87, 1.00)	0.039	0.94(0.87, 1.00)	0.066	0.90(0.83, 0.96)	0.003	0.80(0.67,0.9)	0.015
Model C	Ref.	-	0.91(0.85, 0.98)	0.011	0.91(0.85, 0.98)	0.011	0.86(0.80, 0.93)	< 0.001	0.76(0.63,0.9)	0.003
Cardiovascular mortality										
Model A	Ref.	-	1.04(0.90, 1.20)	0.610	1.12(0.97, 1.29)	0.125	1.17(1.01, 1.34)	0.033	1.31(0.94,1.8)	0.113
Model B	Ref.	-	0.93(0.80, 1.07)	0.301	0.99(0.85, 1.14)	0.839	0.97(0.84, 1.12)	0.706	1.32(0.93,1.8)	0.124
Model C	Ref.	-	0.91(0.79, 1.05)	0.209	0.96(0.84, 1.11)	0.618	0.95(0.83, 1.10)	0.524	1.13(0.79,1.6)	0.504

Table 2. HRs and 95% CI for all-cause and Cardiovascular mortality according to quartiles of DKR. Model A: unadjusted covariates. Model B: adjusted by gender, age, race, education level, marital status, and PIR. Model C: adjusted by gender, age, race, education level, marital status, PIR, BMI, smoke, hypertension, diabetes, CVD, stroke, and cancer. Abbreviations: HRs, Hazard Ratios; CI, confidence interval; DKR, Dietary ketogenic ratio; PIR, Ratio of family income to poverty; BMI, Body Mass Index; CVD, Cardiovascular Disease.

non-hypertensive and non-diabetic patients. Regarding the association between DKR and CVD mortality, no significant cross-over effect was detected following corresponding subgroup analyses.

Sensitivity analyses, excluding participants who died within 2 years after study entry or had missing information on covariates (refer to Supplementary Tables 1 and 2), as well as results that excluded patients with stroke or cancer (refer to Supplementary Tables 3 and 4), yielded consistent findings with the primary DKR analysis.

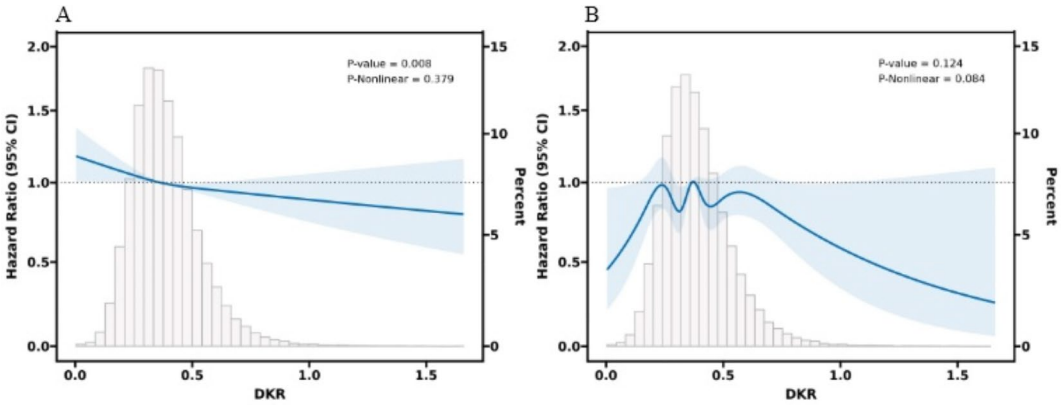

Fig. 2. RCS analysis on the association between the DKR and the risk of all-cause mortality and CVD mortality. (A) RCS curve of the association between the DKR and all-cause mortality, (B) RCS curve of the association between the DKR and CVD mortality. RCS: restricted cubic spline; CVD, Cardiovascular Disease; DKR, Dietary ketogenic ratio.

Discussion

- The KD has gained significant traction in recent years due to its potential health benefits, such as weight loss[1] and improved metabolic health[3]. This study aims to investigate the impact of the KD on all-cause mortality and cardiovascular-related mortality by analyzing data from the NHANES spanning from 2001 to 2018. The findings demonstrate that the KD shows promise in reducing overall mortality risk without a concurrent increase in cardiovascular-related mortality, suggesting a potential protective effect against all-cause mortality. In this discussion, we will delve into the underlying mechanisms through which the KD may mitigate all-cause mortality while exploring reasons for its apparent lack of increased cardiovascular- related mortality risk.
- Our analysis of the NHANES dataset revealed a significant association between adherence to a KD and a reduction in overall mortality rates. This finding is consistent with previous research suggesting that following a KD may confer protective effects against various chronic diseases and conditions contributing to mortality.
- The KD exerts a multifaceted protective effect on all-cause mortality. Firstly, it has been demonstrated that the KD promotes metabolic health by facilitating weight loss[15], attenuating inflammation[16], and enhancing insulin sensitivity[3]. These factors play a pivotal role in reducing the risk of chronic conditions such as diabetes[17], CVD[18], and cancer[19], which collectively contribute to overall mortality. Secondly, the KD has demonstrated neuroprotective effects, potentially contributing to a reduction in mortality rates. Research indicates that ketones, which are metabolic byproducts of fat breakdown in the KD, possess anti-inflammatory and antioxidant properties that can safeguard against neurodegenerative disorders[20] and cognitive decline[21]-both of which are linked to an elevated risk of mortality. Furthermore, the KD has been demonstrated to modulate the gut microbiota, exerting a profound impact on overall health[22]. By fostering the proliferation of beneficial bacteria and mitigating harmful pathogens, the KD may contribute to the prevention of gastrointestinal diseases and enhancement of immune function, thereby diminishing mortality risk[23]. In addition, the KD has demonstrated efficacy in attenuating oxidative stress and enhancing mitochondrial function, both of which are pivotal determinants of aging and longevity[24]. By mitigating oxidative damage and facilitating efficient energy production, the KD holds promise for extending lifespan and reducing the susceptibility to age-related diseases. Finally, the KD has demonstrated its efficacy in exerting anti-inflammatory effects, which may also contribute to the reduction of all-cause mortality[25]. Chronic inflammation serves as a pivotal driver for numerous chronic diseases, and the anti-inflammatory properties associated with the KD have the potential to mitigate this risk and promote overall health and longevity.
- The impact of the KD on cardiovascular health has been a subject of debate due to its high-fat content. However, our analysis of the NHANES data suggests that despite its high fat intake, the KD does not increase mortality related to cardiovascular conditions. There are several mechanisms that may explain this phenomenon. Firstly, the KD has been demonstrated to enhance lipid profiles by elevating high-density lipoprotein (HDL) cholesterol and reducing triglyceride levels, both of which confer protection against CVD[26]. Despite its high saturated fat content, the diet primarily comprises unsaturated fats, which have been linked to a decreased risk of heart disease. Secondly, the KD has demonstrated efficacy in reducing inflammation, a pivotal factor in the pathogenesis of atherosclerosis and CVD[27]. Through its ability to attenuate inflammatory markers and cytokines within the body, the KD holds promise in impeding the progression of cardiac ailments and diminishing the risk of mortality associated with cardiovascular disorders. Furthermore, the KD has demonstrated efficacy in enhancing blood pressure regulation, which is a pivotal determinant of cardiovascular well-being[6]. By facilitating weight loss and mitigating insulin resistance, the KD may contribute to blood pressure reduction and diminish the likelihood of developing hypertension, a significant risk factor for CVD. Additionally, the KD has demonstrated efficacy in enhancing endothelial function, a pivotal factor in the pathogenesis of atherosclerosis and CVD. Through mitigation of oxidative stress and inflammation, the KD exhibits potential

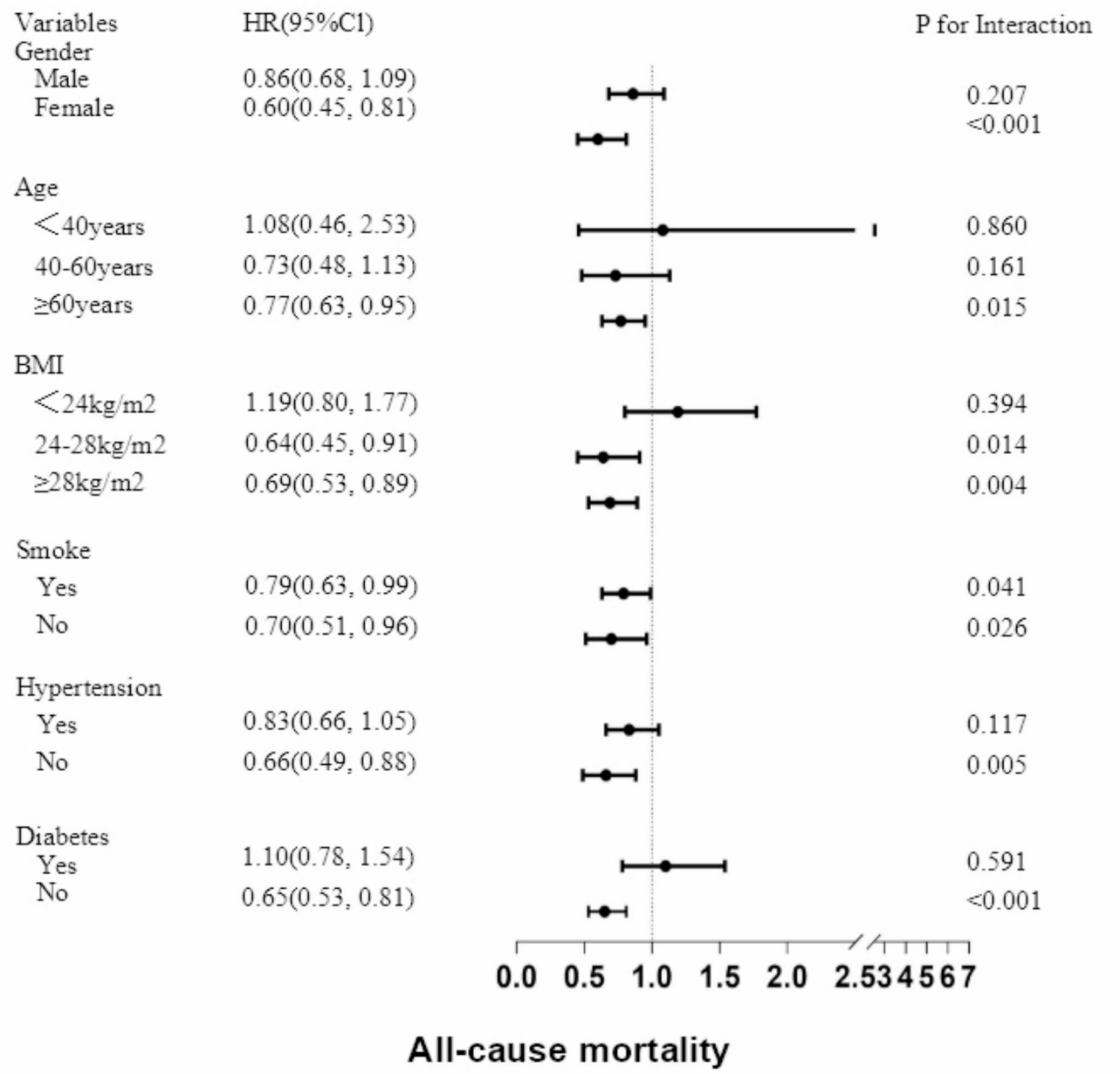

Fig. 3. Stratified analysis of the DKR and risk of all-cause mortality. DKR, dietary ketogenic ratio; BMI, Body Mass Index.

for safeguarding endothelial integrity and preserving vascular health, thereby mitigating the risk of cardiovascular-related mortality[28]. Lastly, the KD has the potential to enhance overall cardiac function and mitigate the risk of arrhythmias[29] and heart failure[30]. Research indicates that ketones, which serve as the primary energy source in a KD, may offer superior efficiency and protection as an energy substrate for the heart[31], resulting in improved cardiac performance and reduced incidence of cardiovascular events.

- In conclusion, our analysis of the NHANES data from 2001 to 2018 indicates that the KD holds potential in reducing all-cause mortality while not increasing cardiovascular-related mortality. The observed mechanisms underly- ing these effects encompass enhancements in metabolic health[3], neuroprotection[20], modulation of gut microbiota[22], antioxidant and anti- inflammatory properties[24], as well as overall prevention of age-related diseases. Further research is warranted to elucidate the specific pathways through which the KD exerts these effects and optimize its implementation for long-term health and longevity.
- Therefore, the ketogenic diet, as a specific dietary pattern, holds potential benefits from a public health perspective by offering innovative therapeutic approaches for patients with obesity, metabolic syndrome, and certain refractory diseases. By implementing scientifically and logically tailored dietary adjustments, the ketogenic diet can contribute to improving the health status of these patients, mitigating the societal medical

Variables	Q1		Q2		Q3		Q4		DKR	
	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value
All-cause mortality										
Gender										
Male	Ref.	-	0.95(0.86, 1.05)	0.316	0.93(0.85, 1.03)	0.165	0.91(0.82, 1.00)	0.049	0.86(0.68, 1.09)	0.207
Female	Ref.	-	0.87(0.79, 0.97)	0.010	0.89(0.80, 0.99)	0.030	0.81(0.72, 0.90)	< 0.001	0.60(0.45, 0.81)	< 0.001
Age, y										
< 40	Ref.	-	1.04(0.75, 1.44)	0.834	0.74(0.51, 1.08)	0.114	1.17(0.83, 1.63)	0.374	1.08(0.46, 2.53)	0.860
40–60	Ref.	-	1.09(0.91, 1.31)	0.364	1.04(0.87, 1.25)	0.636	0.92(0.76, 1.10)	0.346	0.73(0.48, 1.13)	0.161
≥ 60	Ref.	-	0.88(0.81, 0.95)	0.001	0.90(0.83, 0.97)	0.009	0.85(0.78, 0.92)	< 0.001	0.77(0.63, 0.95)	0.015
BMI, kg/m^2										
< 24	Ref.	-	0.91(0.78, 1.04)	0.173	0.93(0.80, 1.07)	0.310	0.98(0.85, 1.14)	0.840	1.19(0.80, 1.77)	0.394
24–28	Ref.	-	1.00(0.88, 1.14)	0.973	0.96(0.84, 1.10)	0.543	0.84(0.73, 0.96)	0.010	0.64(0.45, 0.91)	0.014
≥ 28	Ref.	-	0.85(0.77, 0.95)	0.004	0.88(0.79, 0.97)	0.015	0.82(0.74, 0.91)	< 0.001	0.69(0.53, 0.89)	0.004
Smoking status										
Yes	Ref.	-	0.93(0.85, 1.03)	0.148	0.93(0.85, 1.02)	0.135	0.90(0.82, 0.98)	0.021	0.79(0.63, 0.99)	0.041
No	Ref.	-	0.89(0.80, 0.99)	0.037	0.90(0.80, 1.00)	0.054	0.82(0.73, 0.92)	< 0.001	0.70(0.51, 0.96)	0.026
Hypertension										
Yes	Ref.	-	0.91(0.83, 1.00)	0.046	0.94(0.86, 1.03)	0.185	0.89(0.81, 0.97)	0.012	0.83(0.66, 1.05)	0.117
No	Ref.	-	0.92(0.83, 1.03)	0.151	0.88(0.79, 0.98)	0.024	0.83(0.74, 0.93)	0.002	0.66(0.49, 0.88)	0.005
Diabetes										
Yes	Ref.	-	0.92(0.79, 1.08)	0.306	0.93(0.80, 1.09)	0.359	0.94(0.81, 1.09)	0.435	1.10(0.78, 1.54)	0.591
No	Ref.	-	0.90(0.83, 0.98)	0.010	0.91(0.84, 0.99)	0.021	0.83(0.77, 0.91)	< 0.001	0.65(0.53, 0.81)	< 0.001
Cardiovascular mortality										
Gender										
Male	Ref.	-	1.00(0.82, 1.21)	0.962	0.95(0.78, 1.15)	0.583	1.00(0.83, 1.21)	0.980	0.93(0.59, 1.45)	0.736
Female	Ref.	-	0.83(0.67, 1.03)	0.096	1.01(0.82, 1.25)	0.918	0.86(0.68, 1.08)	0.183	0.79(0.43, 1.46)	0.454
Age, y										
< 40	Ref.	-	1.01(0.46, 2.19)	0.985	0.75(0.31, 1.79)	0.519	1.03(0.45, 2.35)	0.941	0.67(0.08, 5.61)	0.712
40–60	Ref.	-	1.61(1.02, 2.54)	0.039	1.55(1.01, 2.43)	0.045	1.71(1.10, 2.64)	0.017	1.83(0.75, 4.46)	0.181
≥ 60	Ref.	-	0.86(0.73, 1.00)	0.053	0.92(0.79, 1.08)	0.305	0.88(0.75, 1.03)	0.116	0.82(0.55, 1.22)	0.332
BMI, kg/m^2										
< 24	Ref.	-	0.90(0.66, 1.22)	0.489	0.83(0.60, 1.14)	0.240	1.06(0.78, 1.44)	0.720	1.26(0.54, 2.92)	0.595
24–28	Ref.	-	0.89(0.69, 1.16)	0.399	1.16(0.90, 1.50)	0.245	0.84(0.64, 1.11)	0.217	0.68(0.34, 1.38)	0.285
≥ 28	Ref.	-	0.95(0.77, 1.17)	0.640	0.91(0.74, 1.13)	0.405	0.94(0.77, 1.15)	0.555	0.85(0.52, 1.38)	0.517
Smoking status										
Yes	Ref.	-	1.02(0.84, 1.25)	0.824	1.04(0.85, 1.26)	0.707	1.04(0.86, 1.27)	0.658	0.93(0.59, 1.46)	0.757
No	Ref.	-	0.82(0.67, 1.02)	0.073	0.91(0.73, 1.12)	0.365	0.84(0.67, 1.05)	0.116	0.81(0.45, 1.46)	0.484
Hypertension										
Yes	Ref.	-	0.88(0.74, 1.06)	0.188	0.94(0.79, 1.13)	0.510	0.95(0.80, 1.14)	0.603	1.02(0.66, 1.58)	0.934
No	Ref.	-	1.01(0.80, 1.28)	0.950	1.03(0.81, 1.31)	0.799	0.93(0.73, 1.19)	0.586	0.70(0.38, 1.31)	0.268
Diabetes										
Yes	Ref.	-	0.90(0.67, 1.21)	0.474	0.98(0.73, 1.30)	0.866	0.89(0.67, 1.19)	0.437	0.99(0.51, 1.92)	0.983
No	Ref.	-	0.92(0.78, 1.08)	0.296	0.97(0.82, 1.14)	0.678	0.97(0.82, 1.15)	0.705	0.87(0.57, 1.34)	0.536

Table 3. Stratified analyses of the associations between DKR with all-cause and cardiovascular mortality. Model C: adjusted by gender, age, race, education level, marital status, PIR, BMI, smoke, hypertension, diabetes, CVD, stroke, and cancer Abbreviations: HRs, Hazard Ratios; CI, confidence interval; DKR, Dietary ketogenic ratio; PIR, Ratio of family income to poverty; BMI, Body Mass Index;

burden, and enhancing overall well-being. However, it is important to acknowledge that the suitability of the ketogenic diet may vary among individuals. Its stringent restrictions and high fat intake could potentially exert adverse effects on specific populations such as imposing additional strain on liver function and disrupting nutrient balance. Therefore, personalized guidance and vigilant monitoring should be emphasized during the promotion and application of KD to ensure its positive impact on public health.

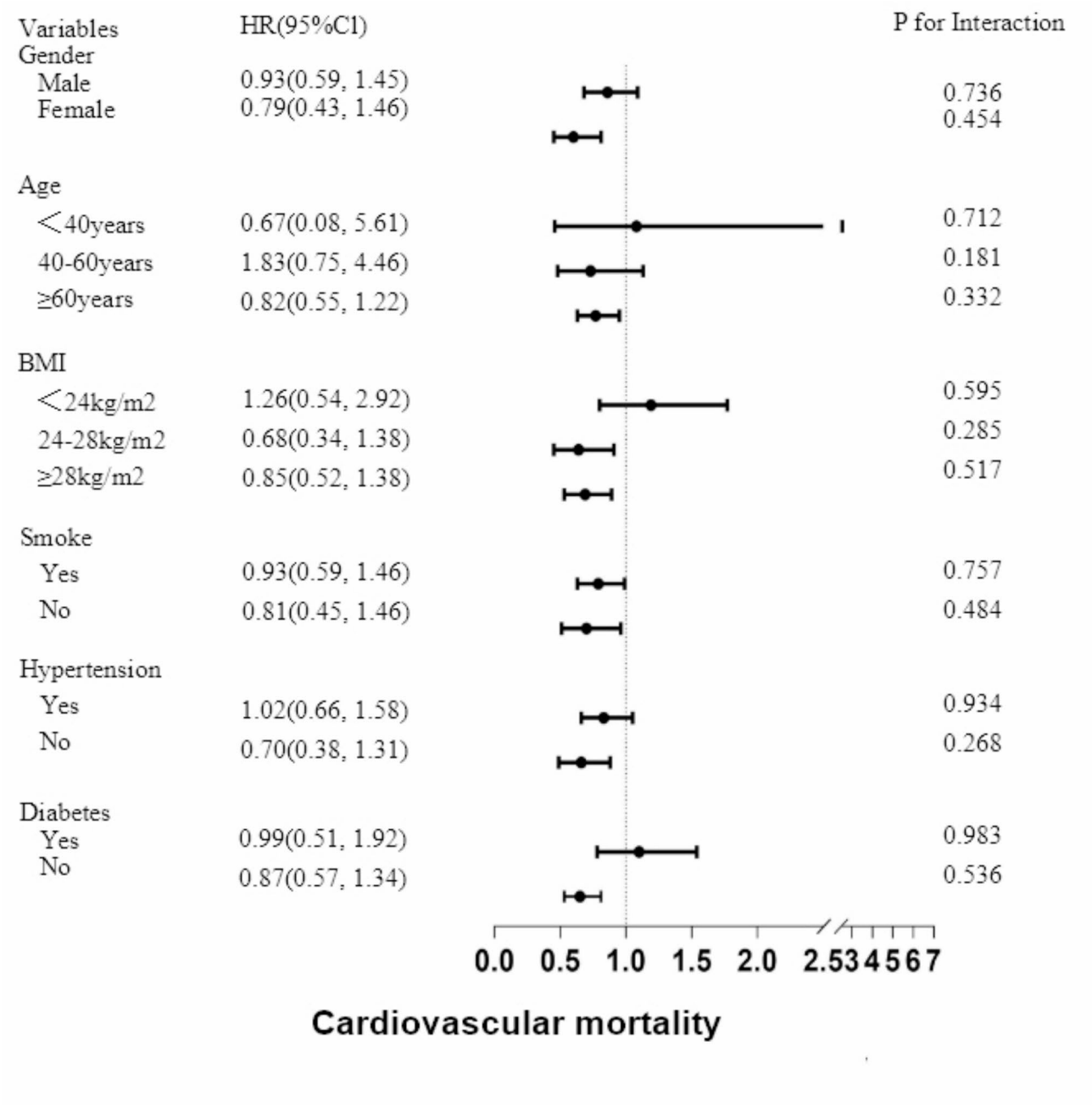

Fig. 4. Stratified analysis of the DKR and risk of cardiovascular mortality. DKR, dietary ketogenic ratio; BMI, Body Mass Index.

Limitations

- To ensure a comprehensive understanding of the findings, it is imperative to address the limitations of this study. Firstly, although rigorous data handling and statistical analysis indicate a potential trend towards reduced all-cause mortality risk without an increased risk of death from cardiovascular causes, the absence of direct measurement of ketosis levels poses a significant constraint in examining the relationship between ketosis and mortality risk. This hypothetical inference may not accurately reflect true ketosis status and could have influenced our study results. Therefore, future studies will employ more precise methods for directly measuring ketosis levels to comprehensively assess its potential association with all-cause mortality.
- Furthermore, the assessment of dietary habits in this study was solely reliant on self-administered questionnaires without repeated measurements, which may introduce temporal instability when estimating dietary patterns. Although the dietary data in the NHANES database are derived from cross-sectional sampling with appropriate research design, data selection, and statistical analysis methods to provide valuable insights into associations between disease or health conditions and exposure factors, they cannot establish direct causal

relationships.To address this limitation, future studies will explicitly discuss employing more rigorous methods for measuring dietary habits such as utilizing multiple repeated questionnaires or other objective dietary assessment tools to ensure precise and consistent evaluation of dietary patterns. In the future, through further research and technological advancements, we aim to acquire a more comprehensive understanding of the benefits and risks associated with ketogenic diets while making significant contributions to public health and well-being.

Conclusions

Our retrospective study suggests that the ketogenic diet may potentially reduce all-cause mortality without a concurrent increase in cardiovascular-related mortality. This finding underscores the significance of further research and exploration into the potential advantages of the ketogenic diet in promoting overall health and longevity. It is imperative for healthcare providers and policymakers to consider the potential impact of dietary interventions, such as the ketogenic diet, on reducing mortality rates and improving public health outcomes. Additional investigations are warranted to comprehensively comprehend the mechanisms underlying these observed associations and ascertain the feasibility and long-term sustainability of implementing a ketogenic diet for population-wide health benefits.

Data availability

The present study utilized publicly available datasets, which can be accessed at the National Center for Health Statistics (NHANES) website: https://wwwn.cdc.gov/nchs/nhanes.

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Author contributions

The conception and design were collaboratively contributed by all authors. X.Q. took responsibility for recruitment, data collection, data analysis, interpretation of the data, and manuscript writing. L.H. conducted data analysis and interpretation while also contributing to the writing process. L.H. and J.R. participated in recruitment and data collection as well as contributing to the writing process. The authors X.Q. and L.H. have made equal contributions to this paper. Finally, all authors reviewed and approved the final manuscript submitted for publication.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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