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Association of dietary niacin intake with all-cause and cardiovascular mortality: National Health and Nutrition Examination Survey (NHANES) 2003–2018

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The long-term health impacts of niacin are still debated, and the association between dietary niacin and mortality risk in populations hasn't been extensively explored. This study included 26,746 US adults aged 20 years or older from the National Health and Nutrition Examination Survey 2003–2018, with a median follow-up of 9.17 years. During this period, there were 3,551 all-cause deaths, including 1,096 cardiovascular deaths. Cox models were used to compare hazard ratios (HRs) for mortality among participants grouped into different dietary niacin intake quartiles. Participants with the highest dietary niacin intake had a lower risk of all-cause mortality (HR 0.74, 95%CI 0.63–0.86) compared to those in the lowest intake quartile. For cardiovascular mortality, the HR was 0.73 (95%CI 0.57–0.95) in the highest niacin intake quartile. A dose-response relationship was revealed between dietary niacin intake and mortality by restricted cubic spline. Subgroup analysis showed a significant interaction between dietary niacin intake and diabetes concerning all-cause mortality ($P = 0.046$). In this population-based cohort study, higher dietary niacin intake correlates with lower risk of all-cause and cardiovascular mortality among US adults. The influence of niacin intake on all-cause mortality appears to be more significant in non-diabetic individuals compared to those with diabetes.

Keywords Cardiovascular risk, Dietary niacin intake, Mortality, NHANES

Niacin, vitamin B3, is a vital water-soluble nutrient crucial for various physiological processes in the human body. Niacin deficiency has been linked to pellagra, a severe condition marked by dermatitis, diarrhea, dementia, and fatality[1]. Some nations have adopted fortification measures to niacin fortification of wheat flour and cereals, specifically targeting the prevention of pellagra[2]. And many common foods are rich in niacin, such as beef, pork, chicken, coffee, and tea[3,4]. Therefore, niacin is prevalent in modern western diets, with many individuals consuming niacin levels far exceeding the recommended dietary allowance, particularly in the US where intake surpasses the recommended dietary allowance by threefold[5].

Niacin is one of the earliest medications employed for dyslipidemia[6]. It was widely utilized, especially prior to the introduction of statins. Niacin can significantly reduce low density lipoprotein cholesterol and triglycerides, and raise high density lipoprotein cholesterol. The cardiovascular benefits of niacin were first demonstrated in the Coronary Drug Program (a classic randomized controlled trial), where niacin modestly reduced cardiovascular events in high-risk populations and reduced mortality at long-term follow-up after the randomized treatment period[7,8]. However, two randomized controlled trials in recent years have found that niacin does not reduce the risk of cardiovascular events on the basis of statin therapy, even with improvements in lipid levels[9,10].And a recent meta-analysis even found that niacin increased the risk of all-cause mortality[11]. This leads to what's known as the "niacin paradox", which highlights the discrepancy between niacin's favorable lipid profile changes and its failure

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to reduce cardiovascular events risk. Recent advancement has further complicated the understanding of niacin's role in cardiovascular health. A study involving over 4300 stable coronary artery disease patients revealed that niacin-derived end products of Nicotinamide adenine dinucleotide (NAD) metabolism, 2PY and 4PY, promote vascular inflammation, thereby increasing the risk of cardiovascular disease[12]. This underscores the need for continued evaluation of niacin's impact on cardiovascular disease risk and long-term health outcomes, particularly concerning dietary niacin intake.

Niacin is a key precursor of NAD. NAD plays a crucial role in numerous biological processes and functions, including but not limited to cell aging, cell death, cell metabolism, DNA repair, mitochondrial function, redox reactions, and inflammation[13]. Recent research has demonstrated that niacin can modulate NAD metabolism, thereby improving the aging process and mitigating related diseases, including neurodegenerative disorders, cardiovascular conditions, cancer, and diabetes[14–17].

The intricate impact of niacin on cardiovascular disease risk and long-term health remains contentious, with limited research exploring the association between dietary niacin intake and long-term health outcomes in various populations. The purpose of this study was to assess the association of dietary niacin intake and all-causes and cardiovascular mortality, providing valuable insights into recommended dietary niacin intake for the general population.

Methods

Study population

Study participants aged 20 years or older included in the National Health and Nutrition Examination Survey (NHANES) 2003–2018 were analyzed for this study ($n=44790$). Then, participants with missing follow-up information were excluded ($n=1965$). Additionally, participants with missing information on dietary niacin intake were excluded ($n=7849$). Further, participants with missing covariates were excluded ($n=8230$). Finally, total 26,746 participants were included for analysis, with a follow-up period from their survey participation date until December 31, 2019[20]. All open data used in this study are sourced from the official NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm). US National Center for Health Statistics Research Ethics Review Board approved NHANES protocol, and each participant signed the informed consent[21].

Dietary niacin intake

Since 2003, every NHANES participants have been subject to two 24-hour dietary recall interviews. These interviews are conducted to assess the types and quantities of beverages (including water) and foods consumed in the 24-hour period (midnight to midnight). Detailed niacin content data for various beverages and foods items were sourced from the Food and Nutrient Database for Dietary Studies[22]. Based on the quartiles of the average intake of dietary niacin over two days, participants were divided into four groups.

Outcome assessment

The study focused on two outcomes: all-cause mortality (deaths from all cause) and cardiovascular mortality (the International Classification of Diseases 10th revision codes I00-I09, I11, I13, I20-I51, and I60-I69). NHANES-linked mortality information have been updated through December 31, 2019[20].

Covariate assessment

The interview questionnaire provided data on the following variables: age, sex, ethnicity, educational level, smoking (yes, no), alcohol consumption (less than 12 alcohol drinks/year, at least 12 alcohol drinks/year), medical conditions (including hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer) and medication use. According to standard protocols, the following variables were measured: blood pressure, body mass index (BMI), glycohemoglobin, serum creatinine. The serum creatinine based Chronic Kidney Disease Epidemiology Collaboration equation was employed to calculate the estimated glomerular filtration rate (eGFR)[23]. The definition of hypertension encompassed a systolic blood pressure (SBP) of ≥ 140 mmHg, or a diastolic blood pressure (DBP) of ≥ 90 mmHg, or a hypertension history, or treatment with antihypertensive medication. The definition of diabetes encompassed a glycohemoglobin level of $\geq 6.5\%$, a diabetes history, or treatment with anti-diabetes medication.

Statistical analysis

Based on the guidelines provided by the Centers for Disease Control and Prevention regarding the NHANES data (21), The weights utilized in each analysis were tailored to the selected variables. Mean $\pm$ standard error (SE) was used to represent continuous variables, with group comparisons analyzed through analysis of variance. Percentages were utilized for categorical variables, with group comparisons assessed using the chi-square test. Cox models were employed to examine the hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality among dietary niacin intake quartiles. Model 1 was adjusted for age, sex, ethnicity, educational level, smoking, alcohol consumption and BMI. Model 2 was further adjusted for disease conditions (including hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer) and eGFR. Subgroup analyses stratified by age, sex, ethnicity, educational level, smoking, alcohol consumption, BMI, disease conditions and eGFR were conducted. Restricted cubic spline (RCS) analysis with three knots was employed to investigate dose-response relationship between dietary niacin intake and mortality outcome. Statistical analyses were conducted using R version 4.3.2 (R Project for Statistical Computing), with a significance level set at $P<0.05$ for all tests.

Results

Baseline characteristics

The study involved 26,746 US adults aged 20 years or older, with a median follow-up of 9.17 years (interquartile range, 6.0–12.5). A total of 3551 deaths from all causes occurred, including 1096 cardiovascular deaths. Baseline information of participants grouped according to dietary niacin intake quartiles were listed in Table 1. Participants with higher dietary niacin intake, as opposed to those with lower intake, were characterized by being younger, more predominantly male and non-Hispanic white, smokers, and drinkers. Additionally, they demonstrated higher education and eGFR levels, along with a lower prevalence of hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer.

Association of dietary niacin Intake and mortality outcome

Multiple Cox models have shown negative associations of dietary niacin intake with all-cause and cardiovascular mortality (Table 2). For all-cause mortality, Model 2 have shown that participants in the highest quartile of dietary niacin intake have a HR of 0.74 [95%CI, 0.63–0.86] compared to participants in the lowest quartile. For cardiovascular mortality, Model 2 have shown that participants in the highest quartile of dietary niacin intake have a HR of 0.73 [95%CI, 0.57–0.95] compared to participants in the lowest quartile.

Dose-response curves for dietary niacin intake and mortality

A dose-response connection between dietary niacin intake and all-cause as well as cardiovascular mortality was observed through restricted cubic spline analysis: As dietary niacin intake increased, the risk of all-cause and cardiovascular mortality decreased, while dietary niacin intake exceeds the median (22.45 mg/day), the risk of all-cause and cardiovascular mortality risk reduced slowed down (Fig. 1).

Subgroup Analysis

Subgroup analysis based on Model 2 showed that a significant association between dietary niacin intake and all-cause mortality was observed in most subgroups (Table 3). In addition, a significant interaction of dietary niacin intake and diabetes on all-cause mortality was observed ($P = 0.046$). Compared to participants with the lowest quartile of dietary niacin intake, HRs were 0.66 (95%CI, 0.56–0.79) and 1.01 (95%CI, 0.76–1.35) for participants with and without diabetes, respectively. Subgroup analysis based on Model 2 showed that dietary niacin intake associated with cardiovascular mortality in some subgroups, including the older, female, white, more than high school, obesity, smoking, non-hypertension, non-diabetes, non-dyslipidemia, non-cardiovascular disease, and high eGFR subgroups (Table 4). Despite the lack of significant interaction, relatively lower HR values of cardiovascular mortality were observed in these subgroups.

Sensitivity analysis

To evaluate the robust association between dietary niacin intake and mortality, sensitivity analysis was carried out, such as excluding participants with CVD or cancer, NHANES 2003–2016, and further adjustment for low density lipoprotein cholesterol. The significant negative associations consistent in sensitivity analysis (Table 5).

Discussion

We found a negative correlation between dietary niacin intake and all-cause and cardiovascular mortality in the US population. Additionally, we identified a significant interaction for dietary niacin intake and diabetes on all-cause mortality. The potential benefits of dietary niacin intake on all-cause mortality may be more prominent in non-diabetic individuals compared to those with diabetes. No significant interaction was observed between dietary niacin intake and stratification factors on cardiovascular mortality, the relationship between dietary niacin intake and cardiovascular mortality may differ among diverse populations.

Since niacin is one of the earliest lipid-regulating drugs, many studies have explored the effect of niacin on patients with coronary heart disease (CHD). Several older studies from the Coronary Drugs Program have demonstrated the efficacy of niacin in reducing the risk of cardiovascular events and mortality[7,8]. This was also confirmed in the Stockholm Ischemic Heart Disease Secondary Prevention Study[24]. A meta-analysis based on these older studies proposed that niacin reduce the risk of certain cardiovascular events among patients without statin treatment[25]. Due to the widespread use of statins, most studies in recent years have explored the effects of niacin on cardiovascular events and prognosis on the basis of statin therapy, suggesting that niacin does not reduce the risk of cardiovascular events and mortality in patients with CHD[26–29]. Recently, a meta-analysis suggested that niacin supplementation increased all-cause death risk of patients treated with statins[11]. This may be due to the effective control of lipids by statin therapy, and the improvement of lipids brought by niacin cannot further affect the prognosis of patients with CHD. However, in the general population or those in the early stages of CHD, dietary niacin intake is likely to have cardiovascular benefits. Few previous studies have assessed the relationship between dietary niacin intake and mortality. Ying et al. observed more dietary niacin intake associated with lower risk of all-cause and cancer-related mortality in cancer patients[30]. Pan et al. found a correlation between higher dietary niacin intake and reduced risk of all-cause mortality in patients with nonalcoholic fatty liver disease[31]. Although these two studies suggest potential benefits of dietary niacin intake in specific populations. The effect of dietary niacin intake on the overall population and on other specific populations remains unclear.

This study based on a population-based cohort study investigated the association of dietary intake with mortality in the general US population. We also conducted a number of stratified analyses to assess differences in the association of dietary niacin intake and mortality among various populations. This study contributes to the understanding of the relationship between dietary niacin intake and mortality across different populations.

Characteristic	Total	Dietary niacin intake, mg/day				*P* value
		Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)	
Unweighted sample	26,746	6688	6686	6685	6687	
Age, years	47.31 ± 0.26	50.54 ± 0.38	49.16 ± 0.38	47.56 ± 0.38	43.03 ± 0.33	< 0.001
Gender, n (%)						< 0.001
Male	12,951 (48.42)	1825 (27.29)	2634 (39.4)	3550 (53.1)	4942 (73.9)	
Female	13,795 (51.58)	4863 (72.71)	4052 (60.6)	3135 (46.9)	1745 (26.1)	
Race, n (%)						< 0.001
Mexican American	4333 (16.2)	1185 (17.72)	1089 (16.29)	1024 (15.32)	1035 (15.48)	
Other Hispanic	2273 (8.5)	647 (9.67)	557 (8.33)	561 (8.39)	508 (7.6)	
Non-Hispanic White	12,727 (47.58)	2885 (43.14)	3163 (47.31)	3324 (49.72)	3355 (50.17)	
Non-Hispanic Black	5312 (19.86)	1523 (22.77)	1326 (19.83)	1217 (18.2)	1246 (18.63)	
Other Race	2101 (7.86)	448 (6.7)	551 (8.24)	559 (8.36)	543 (8.12)	
Education level, n (%)						< 0.001
Less than high school	6401 (23.93)	2152 (32.18)	1634 (24.44)	1409 (21.08)	1206 (18.03)	
High school graduation/GED	6209 (23.21)	1553 (23.22)	1591 (23.8)	1505 (22.51)	1560 (23.33)	
More than high school	14,136 (52.85)	2983 (44.6)	3461 (51.76)	3771 (56.41)	3921 (58.64)	
Body mass index, kg/m2	28.83 ± 0.09	28.86 ± 0.13	28.89 ± 0.13	28.77 ± 0.14	28.80 ± 0.15	0.873
Body mass index, n (%)						0.012
<25	7579 (28.34)	1830 (27.36)	1902 (28.45)	1915 (28.65)	1932 (28.89)	
25–29.9	9080 (33.95)	2232 (33.37)	2161 (32.32)	2328 (34.82)	2359 (35.28)	
≥30	10,087 (37.71)	2626 (39.26)	2623 (39.23)	2442 (36.53)	2396 (35.83)	
Smoking, n (%)						0.013
Yes	12,193 (45.59)	2939 (43.94)	2928 (43.79)	3041 (45.49)	3285 (49.13)	
No	14,553 (54.41)	3749 (56.06)	3758 (56.21)	3644 (54.51)	3402 (50.87)	
Alcohol consumption, n (%)						< 0.001
less than 12 alcohol drinks/year	7646 (28.59)	2650 (39.62)	2090 (31.26)	1697 (25.39)	1209 (18.08)	
at least 12 alcohol drinks/year	19,100 (71.41)	4038 (60.38)	4596 (68.74)	4988 (74.61)	5478 (81.92)	
Hypertension, n (%)						< 0.001
Yes	11,390 (42.59)	3310 (49.49)	2956 (44.21)	2727 (40.79)	2397 (35.85)	
No	15,356 (57.41)	3378 (50.51)	3730 (55.79)	3958 (59.21)	4290 (64.15)	
Diabetes, n (%)						< 0.001
Yes	4052 (15.15)	1230 (18.39)	1114 (16.66)	942 (14.09)	766 (11.46)	
No	22,694 (84.85)	5458 (81.61)	5572 (83.34)	5743 (85.91)	5921 (88.54)	
dyslipidemia, n (%)						< 0.001
Yes	9294 (34.75)	2481 (37.1)	2408 (36.02)	2360 (35.3)	2045 (30.58)	
No	17,452 (65.25)	4207 (62.9)	4278 (63.98)	4325 (64.7)	4642 (69.42)	
eGFR	93.50 ± 0.34	90.87 ± 0.53	92.31 ± 0.51	93.71 ± 0.46	96.36 ± 0.42	< 0.001
eGFR, n (%)						< 0.001
<60	2468 (9.23)	908 (13.58)	710 (10.62)	522 (7.81)	328 (4.91)	
≥60	24,278 (90.77)	5780 (86.42)	5976 (89.38)	6163 (92.19)	6359 (95.09)	
Cardiovascular disease, n (%)						< 0.001
Yes	2857 (10.68)	936 (14)	812 (12.14)	621 (9.29)	488 (7.3)	
No	23,889 (89.32)	5752 (86)	5874 (87.86)	6064 (90.71)	6199 (92.7)	
Cancer, n (%)						< 0.001
Yes	2608 (9.75)	722 (10.8)	722 (10.8)	674 (10.08)	490 (7.33)	
No	24,138 (90.25)	5966 (89.2)	5964 (89.2)	6011 (89.92)	6197 (92.67)	

eGFR, estimated glomerular filtration rate.
Continuous variables are expressed as means and standard error and categorical variables as unweighted sample and percentages.
Means and standard errors are weighted.

Table 1. Baseline characteristics of participants according to dietary niacin intake quartiles.

Outcomes	Dietary niacin intake, mg/day				*P* value for trend
	Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)	
All-cause mortality					
Unadjusted HR	1 [Ref]	0.82(0.71–0.95)	0.65(0.58–0.74)	0.42(0.36–0.49)	< 0.001
P value		0.007	< 0.001	< 0.001	
Model 1 h	1 [Ref]	0.89(0.79–1.01)	0.78(0.69–0.89)	0.71(0.61–0.83)	< 0.001
P value		0.065	< 0.001	< 0.001	
Model 2 h	1 [Ref]	0.88(0.79–0.99)	0.80(0.71–0.91)	0.74(0.63–0.86)	< 0.001
P value		0.039	0.001	< 0.001	
Cardiovascular mortality					
Unadjusted HR	1 [Ref]	0.79(0.62–1.01)	0.63(0.51–0.77)	0.34(0.25–0.45)	< 0.001
P value		0.063	< 0.001	< 0.001	
Model 1 h	1 [Ref]	0.89(0.71–1.11)	0.81(0.67–0.98)	0.68(0.52–0.88)	0.001
P value		0.299	0.029	0.004	
Model 2 h	1 [Ref]	0.90(0.72–1.12)	0.86(0.71–1.05)	0.73(0.57–0.95)	0.011
P value		0.328	0.136	0.017	

HR, Hazard ratio; Ref, reference; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Model 1 was adjusted for age, sex, race/ethnicity, educational level, smoking, alcohol consumption and BMI.
Model 2 was further adjusted for disease conditions (hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer) and eGFR.
P value for trend was obtained from Cox models with the medians of each dietary niacin intake quartile as a continuous variable.

Table 2. HRs (95% CIs) for all-cause and cardiovascular mortality according to dietary niacin intake quartiles.

It is suggested that moderate dietary niacin intake may help reduce mortality risk in populations, especially in those without disease risk.

The potential benefits of dietary niacin intake on mortality may stem from the improvement of NAD metabolism. As a precursor of NAD, niacin can increase the level of NAD and improve cell capacity metabolism, DNA damage, inflammation, mitochondrial function, cell aging, and cell death through multiple mechanisms[13,32]. In recent years, more and more studies have focused on the mechanisms associated with NAD to improve disease. The research by Beltrà et al. indicated that niacin can effectively restore tissue NAD levels, improve mitochondrial metabolism, and alleviate cancer-related cachexia resulting from chemotherapy[16]. Pirinen et al.'s research demonstrates that nicotinic acid treatment alleviates systemic NAD deficiency and enhances muscle performance in adult-onset mitochondrial myopathy by promoting mitochondrial biogenesis and respiratory chain activity[19]. According to Mouchiroud et al., the NAD (+)/Sirtuin pathway regulates longevity by activating mitochondrial UPR and FOXO signaling[33]. These findings offer partial insight into how dietary niacin intake reduces the risk of mortality. However, it has also been suggested that the extent or efficacy of NAD depletion may diminish the disease-modifying effect of NAD elevation methods, thus limiting data interpretation[34]. As for the role of niacin in the pathogenesis of cardiovascular diseases, previous studies have mainly attributed to its lipid-lowering effect. Adipocyte lipolysis is regulated by a number of G protein-coupled receptors (GPR). Niacin is a potent GPR109A agonist, which can effectively inhibit lipolysis and reduce free fatty acids[35]. In addition, niacin also affects cholesterol synthesis and transport by affecting key enzymes of lipid metabolism and cholesteryl ester transfer protein[36,37]. But recent research indicates that elevated niacin end metabolites could elevate the risk of cardiovascular disease by activating inflammatory pathways, such as directly boosting VCAM-1 expression[12]. Overall, niacin is more likely to function as an NAD modulator rather than lipid-lowering medication to improve disease and long-term health risks, warranting further exploration.

This study also found that the effect of dietary niacin intake on all-cause mortality is more pronounced in non-diabetic participants than in diabetic participants. Previous studies have found that niacin may raise blood sugar and increase the risk of diabetes[38–40]. Niacin may impair insulin sensitivity through several pathways[41–43]. Therefore, higher dietary niacin is recommended to reduce the risk of all-cause death in non-diabetic people, but not in diabetic patients. And further research is needed to clarify this result and explore the specific mechanisms.

This study has some limitations. Firstly, the estimation of dietary niacin intake relied on self-reported data, introducing inherent measurement inaccuracies. Secondly, a two-day average of niacin intake may not fully capture long-term dietary patterns. Lastly, despite extensive adjustments for confounding variables, a notable risk of bias from confounding factors persists.

Conclusion

In this population-based cohort study, increased dietary niacin intake is associated with reduced all-cause and cardiovascular mortality in US adults. The impact of niacin intake on all-cause mortality is more pronounced in non-diabetic individuals than in those with diabetes. Although no significant interaction was found between dietary niacin intake and stratification factors regarding cardiovascular mortality, the association between niacin

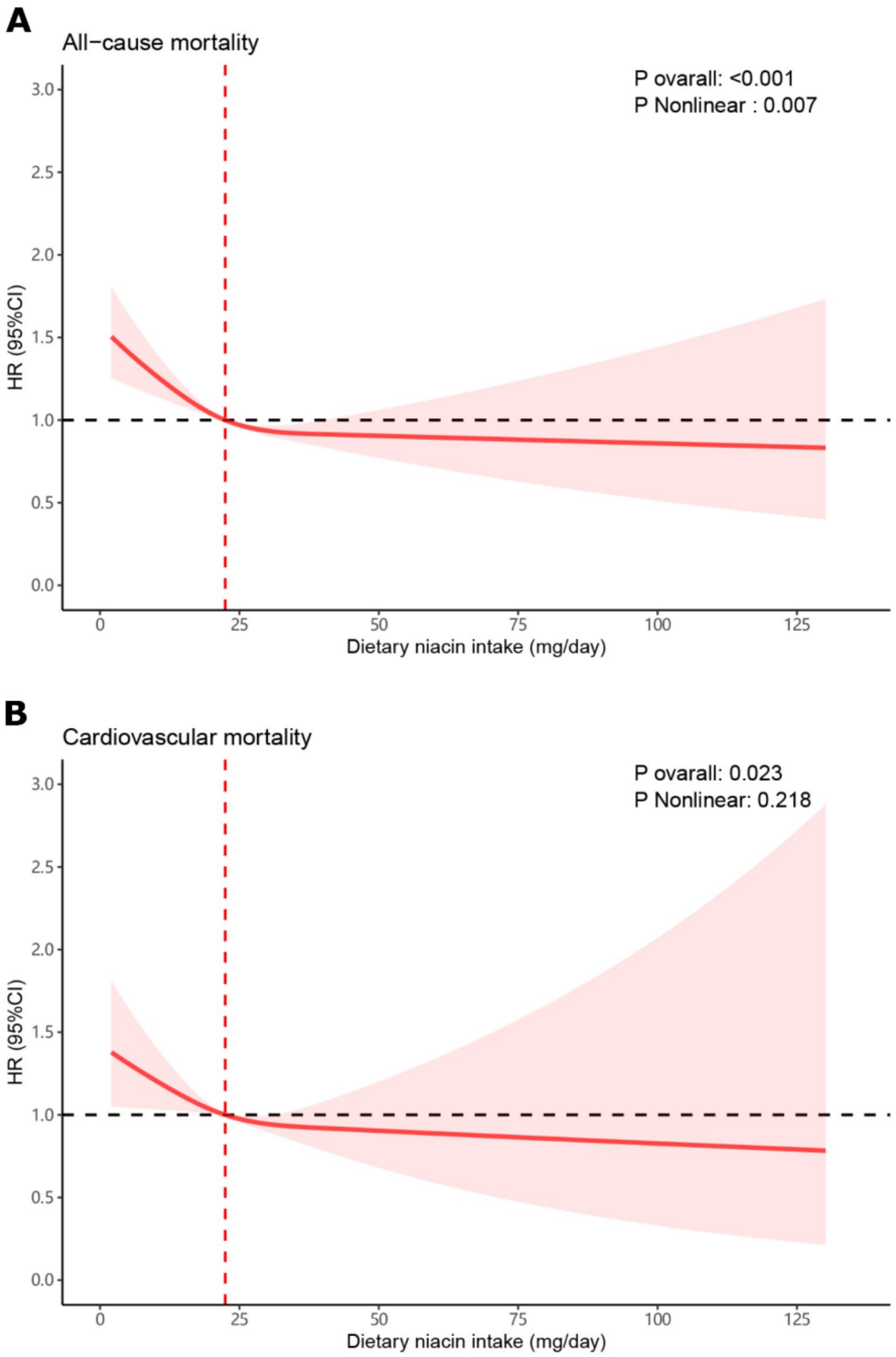

Fig. 1. Dose-response curves for dietary niacin intake and mortality. (A) dietary niacin intake and all-cause mortality. (B) dietary niacin intake and cardiovascular mortality.

intake and cardiovascular mortality may vary across different populations. Further research is needed to clarify the variations in the impact of dietary niacin intake on cardiovascular mortality across different populations.

Outcomes	Total	Cases	Dietary niacin intake, mg/day				*P* value for trend	*P* value for interaction
			Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)		
Age								0.598
< 65	20,204	1022	1 [Ref]	1.00(0.75–1.33)	0.84(0.64–1.09)	0.69(0.51–0.92)	0.002	
P value				0.986	0.185	0.011		
≥ 65	6542	2529	1 [Ref]	0.80(0.69–0.93)	0.74(0.63–0.87)	0.58(0.49–0.68)	< 0.001	
P value				0.003	< 0.001	< 0.001		
Sex								0.486
Male	12,951	2013	1 [Ref]	0.97(0.80–1.17)	0.86(0.71–1.05)	0.73(0.59–0.90)	< 0.001	
P value				0.731	0.145	0.004		
Female	13,795	1538	1 [Ref]	0.83(0.69–1.01)	0.76(0.63–0.91)	0.81(0.61–1.08)	0.025	
P value				0.057	0.003	0.156		
White								0.405
Yes	12,727	2297	1 [Ref]	0.87(0.76–0.99)	0.75(0.65–0.88)	0.67(0.56–0.79)	< 0.001	
P value				0.038	< 0.001	< 0.001		
No	14,019	1254	1 [Ref]	0.85(0.70–1.04)	0.97(0.78–1.19)	1.04(0.77–1.41)	0.695	
P value				0.109	0.763	0.780		
Education								0.680
Less than high school	6401	1236	1 [Ref]	0.90(0.76–1.06)	0.77(0.62–0.96)	0.72(0.53–0.98)	0.021	
P value				0.213	0.022	0.038		
High school graduation/ GED	6209	954	1 [Ref]	0.87(0.71–1.07)	0.82(0.65–1.04)	0.85(0.64–1.12)	0.239	
P value				0.196	0.101	0.244		
More than high school	14,136	1361	1 [Ref]	0.87(0.72–1.06)	0.78(0.64–0.96)	0.69(0.55–0.86)	0.001	
P value				0.165	0.020	0.001		
BMI								0.537
< 25	7579	1049	1 [Ref]	0.97(0.79–1.20)	0.72(0.56–0.92)	0.88(0.68–1.13)	0.103	
P value				0.782	0.008	0.303		
25–29.9	9080	1244	1 [Ref]	0.89(0.71–1.12)	0.81(0.66–1.00)	0.71(0.55–0.91)	0.005	
P value				0.317	0.053	0.007		
≥ 30	10,087	1258	1 [Ref]	0.82(0.66–1.03)	0.88(0.69–1.13)	0.68(0.51–0.90)	0.012	
P value				0.083	0.318	0.008		
Smoking								0.309
Yes	12,193	2172	1 [Ref]	0.85(0.74–0.98)	0.77(0.67–0.89)	0.74(0.64–0.87)	< 0.001	
P value				0.028	0.001	< 0.001		
No	14,553	1379	1 [Ref]	0.93(0.79–1.11)	0.87(0.71–1.07)	0.71(0.53–0.95)	0.020	
P value				0.435	0.183	0.021		
Alcohol consumption								0.879
< 12 alcohol drinks/year	19,100	2396	1 [Ref]	0.92(0.79–1.07)	0.81(0.69–0.97)	0.73(0.62–0.87)	< 0.001	
P value				0.285	0.020	< 0.001		
≥ 12 alcohol drinks/year	7646	1155	1 [Ref]	0.84(0.69–1.02)	0.81(0.64–1.02)	0.78(0.57–1.07)	0.073	
P value				0.080	0.073	0.123		
Hypertension								0.349
Yes	11,390	2564	1 [Ref]	0.90(0.78–1.05)	0.78(0.66–0.92)	0.79(0.65–0.96)	0.004	
P value				0.175	0.003	0.016		
No	15,356	987	1 [Ref]	0.82(0.67–1.01)	0.82(0.68–1.00)	0.63(0.49–0.81)	< 0.001	
P value				0.061	0.049	< 0.001		
Diabetes								0.046
Yes	4052	1030	1 [Ref]	0.90(0.74–1.10)	0.96(0.75–1.23)	1.01(0.76–1.35)	0.841	
P value				0.310	0.753	0.938		
No	22,694	2521	1 [Ref]	0.87(0.76–1.00)	0.76(0.66–0.87)	0.66(0.56–0.79)	< 0.001	
P value				0.047	< 0.001	< 0.001		
Dyslipidemia								0.576
Yes	9294	1712	1 [Ref]	0.92(0.76–1.12)	0.82(0.68–0.99)	0.84(0.67–1.05)	0.075	
P value				0.423	0.035	0.117		
No	17,452	1839	1 [Ref]	0.86(0.73–1.01)	0.79(0.66–0.95)	0.66(0.53–0.82)	< 0.001	
Continued								

Outcomes	Total	Cases	Dietary niacin intake, mg/day				*P* value for trend	*P* value for interaction
			Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)		
P value				0.059	0.013	< 0.001		
Cancer								0.330
Yes	2608	834	1 [Ref]	0.77(0.59–0.99)	0.85(0.66–1.08)	0.70(0.54–0.89)	0.014	
P value				0.043	0.187	0.004		
No	24,138	2717	1 [Ref]	0.93(0.80–1.07)	0.78(0.68–0.90)	0.75(0.62–0.91)	0.001	
P value				0.320	0.001	0.004		
Cardiovascular disease								0.735
Yes	2857	1173	1 [Ref]	0.88(0.74–1.04)	0.79(0.66–0.95)	0.84(0.65–1.08)	0.106	
P value				0.136	0.013	0.174		
No	23,889	2378	1 [Ref]	0.89(0.77–1.03)	0.81(0.69–0.96)	0.70(0.58–0.85)	< 0.001	
P value				0.127	0.015	< 0.001		
eGFR								0.723
< 60	2468	1175	1 [Ref]	0.81(0.66–0.99)	0.81(0.65–1.01)	0.76(0.56–1.03)	0.049	
P value				0.042	0.062	0.080		
≥ 60	24,278	2376	1 [Ref]	0.92(0.80–1.06)	0.80(0.68–0.94)	0.72(0.61–0.86)	< 0.001	
P value				0.236	0.005	< 0.001		

HR, Hazard ratio; Ref, reference; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Model 2 was adjusted for age, sex, race/ethnicity, educational level, smoking, alcohol consumption, BMI, disease conditions (hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer) and eGFR.
P value for trend was obtained from Cox models with the medians of each dietary niacin intake quartile as a continuous variable.

Table 3. Subgroup analyses for the association of dietary niacin intake with all-cause mortality.

Outcomes	Total	Cases	Dietary niacin intake, mg/day				*P* value for trend	*P* value for interaction
			Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)		
Age								0.723
< 65	20,204	236	1 [Ref]	1.06(0.64–1.77)	1.04(0.63–1.72)	0.74(0.44–1.25)	0.162	
P value				0.823	0.874	0.265		
≥ 65	6542	860	1 [Ref]	0.80(0.60–1.05)	0.75(0.59–0.95)	0.56(0.42–0.74)	< 0.001	
P value				0.111	0.017	< 0.001		
Sex								0.096
Male	12,951	625	1 [Ref]	1.10(0.80–1.51)	0.99(0.74–1.33)	0.90(0.65–1.26)	0.324	
P value				0.555	0.963	0.550		
Female	13,795	471	1 [Ref]	0.79(0.56–1.11)	0.82(0.60–1.13)	0.42(0.24–0.75)	0.008	
P value				0.176	0.220	0.003		
White								0.483
Yes	12,727	727	1 [Ref]	0.87(0.68–1.11)	0.81(0.65–0.99)	0.65(0.49–0.88)	0.002	
P value				0.260	0.044	0.004		
No	14,019	369	1 [Ref]	0.93(0.64–1.35)	1.05(0.68–1.63)	1.09(0.61–1.92)	0.731	
P value				0.704	0.827	0.780		
Education								0.347
Less than high school	6401	393	1 [Ref]	1.06(0.81–1.39)	1.04(0.76–1.43)	0.78(0.49–1.25)	0.416	
P value				0.654	0.802	0.305		
High school graduation/ GED	6209	292	1 [Ref]	0.85(0.58–1.26)	0.94(0.63–1.39)	0.97(0.65–1.43)	0.977	
P value				0.423	0.748	0.870		
More than high school	14,136	411	1 [Ref]	0.78(0.57–1.08)	0.65(0.45–0.94)	0.55(0.36–0.83)	0.004	
P value				0.136	0.024	0.005		
BMI								0.181
< 25	7579	298	1 [Ref]	0.88(0.59–1.31)	0.65(0.41–1.02)	0.89(0.56–1.41)	0.401	
P value				0.530	0.063	0.615		
25–29.9	9080	379	1 [Ref]	1.11(0.75–1.63)	0.98(0.74–1.30)	0.90(0.61–1.32)	0.446	
P value				0.602	0.882	0.589		
≥ 30	10,087	419	1 [Ref]	0.79(0.55–1.12)	0.97(0.67–1.42)	0.52(0.30–0.88)	0.035	
P value				0.182	0.893	0.015		
Smoking								0.131
Yes	12,193	614	1 [Ref]	0.72(0.56–0.94)	0.76(0.58–0.99)	0.71(0.53–0.96)	0.044	
P value				0.014	0.045	0.027		
No	14,553	482	1 [Ref]	1.14(0.79–1.64)	1.01(0.74–1.38)	0.70(0.46–1.09)	0.095	
P value				0.474	0.934	0.114		
Alcohol consumption								0.707
< 12 alcohol drinks/year	19,100	711	1 [Ref]	0.90(0.71–1.13)	0.90(0.70–1.17)	0.78(0.58–1.05)	0.127	
P value				0.347	0.438	0.105		
≥ 12 alcohol drinks/year	7646	385	1 [Ref]	0.92(0.62–1.35)	0.78(0.52–1.17)	0.62(0.37–1.03)	0.050	
P value				0.661	0.235	0.064		
Hypertension								0.342
Yes	11,390	853	1 [Ref]	0.88(0.68–1.14)	0.85(0.67–1.08)	0.82(0.62–1.10)	0.163	
P value				0.328	0.186	0.186		
No	15,356	243	1 [Ref]	0.89(0.56–1.42)	0.86(0.58–1.27)	0.46(0.24–0.87)	0.007	
P value				0.635	0.441	0.016		
Diabetes								0.125
Yes	4052	353	1 [Ref]	1.07(0.80–1.44)	1.16(0.81–1.65)	0.85(0.53–1.36)	0.557	
P value				0.652	0.419	0.497		
No	22,694	743	1 [Ref]	0.82(0.63–1.08)	0.76(0.61–0.94)	0.68(0.50–0.93)	0.007	
P value				0.164	0.012	0.015		
Dyslipidemia								0.122
Yes	9294	569	1 [Ref]	0.93(0.69–1.25)	0.99(0.77–1.26)	0.78(0.54–1.11)	0.188	
P value				0.622	0.908	0.169		
No	17,452	527	1 [Ref]	0.84(0.62–1.14)	0.70(0.53–0.93)	0.67(0.48–0.94)	0.012	
Continued								

Outcomes	Total	Cases	Dietary niacin intake, mg/day				*P* value for trend	*P* value for interaction
			Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)		
P value				0.266	0.014	0.021		
Cancer								0.120
Yes	2608	219	1 [Ref]	0.54(0.33–0.90)	0.80(0.52–1.24)	0.59(0.33–1.05)	0.201	
P value				0.017	0.322	0.074		
No	24,138	877	1 [Ref]	1.06(0.83–1.34)	0.88(0.69–1.11)	0.78(0.58–1.06)	0.054	
P value				0.650	0.273	0.114		
Cardiovascular disease								0.630
Yes	2857	465	1 [Ref]	0.99(0.73–1.35)	0.93(0.67–1.28)	0.94(0.64–1.37)	0.687	
P value				0.958	0.653	0.744		
No	23,889	631	1 [Ref]	0.83(0.61–1.13)	0.83(0.61–1.12)	0.61(0.42–0.89)	0.007	
P value				0.243	0.223	0.010		
eGFR								0.563
< 60	2468	433	1 [Ref]	0.90(0.65–1.26)	1.02(0.74–1.41)	0.73(0.45–1.19)	0.328	
P value				0.555	0.887	0.211		
≥ 60	24,278	663	1 [Ref]	0.87(0.69–1.09)	0.76(0.57–1.00)	0.69(0.49–0.97)	0.027	
P value				0.227	0.050	0.034		

HR, Hazard ratio; Ref, reference; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Model 2 was adjusted for age, sex, race/ethnicity, educational level, smoking, alcohol consumption, BMI, disease conditions (hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer) and eGFR.
P value for trend was obtained from Cox models with the medians of each dietary niacin intake quartile as a continuous variable.

Table 4. Subgroup analyses for the association of dietary niacin intake with cardiovascular mortality.

Outcomes	Total	Cases	Dietary niacin intake, mg/day				*P* value for trend
			Quintile 1 (< 16.51)	Quintile 2 (16.51–22.45)	Quintile 3 (22.46–30.15)	Quintile 4 (≥ 30.16)	
All-cause mortality							
Removing participants with CVD or cancer at baseline	21,903	1860	1 [Ref]	0.92(0.78–1.09)	0.80(0.67–0.95)	0.69(0.67–0.95)	< 0.001
P value				0.346	0.012	0.002	
NHANES 2003–2016	23,018	3392	1 [Ref]	0.88(0.78–0.99)	0.79(0.69–0.90)	0.71(0.61–0.83)	< 0.001
P value				0.032	< 0.001	< 0.001	
Further adjustment for low density lipoprotein cholesterol	11,941	1582	1 [Ref]	0.83(0.70–0.98)	0.76(0.65–0.90)	0.64(0.51–0.81)	< 0.001
P value				0.026	0.001	< 0.001	
Cardiovascular mortality							
Removing participants with CVD or cancer at baseline	21,903	528	1 [Ref]	0.82(0.67–1.26)	0.81(0.59–1.10)	0.60(0.39–0.92)	0.008
P value				0.600	0.177	0.018	
NHANES 2003–2016	23,018	1060	1 [Ref]	0.90(0.72–1.12)	0.83(0.69–1.01)	0.69(0.53–0.89)	0.002
P value				0.347	0.066	0.005	
Further adjustment for low density lipoprotein cholesterol	11,941	500	1 [Ref]	1.06(0.82–1.38)	0.85(0.64–1.14)	0.67(0.46–0.97)	0.013
P value				0.638	0.276	0.033	

CVD, cardiovascular diseases; Ref, reference; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Model 2 was adjusted for age, sex, race/ethnicity, educational level, smoking, alcohol consumption, BMI, disease conditions (hypertension, diabetes, dyslipidemia, cardiovascular disease, and cancer) and eGFR.
P value for trend was obtained from Cox models with the medians of each dietary niacin intake quartile as a continuous variable.

Table 5. Sensitivity analyses for the association of dietary niacin intake with all-cause and cardiovascular mortality.

Data availability

The data used in this study are openly available in the NHANES website: NHANES Questionnaires, Datasets, and Related Documentation (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

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Author contributions

YF and LL conceived and designed research. SJC, LL, ZCH, LL and CY processed data and performed statistical analysis. LL and CSJ wrote the initial paper; YF, LDL, CQR and ZXY reviewed and corrected the article. All authors read and approved the final manuscript. LL and SJC have contributed equally to this work and share first authorship.

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Declarations

Ethics approval and consent to participate

This study is an analysis derived from publicly available NHANES data. The National Center for Health Statistics Research Ethics Review Board approved the NHANES protocol (https://www.cdc.gov/nchs/nhanes/irba98.htm). The NHANES has obtained written informed consent from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Additional information

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