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Dietary vitamin K intake associates with reduced all-cause mortality in non-alcoholic fatty liver disease patients

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This study aimed to investigate the association between dietary vitamin K intake and all-cause mortality in individuals with non-alcoholic fatty liver disease (NAFLD). We analyzed data from 7857 NAFLD participants in the National Health and Nutrition Examination Survey (NHANES 2005–2018) linked to mortality outcomes from the National Death Index (NDI). Dietary vitamin K intake was log-transformed (ln[VK]) for analysis. Multivariable Cox proportional hazards models and restricted cubic splines were used to evaluate dose-response relationships. Sensitivity analyses, subgroup analyses, and receiver operating characteristic (ROC) curves were performed to validate findings. Over 180 months of follow-up, 842 deaths occurred. Higher ln[VK] was associated with reduced mortality risk, demonstrating an adjusted hazard ratio (HR) of 0.81 per 1-unit increasement (95% confidence interval CI 0.67–0.98, P-trend = 0.028). Restricted cubic splines revealed a U-shaped relationship (P-nonlinear = 0.0009), with an optimal threshold at 121 µg/day (ln[VK] = 4.71). Below this threshold, each unit increase in ln[VK] corresponded to a 33% lower mortality risk (HR = 0.67; 95% CI 0.55–0.81), whereas no significant association was observed above it (HR 1.07; 95% CI 0.67–1.71). The fully adjusted prediction model showed robust discriminative ability, with an area under the curve (AUC) of 0.832. Results remained consistent across sensitivity analyses. Moderate dietary vitamin K intake (up to 121 µg/day) is associated with reduced all-cause mortality in NAFLD patients, with a threshold effect informing tailored dietary recommendations. This study provides novel evidence for optimizing vitamin K intake in NAFLD management.

Keywords Dietary vitamin K, Non-alcoholic fatty liver disease, All-cause mortality, NHANES

Abbreviations

Anova	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
DGA	Dietary guidelines for Americans
EFSA	European Food Safety Authority
FLI	Fatty liver index
HEI	Healthy eating index
HbA1c	Hemoglobin A1c
NCHS	National Center for Health Statistics
NDI	National death index
ROC	Receiver operating characteristic
HEI-2020	Healthy Eating Index 2020
HR	Hazard ratio
CKD	Chronic kidney disease
ASCVD	Atherosclerotic cardiovascular disease
MGP	Matrix Gla protein

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FNDDS   Food and Nutrient Database for Dietary Studies
AI   Adequate intake

Non-alcoholic fatty liver disease (NAFLD) is a growing global public health concern, characterized by an excessive accumulation of fat in the liver. Its prevalence has risen significantly, from 25.3% between 1990–2006 to 38.0% in 2016–2019[1,2]. The pathogenesis of NAFLD involves multiple factors such as diet, insulin resistance, oxidative stress, and mitochondrial dysfunction[3–5]. Recent studies suggest a potential link between vitamin deficiencies and NAFLD[6–8], with particular attention to vitamin K due to its antioxidant, anti-inflammatory, and lipid metabolism regulatory properties[9,10].

Vitamin K, a fat-soluble vitamin, has been shown to reduce oxidative stress and mitigate liver cell damage caused by reactive oxygen species (ROS)[11]. It may also regulate lipid metabolism by influencing fatty acid synthesis and breakdown, potentially reducing hepatic fat accumulation[12]. Preclinical studies, particularly in high-fat diet mouse models, suggest that vitamin K2 may protect against NAFLD progression by modulating key enzymes such as 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and reducing body weight and fat accumulation[13].

However, the association between vitamin K and long-term outcomes, particularly all-cause mortality in NAFLD patients, remains unclear. To address this gap, this study aims to investigate the relationship between dietary vitamin K intake and long-term all-cause mortality in NAFLD patients, utilizing data from the National Health and Nutrition Examination Survey (NHANES) and the National Death Index (NDI).

Materials and methods

Study design

The NHANES data were used to assess the nutritional and health status of the non- institutionalized U.S. population[14]. The study protocol was approved by the Institutional Review Board of the National Center for Health Statistics, and relevant data are freely available for download from the NHANES website. Interview data were collected from participants between 2005 and 2018. These data were linked with the National Death Index (NDI) to establish a longitudinal follow-up cohort for determining participant survival status[15]. The National Center for Health Statistics (NCHS) Ethics Review Board approved this study, and all participants provided informed consent forms. No additional informed consent or ethical review was required for this analysis. Of the 60,041 participants from 2005 to 2018, 12,727 with U.S. Multi-Ethnic Fatty Liver Index (US-FLI) ≥ 30 were selected for further analysis (Fig. 1). The final study population included 7857 participants. The patient selection process is illustrated in Fig. 1.

Measurement of dietary vitamin K intake

Dietary data were derived from two 24-h recall interviews, one conducted at the Mobile Examination Center (MEC) and the other via telephone 3 to 10 days later. All eligible participants completed both interviews, during which they reported the types and quantities of food consumed in the 24 h preceding each interview. The dietary data were analyzed using the Food and Nutrient Database for Dietary Studies (FNDDS) and the standardized Automated Multiple-Pass Method (AMPM) to ensure accuracy. Finally, the daily dietary vitamin K intake was calculated as the average of the two dietary recalls; if only one recall was available, that value was used. Based on NHANES data, primary dietary sources of vitamin K in our cohort included leafy greens (spinach, kale), vegetable oils).

Definition of fatty liver based on the U.S. multi-ethnic fatty liver index

NAFLD was defined using the U.S. Multi-Ethnic Fatty Liver Index (US-FLI), The US-FLI is calculated using the following validated formula[16]: $x = (e^{-0.8073*non-Hispanic\ black+0.3458*}$ $Mexican\ American+0.0093*age+0.6151*\log_e(GGT)\ +0.0249*waist\ circumference+1.1792*\log_e(insulin)+0.8242*$
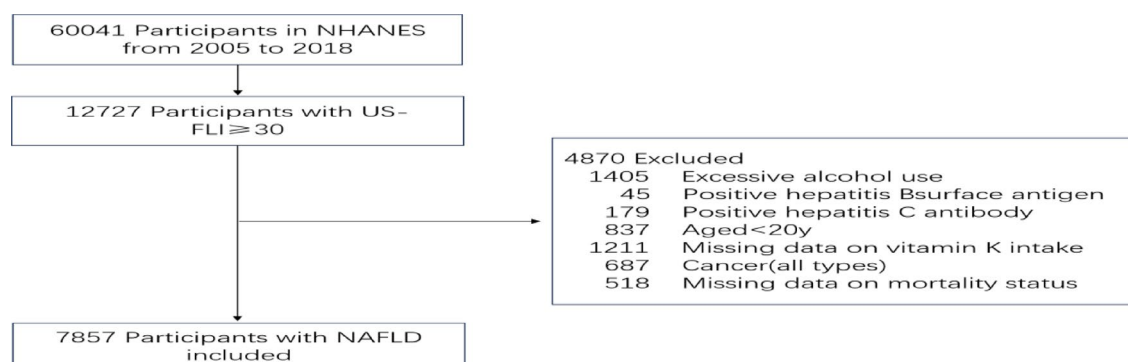

Fig. 1. Flowchart of the non-alcoholic fatty liver disease (NAFLD) study population from NHANES (2005–2018). Note: Some exclusion criteria may overlap or not be listed separately, causing discrepancies in the total excluded count; Participants with cancer were excluded during initial screening due to high missing values of cancer history data across survey cycles.

$$\log_e(glucose) - 14.7812 / (1 + e^{-0.8073*non-Hispanic\ black\ +0.3458*Mexican\ American+0.0093*age+0.6151*}$$

$$\log_e(GGT)+0.0249*waist\ circumference+1.1792*\log_e(insulin)+0.8242*\log_e(glucose)-14.7812}) * 100$$

Which incorporates demographic factors (age, race/ethnicity) and biochemical markers (insulin, glucose, γ-glutamyltransferase, and waist circumference). Participants classified as "Non Hispanic Black " or "Mexican American" are assigned a value of 1 for the corresponding variable; otherwise, the value is set to 0. A US-FLI score greater than 30 indicates the presence of fatty liver. This definition has been validated with an area under the receiver operating characteristic (ROC) curve of 0.80 (95% CI 0.77–0.83) for predicting NAFLD, as confirmed by ultrasound.

Survival status

The National Center for Health Statistics (NCHS) established the NDI in collaboration with states, utilizing a series of identifiers including social security numbers and birth dates. In this study, the NCHS linked NHANES data with the NDI to determine the survival status of participants. The follow-up for the participants ended on December 31, 2019. All-cause mortality is defined as death resulting from any cause.

Covariates

Age was categorized into three groups (20–40, 40–60, and over 60 years), and race/ethnicity into four groups (Mexican American, Non-Hispanic Black, Non-Hispanic White, and Other). Educational level was classified into three categories: below high school, high school, and above high school. Smoking status was divided into three groups: never smokers (those who have smoked fewer than 100 cigarettes in their lifetime), former smokers (those who have smoked more than 100 cigarettes and have since quit), and current smokers (those who have smoked more than 100 cigarettes and currently smoke daily or occasionally). Body mass index (BMI) was calculated as weight divided by height squared and classified into three categories: normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obese (BMI > 30 kg/m^2). Diabetes was defined as meeting any of the following criteria: (1) HbA1c ≥ 6.5% or fasting blood glucose > 7.0 mmol/L; (2) self-reported diabetes diagnosis or current insulin use. Hypertension and total cholesterol intake were both estimated based on self-reported data from the 24-h recall interviews. Heavy drinking was defined as an average daily alcohol intake exceeding 20 g for men or 10 g for women. Cardiovascular disease history was defined as self-reported diagnosis of congestive heart failure, coronary artery disease, angina pectoris, or myocardial infarction. Individuals affirming ≥ 1 condition were categorized as positive. The Healthy Eating Index 2020 (HEI-2020), based on the 2020–2025 Dietary Guidelines for Americans (DGA), assesses diet quality across 13 food components, with scores ranging from 0 to 100[17]. Higher scores indicate better diet quality and greater adherence to the DGA. Cancer history (self-reported via MCQ220) was not included as a covariate due to extensive missing data (90.4%) alongside potential misclassification bias in self-reports.

Statistical analysis

Analyses of NHANES incorporated sample weights, stratification, and primary sampling units. Continuous variables were presented as medians with interquartile ranges, while categorical variables were reported as counts and percentages. The three groups were compared using either ANOVA or the Kruskal–Wallis test for continuous variables, and the χ^2 test for categorical variables. To reduce skewness in dietary vitamin K intake and approximate a normal distribution, a log transformation was applied. The characteristics of the study population were stratified based on the tertiles of the natural logarithm of dietary vitamin K intake.

A weighted multivariate Cox proportional hazards regression model was applied to assess the association between dietary vitamin K intake and all-cause mortality. The proportional hazards assumption was validated through residual analysis using Schoenfeld residuals, and no violations were detected. Three regression models were constructed. The non-adjusted Model included only the dietary vitamin K intake. The model I adjusted for age, gender, race, and educational level, while model II was fully adjusted for all covariates, including lifestyle factors and comorbidities. To avoid multicollinearity, variables with a variance inflation factor (VIF) greater than 10 were excluded (Tale A1 in the Appendix). Additional adjustments were made for characteristics that, when added to the model, altered the hazard ratio by at least 10%[18]. We used a weighted multivariate Cox regression model with restricted cubic splines to detect non-linearity and identify inflection points. Based on these points, we developed segmented Cox proportional hazards models, along with Kaplan–Meier analyses and Log-Rank tests, to identify significant predictors of survival. Model performance was evaluated using Receiver operating characteristic curves (ROC) and AUC, with differences in AUCs compared using the z-test.

Stratified analyses were conducted for significant covariates, taking into account potential effect modifiers including age, gender, race, education level, history of hypertension, alcohol consumption, dietary supplement usage, HEI-2020 score, diabetes history, triglycerides, hypertension history, total energy intake, cardiovascular disease, smoking status and cholesterol levels. Sensitivity analyses included: (1) excluding participants who died within 2 years of follow-up to minimize reverse causality bias; (2) excluding participants with only one dietary recall; (3) examining the predictive value of serum vitamin K for mortality using FLI (Fatty Liver Index) ≥ 60 as the diagnostic criterion for NAFLD[19]. The E-value was calculated to assess the impact of unmeasured confounders on the relationship between dietary vitamin K intake and all-cause mortality[20,21], with higher E-values indicating greater robustness of the observed association. (4) Sensitivity analyses evaluated potential confounding by vitamin E, including interaction tests and multicollinearity diagnostics. Full details of sensitivity analyses are provided in Supplementary Material. Data analysis was performed using R software (version 4.3.1). A P-value < 0.05 was considered statistically significant.

Results

General characteristics of participants

Based on the tertiles of dietary vitamin K intake, baseline characteristics of 7857 participants are summarized in Table 1. Compared with those in the lowest tertile, participants in the higher tertiles (T2 and T3) were more likely to be men, aged 40–60 years, and to have education above high school. They generally have significantly higher HEI-2020 scores, and dietary supplement use. No significant differences were found among groups for hypertension history, diabetes history, triglyceride levels, total cholesterol, BMI categories, cardiovascular disease, or moderate-intensity exercise duration.

Univariate cox regression of factors predicting all-cause mortality in NAFLD

Univariate analysis identified several factors significantly associated with all-cause mortality in NAFLD. These factors included demographic and clinical characteristics (age, sex, race, educational level, BMI category, diabetes history, hypertension history, cardiovascular disease status), lifestyle factors (alcohol consumption history, smoking status, dietary supplement use), and dietary factors (total energy intake, total cholesterol intake, HEI-2020 score, and dietary vitamin K intake). All variables were statistically significant (P < 0.05) (Table A2 in the Appendix).

Association of dietary vitamin K intake with all-cause mortality in NAFLD

Weighted Cox proportional hazards regression model was conducted to analyze the relationship between In (dietary vitamin K intake) and all-cause mortality risk in participants with NAFLD. Over a total follow-up period of 180 months, 842 all-cause deaths were recorded. Table 2 presents the results from three Weighted Cox regression model analyses. Non-adjusted Model and Adjust Model I indicate downward trends between In (dietary vitamin K intake) and all-cause mortality in participants with NAFLD (P for trend < 0.05). After adjusting for age, sex, race, educational level, BMI category, alcohol consumption status, HEI-2020 score, dietary supplement use, total cholesterol, triglycerides, hypertension history, diabetes history, total energy intake, cardiovascular disease and smoking status in the Adjusted Model II, the HRs and 95% confidence intervals (CIs) were 1.00 (reference), 0.76(0.62,0.93), 0.76(0.54,1.08), for the T1,T2, and T3 groups, respectively, for all-cause mortality (P for trend = 0.028). The continuous models indicate that every one-unit increase in the In(dietary vitamin K intake) was associated with an reduced risk of 0.81(0.67,0.98) for all-cause mortality after adjusting for confounding factors (Table 2).

Non-linear relationship between dietary vitamin K intake and all-cause mortality

Utilizing Cox proportional hazards regression models with restricted cubic splines, the association between the In (dietary vitamin K intake) and all-cause mortality was examined. A non-linear relationship was observed between the In (dietary vitamin K intake) and mortality incidence (Fig. 2). Additionally, inflection points for all-cause mortality were identified as 4.71 (Table 3).

Impact of dietary vitamin K intake on all-cause mortality risk: threshold analysis

As shown in Table 3, after adjusting for various factors, the risk of all-cause mortality decreased by 33% (HR: 0.67, 95% CI 0.55, 0.81) for each unit increase in In(dietary vitamin K intake) below the threshold value (P < 0.001). However, the In (dietary vitamin K intake) above the threshold value did not significantly associate with the risk of all-cause mortality (P > 0.05).

Survival analysis of dietary vitamin K intake: stratified mortality rates by intake levels

We grouped the study population based on In (dietary vitamin K intake) (< 4.71, ≥ 4.71) and divided these two groups into three quantiles to generate survival curves. Interestingly, In (dietary vitamin K intake) stratified survival curves demonstrated that significant differences in mortality rates among groups persisted in the population with In (dietary vitamin K intake) < 4.71 (All-cause mortality: P $_{\text{for log-rank test}}$ = 0.0037, Fig. 3B). However, the differences in mortality among patients with In (dietary vitamin K intake) ≥ 4.71 did not reach statistical significance (All-cause mortality: P for log-rank test = 0.20, Fig. 3A).

E-value

The E-value of 1.88 suggests that an unmeasured confounder would need a relative risk of at least 1.88 for both dietary vitamin K intake and NAFLD mortality to explain the observed association, indicating the relationship is robust against confounding.

Subgroup analysis and model evaluation

Table 4 presents the results of a stratified subgroup analysis by age, sex, education level, hypertension history, alcohol consumption history, dietary supplement use, HEI-2020 score, diabetes history, and cholesterol levels. No significant interactions were observed among the subgroups. The ROC curve in Fig. 4 illustrates that when using In (dietary vitamin K intake) to assess survival status, the fully adjusted model demonstrated superior discriminatory power and accuracy than the univariate Cox regression model. The AUC value of the fully adjusted model was 0.832, which is significantly higher than that of the unadjusted model (P < 0.001).

Discussion

This nationwide study revealed a nonlinear association between dietary vitamin K intake and all-cause mortality in U.S. adults with NAFLD, characterized by a threshold at 121 μg/day using restricted cubic spline analysis (P-nonlinearity < 0.001). These findings suggest that maintaining dietary vitamin K intake near the identified

Variables	T1, N = 2922(33%)	T2, N = 2602(33%)	T3, N = 2333(34%)	P-value
Age(years)				0.001
20–40 y	706 (28%)	608 (27%)	479 (21%)	
40–60 y	1213 (45%)	1204 (48%)	1128 (52%)	
>60 y	1003 (27%)	790 (25%)	726 (27%)	
Gender, n (%)				0.010
Female	1435 (47%)	1144 (44%)	1020 (41%)	
Male	1487 (53%)	1458 (56%)	1313 (59%)	
Race, n (%)				< 0.001
Mexican American	1000 (20%)	845 (20%)	532 (12%)	
Non-hispanic black	215 (4.2%)	195 (4.1%)	228 (4.6%)	
Non-hispanic white	1147 (62%)	1045 (63%)	1029 (68%)	
Other race	560 (14%)	517 (13%)	544 (15%)	
Education level, n (%)				< 0.001
Above high school	987 (42%)	1163 (52%)	1325 (65%)	
High school	729 (30%)	658 (29%)	491 (22%)	
Below high school	1206 (28%)	781 (20%)	517 (13%)	
Hypertension history, n (%)				0.20
Yes	1291(44%)	1145 (43%)	1123(47%)	
No	1625(56%)	1451(57%)	1208(53%)	
Diabetes History, n (%)	990 (29%)	849 (27%)	807 (29%)	0.50
Triglyceride (mmol/L)	1.75(1.24,2.56)	1.75(1.25,2.50)	1.73(1.20,2.63)	0.80
Total cholesterol (mmol/L)	5.02(4.32,5.74)	4.99(4.32,5.66)	5.02(4.37,5.77)	0.40
BMI group, n (%)				0.20
Normal weight group	184 (5.4%)	115 (3.6%)	127 (4.5%)	
Overweight group	790 (24%)	722 (25%)	631 (26%)	
Obesity group	1948(71%)	1765 (71%)	1575 (70%)	
Alcohol consumption history, n (%)	292(11%)	313(14%)	332(17%)	< 0.001
Smoking Status, n (%)				< 0.001
Current smoker	599(22%)	424(18%)	298(13%)	
Former smoker	776(27%)	716(27%)	679(30%)	
Never smoker	1545(51%)	1461(56%)	1355(57%)	
Total energy intake(kcal)	1638(1244,2061)	2029(1622,2563)	2136(1741,2679)	< 0.001
HEI-2020 Score(0–100)	45(37,53)	48(41,57)	53(45,61)	< 0.001
GGT(U/L)	28(20,42)	27(20,42)	28(21,44)	0.20
Total bilirubin (μmol/L)	10.3 (6.8, 12.0)	10.3 (6.8, 13.7)	10.3 (6.8, 12.0)	0.12
AST (U/L)	24 (20, 29)	24 (20, 29)	24 (20, 29)	> 0.9
ALP(IU/L)	73 (60, 91)	73 (60, 87)	72 (59, 86)	0.062
ALT(U/L)	25 (19, 35)	26 (20, 37)	26 (19, 36)	0.2
Dietary supplement use, n (%)				< 0.001
Yes	1198(44%)	1274(51%)	1324(59%)	
No	1722(56%)	1328(49%)	1009(41%)	
Moderate-intensity exercise duration (min/day)	45 (30, 60)	45 (30, 60)	45 (30, 60)	0.8
Cardiovascular disease, n (%)	395 (12%)	292 (10%)	271 (10%)	0.2

Table 1. Baseline characteristics of In(dietary vitamin K intake) in different subgroups of NAFLD. AST, aspartic transaminase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index (kg/m^2). Normal weight group: BMI < 25 kg/m^2, Overweight group: BMI 25–30 kg/m^2, Obesity group: BMI > 30 kg/m^2. HEI2020 = Healthy Eating Index 2020. Scores range from 0 to 100, with higher scores indicating better adherence to dietary guidelines; aminotransferase; GGT: Gamma-glutamyltransferase. T: tertiles of dietary vitamin K intake (T1: lowest tertile of dietary vitamin K intake, T2: middle tertile of dietary vitamin K intake, T3: highest tertile of dietary vitamin K intake); P: Probability value indicating the likelihood that the observed results occurred by chance. A lower P-value (typically < 0.05) suggests statistical significance.

Subgroup	Non-adjusted model		Adjust model I		Adjust model II	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
In(dietary vitamin K intake)	0.8(0.68,0.93)	0.004	0.80(0.69,0.94)	0.006	0.81(0.67,0.98)	0.033
T1	Reference		Reference		Reference	
T2	0.70(0.59,0.84)	< 0.001	0.74(0.61,0.89)	0.002	0.76(0.62,0.93)	0.008
T3	0.73(0.56,0.96)	0.024	0.74(0.55,0.99)	0.039	0.76(0.54,1.08)	0.12
P for trend	< 0.001		0.004		0.028	

Table 2. Relationship between In (dietary vitamin K intake) and all-cause mortality in NAFLD. HR, hazard ratio; CI, confidence interval; T, tertiles of dietary vitamin K intake (T1: lowest tertile of dietary vitamin K intake, T2: middle tertile of dietary vitamin K intake, T3: highest tertile of dietary vitamin K intake); P: Probability value indicating the likelihood that the observed results occurred by chance. A lower P-value (typicall < 0.05) suggests statistical significance. Adjusted Model I: Age, sex, race, educational level. Adjusted Model II: Age, sex, race, educational level, BMI category, alcohol consumption status, HEI-2020 score, dietary supplement use, total cholesterol, triglycerides, hypertension history, diabetes history, total energy intake, cardiovascular disease, and smoking status.
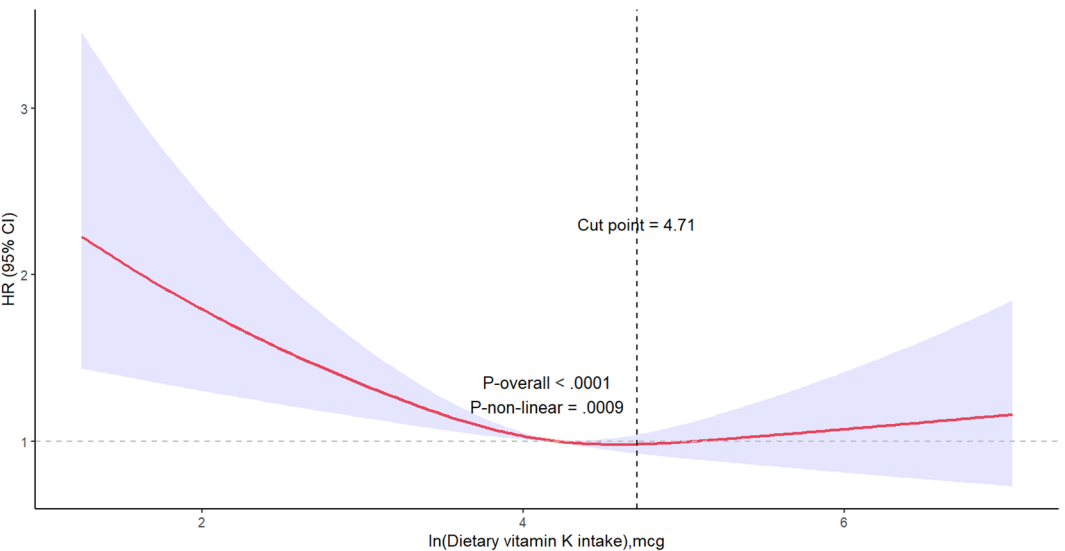

Fig. 2. Nonlinear relationship between In(Dietary Vitamin K Intake) and All-Cause Mortality in NAFLD Adjust for: Age, sex, race, education level, BMI group, alcohol consumption status, HEI-2020 score, dietary supplement use, total cholesterol, triglycerides, hypertension history, diabetes history, total energy intake, cardiovascular disease and smoking status. HR: Hazard Ratio. The red line represents HR, and the blue shaded area represents the 95% confidence interval.

threshold (121 µg /day)-equivalent to 100 g of cooked spinach or 150 g of broccoli daily-may optimize survival benefits in NAFLD, avoiding both insufficiency and pharmacologically redundant high intake.

The observed non-linear relationship between dietary vitamin K intake and mortality in NAFLD patients-marked by a maximal protective effect at 121 µg/day—aligns with biological saturation kinetics. Vitamin K serves as an obligate cofactor for the γ-carboxylation of glutamic acid residues in hepatic proteins, most notably matrix Gla protein (MGP) and osteocalcin[22–24]. In cardiovascular health, carboxylated MGP (cMGP) directly inhibits vascular calcification by sequestering calcium phosphate crystals[25], a process critical for NAFLD patients who exhibit amplified calcification risks due to chronic inflammation and insulin resistance[26]. Our threshold of 121 µg/day likely represents the intake required to achieve near-maximal carboxylation of these proteins; beyond this point, excess vitamin K no longer enhances activity, as evidenced by the plateau in mortality reduction (HR 1.07 beyond 121 µg/day).

Significant thresholds were identified in previous studies. For example, In the Danish cohort (n = 56,048), mortality risk decreased by 24% (HR 0.76) when vitamin K1 intake increased from the lowest quintile (median 57 µg/day) to the highest (192 µg/day), with benefits plateauing at ≥ 87 µg/day[27]. In U.S. adults (n = 37,037), achieving sex-specific Adequate Intake (AI) levels (90 µg/day for women; 120 µg/day for men) via diet reduced mortality by 21% (RR = 0.79)[28]. High-risk cohorts further illustrate threshold variability. Chronic kidney disease (CKD) patients meeting AI levels (men = 120 µg/day; women = 90 µg/day) exhibited a 15% mortality reduction (HR 0.85), though only 28% achieved this intake[29], while Danish atherosclerotic cardiovascular disease (ASCVD) cohorts required higher doses (192 µg/day) for maximal protection (HR 0.76, highest quintile [192

	Non-adjusted model		Adjusted model I		Adjusted model II	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
In(dietary vitamin K intake) > 4.71	1.09 (0.69,1.73)	0.7	1.03 (0.68,1.56)	0.90	1.07(0.67,1.71)	0.80
In(dietary vitamin K intake) tertile						
T1	Reference		Reference		Reference	
T2	1.07 (0.69,1.65)	0.80	1.08 (0.70,1.68)	0.70	1.21(0.76,1.92)	0.40
T3	1.11 (0.66,1.87)	0.70	1.17 (0.71,1.93)	0.50	1.32(0.73,2.37)	0.40
P for trend	> 0.90		0.9		0.6	
In (dietary vitamin K intake) < 4.71	0.66 (0.54,0.81)	< 0.001	0.67 (0.54,0.84)		0.67 (0.55,0.81)	< 0.001
In (dietary vitamin K intake) tertile						
T1	Reference		Reference		Reference	
T2	0.74 (0.58,0.96)	0.021	0.70 (0.54,0.90)	0.005	0.70 (0.57,0.86)	< 0.001
T3	0.60 (0.49,0.74)	< 0.001	0.66 (0.52,0.83)	< 0.001	0.67 (0.50,0.90)	0.007
P for trend	< 0.001		< 0.001		0.001	

Table 3. Segmented Cox regression analysis and trend test of In (dietary vitamin K intake). Adjusted Model I: Age, sex, race, educational level. Adjusted Model II: Age, sex, race, educational level, BMI category, alcohol consumption status, HEI-2020 score, dietary supplement use, total cholesterol, triglycerides, hypertension history, diabetes history, total energy intake, cardiovascular disease and smoking status.
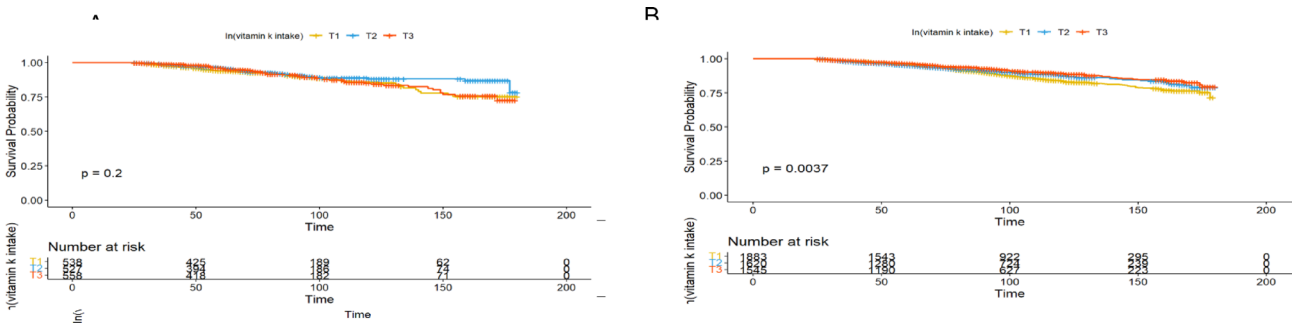

Fig. 3. Kaplan–Meier survival curves based on Ln (dietary vitamin K intake). A: In (dietary vitamin K intake) > 4.71, B: In (dietary vitamin K intake) < 4.71. T: tertiles of dietary vitamin K intake (T1: lowest tertile, T2: middle tertile,T3: highest tertile). Note: The cutoff point of 4.71 was identified based on a segmented Cox regression analysis, corresponding to a dietary vitamin K intake of 121 µg/day.

ug/day]) vs. lowest quintile [57ug/day])[27]. This variability extends to populations with baseline intakes exceeding physiological demands. In the EPIC-NL cohort (median = 170 µg/day)[30], no incremental benefit was observed, mirroring our findings of a plateau above 121 µg/day in NAFLD patients. The threshold in our NAFLD cohort (121 µg/day) approximates the U.S. male AI (120 µg/day)[31], yet exceeds the median national intake range (85–120 µg/day) and general population thresholds (87–90 µg/day). This divergence likely reflects disease-specific metabolic demands, such as upregulated hepatic MGP carboxylation in steatosis to counteract inflammation and calcification[26]. In NAFLD patients, vitamin K intake below 121ug/day was associated with a 33% reduction in all-cause mortality (adjusted HR 0.67), significantly greater than the reductions observed in CKD (15%[28] and general populations (21–24%)[25,26]. This discrepancy underscores the necessity of higher vitamin K intake for optimal protection in NAFLD. Notably, our identified threshold (120 µg/day) aligns closely with the USDA Dietary Guidelines' Adequate Intake (AI) for men (120 µg/day) but exceeds the recommended level for women (90 µg/day)[29].While the median U.S. vitamin K intake (85–120 µg/day) recorded in the Food and Nutrient Database for Dietary Studies (FNDDS) meets nutritional adequacy standards, it remains below the optimal threshold (121 µg/day) associated with maximal mortality reduction in NAFLD patients. This disparity suggests that NAFLD imposes unique physiological demands-likely through increased hepatic requirements for vitamin K-dependent processes (e.g., MGP activation to counteract steatosis-related calcification)-rather than reflecting simple population-wide deficiency[26]. These findings underscore that vitamin K thresholds are not fixed; instead, they dynamically adapt to three key factors: baseline intake levels, disease-driven metabolic priorities (e.g., MGP activation in NAFLD vs. vascular protection in CKD), and clinical endpoints (all-cause vs. disease-specific mortality).

Beyond cardiovascular benefits, vitamin K may mitigate NAFLD progression by suppressing inflammatory drivers. Chronic inflammation promotes steatosis-to-NASH transition via NF-kB-mediated cytokine release (e.g., TNF-α, IL-6)[26,32]. Vitamin K attenuates this process by inhibiting NF-kB nuclear translocation, potentially reducing fibrosis and hepatocellular carcinoma risk. Vitamin K has been shown to improve insulin sensitivity

	Non-adjusted model		Adjust model I		Adjust model II		
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	$P_{interaction}$
Age group (n, %)							0.50
20–64	0.58 (0.41,0.81)	0.002	0.59 (0.43,0.81)	0.001	0.65 (0.51,0.84)	< 0.001	
> 64	0.74 (0.63,0.88)	< 0.001	0.75(0.63,0.89)	< 0.001	0.76 (0.61,0.94)	0.012	
Gender (n, %)							0.80
Male	0.66(0.50,0.89)	0.005	0.71(0.51,0.97)	0.034	0.72 (0.52,0.98)	0.035	
Female	0.65(0.54,0.78)	< 0.001	0.62(0.51,0.74)	< 0.001	0.64(0.50,0.80)	< 0.001	
Education Level (n, %)							0.60
High school or below	0.57 (0.37,0.87)	0.009	0.61 (0.39,0.94)	0.026	0.58(0.42,0.80)	0.001	
High school	0.80 (0.62,1.04)	0.10	0.74(0.56,0.97)	0.030	0.78(0.58,1.05)	0.100	
Above high school	0.69 (0.55,0.85)	< 0.001	0.68(0.55,0.85)	< 0.001	0.70(0.54,0.92)	0.010	
Hypertension History (n,%)							0.20
Yes	0.66(0.53,0.82)	< 0.001	0.65(0.51,0.83)	< 0.001	0.67(0.51,0.87)	0.003	
No	0.67(0.50,0.90)	0.009	0.71(0.54,0.94)	0.016	0.73(0.54,0.98)	0.036	
Alcohol consumption history (n, %)							0.40
Yes	0.65(0.35,1.20)	0.200	0.51(0.26,1.00)	0.050	0.43(0.20,0.92)	0.030	
No	0.67(0.55,0.81)	< 0.001	0.69(0.56,0.86)	< 0.001	0.69(0.56,0.87)	0.001	
Dietary supplements use (n, %)							0.80
Yes	0.62(0.49,0.77)	< 0.001	0.63(0.48,0.81)	< 0.001	0.65(0.50,0.86)	0.002	
No	0.76(0.60,0.95)	0.015	0.78(0.62,0.98)	0.031	0.73(0.58,0.93)	0.010	
HEI-2020 Score							> 0.90
Higher group	0.68(0.56,0.81)	< 0.001	0.69(0.58,0.83)	< 0.001	0.83(0.65,1.05)	0.11	
Lower group	0.59(0.46,0.77)	< 0.001	0.63(0.47,0.85)	0.002	0.66(0.49,0.89)	0.006	
Diabetes History (n, %)							0.14
Yes	0.59(0.45,0.78)	< 0.001	0.60(0.44,0.80)	< 0.001	0.60(0.44,0.80)	< 0.001	
No	0.74(0.63,0.86)	< 0.001	0.76(0.64,0.91)	0.002	0.76(0.64,0.91)	0.002	
Cholesterol Levels							0.10
Hypercholesterolemia	0.66(0.55,0.78)	< 0.001	0.67(0.55,0.81)	< 0.001	0.67(0.55,0.81)	< 0.001	
Hypocholesterolemia	0.70(0.60,0.82)	< 0.001	0.78(0.65,0.94)	0.010	0.81 (0.61,1.01)	0.059	

Table 4. Segmented subgroup analysis of In (dietary vitamin K intake). Adjusted Model I: Age, sex, race, educational level. Adjusted Model II: Age, sex, race, educational level, BMI category, alcohol consumption status, HEI-2020 score, dietary supplement use, total cholesterol, triglycerides, hypertension history, diabetes history, total energy intake, cardiovascular disease and smoking status.
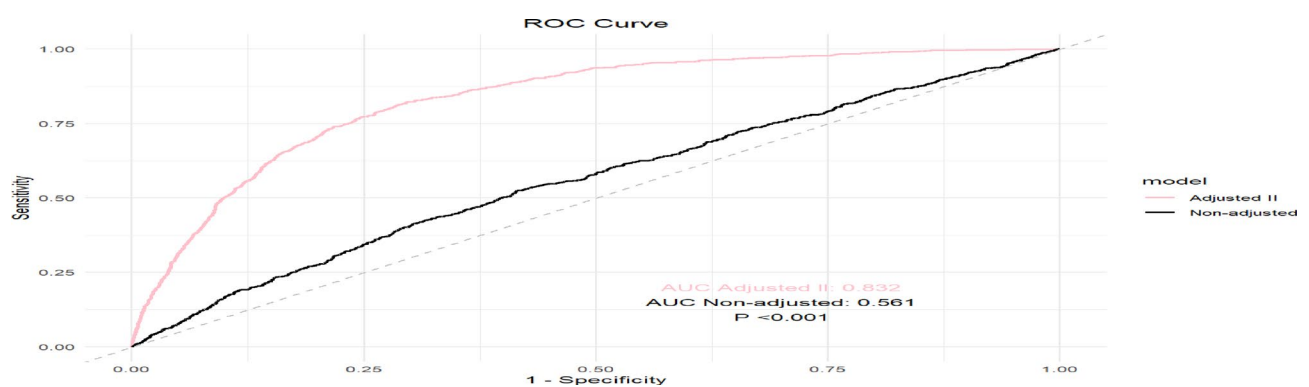

Fig. 4. Comparison of ROC curves for fully adjusted and univariate cox regression models in asessing survival status using In (Dietary Vitamin K intake). The ROC curves compare the performance of the Multivariate Cox Model (Adjusted II model, adjusted for Age, sex, race, educational level, BMI category, alcohol consumption status, HEI-2020 score, dietary supplement use, total cholesterol, triglycerides, hypertension history, diabetes history, total energy intake, cardiovascular disease and smoking status.) and the Univariate Cox Model in predicting survival based on natural log-transformed dietary vitamin K intake without additional covariates.

by enhancing insulin receptor substrate (IRS) phosphorylation, which promotes insulin signaling. This is particularly relevant for NAFLD patients, as insulin resistance is a major driver of hepatic fat accumulation and subsequent liver injury.

The null association above 121 µg/day may also reflect nutrient interactions. High-dose vitamin K and E compete for hepatic metabolism via CYP4F2-mediated ω-hydroxylation[33] and rodent studies show α-tocopherol (vitamin E) supplementation reduces plasma phylloquinone (vitamin K1) levels[34]. This aligns with our sensitivity analysis showing attenuation of the vitamin K-mortality association after vitamin E adjustment (HR: 0.81 → 0.85, ΔHR = +0.04). This effect may primarily reflect dietary collinearity (e.g., shared food sources like spinach and broccoli) rather than direct biological antagonism, as the threshold effect persisted in fully adjusted models. Finally, the observed threshold (121 µg/day) likely represents synergistic benefits of nutrient-dense diets (e.g., combined effects of vitamin K, polyphenols, and fiber) rather than isolated vitamin K effects. While we adjusted for the Healthy Eating Index-2020, residual confounding by unmeasured dietary components cannot be excluded. Future studies should integrate biomarkers (e.g., plasma phylloquinone, α-tocopherol) and metabolomics to disentangle these relationships.

Our study demonstrated that dietary vitamin K intake is a significant predictor of all-cause mortality in NAFLD patients, as indicated by the ROC curve with an AUC value of 0.832. This suggests that dietary vitamin K intake can effectively discriminate between patients at higher and lower risk of mortality. In clinical practice, this finding could help physicians assess patient risk and develop personalized interventions. For example, NAFLD patients with insufficient vitamin K intake may benefit from dietary modifications or supplementation to reduce the mortality risk. However, despite the promising predictive power of vitamin K intake, further randomized controlled trials are needed to establish a causal relationship and confirm the applicability of these findings in broader populations.

This study provides important insights into the role of dietary vitamin K in reducing mortality among NAFLD participants. The identification of a threshold effect at 121 µg/day has significant clinical implications, suggesting that increasing vitamin K intake in patients with low baseline levels may confer significant survival benefits. From a public health policy perspective, these findings support the advocacy of vitamin K-rich diets, particularly in populations at high risk for NAFLD. Achieving the vitamin K threshold of 121 µg/day can be practically accomplished through common dietary sources. For example, 25 g raw spinach (~ 120 µg) or 65 g steamed broccoli (~ 100 µg) alone meet the target. Alternatively, combining smaller portions: 15 g spinach (72 µg) with 50 g romaine lettuce (48 µg) plus 1 tsp olive oil provides sufficient intake (total 128 µg). These strategies align with Mediterranean dietary patterns by emphasizing plant-based fats and vegetables.

Strengths

This study addresses a gap in the existing literature by investigating the long-term relationship between dietary vitamin K intake and all-cause mortality in NAFLD participants. We identified both linear and non-linear associations, calculated cutoff points, and demonstrated the predictive value of vitamin K intake. This study has several notable strengths. We utilized data from the NHANES, a nationally representative cohort with rigorous data collection protocols, ensuring high generalizability to the U.S. population. Our analysis incorporated a comprehensive adjustment for potential confounders, including demographic, lifestyle, and clinical variables, enhancing the robustness of the observed associations. The use of restricted cubic splines allowed us to identify a non-linear relationship and a clinically relevant threshold (121 µg/day), which may guide dietary recommendations. Additionally, sensitivity analyses and subgroup assessments demonstrated consistent results, further supporting the reliability of our findings. Finally, the application of the E-value method strengthened our conclusion by quantifying the potential impact of unmeasured confounding.

Limitations

Despite these strengths, our study has several limitations. hypertension status was self-reported, which may introduce misclassification bias; dietary vitamin K intake was assessed via two non-consecutive 24-h recalls, while this method reduces day-to-day variability compared to single-day records, it may not fully capture habitual intake, and results could be influenced by recall bias or seasonal variations in food consumption (e.g., higher leafy greens intake in summer);the observational design precludes causal inference, necessitating future randomized trials to confirm our findings; NAFLD diagnosis relied on the US-FLI rather than gold-standard methods (e.g., liver biopsy or imaging), potentially misclassifying cases; residual confounding may persist despite extensive adjustments. For instance, we lacked data on physical activity intensity (a potential modifier of NAFLD progression) and socioeconomic factors (e.g., income, healthcare access) that influence dietary patterns; cancer history was not included as a covariate due to extensive missing data (90.4% missingness) and potential misclassification from self-reports (MCQ220). Failure to adjust for this variable may have introduced residual confounding, as cancer survivors may exhibit distinct dietary behaviors (e.g., higher consumption of vitamin K-rich vegetables) and elevated mortality risk unrelated to NAFLD mechanisms. Future studies should integrate longitudinal dietary assessments, such as food frequency questionnaires (FFQs) -with plasma phylloquinone biomarkers to improve validity.

Conclusion

Our study identified dietary vitamin K as a reliable predictor of all-cause mortality in NAFLD participants. Specifically, Higher dietary vitamin K intake is associated with reduced all-cause mortality in NAFLD participants, with a threshold effect observed at 121 µg/day. Dietary vitamin K intake may serve as a useful predictor of survival in this population. These findings have important implications for dietary guidelines and public health approaches targeting the reduction of mortality risk in NAFLD participants.

Data availability

The data used in this study can be accessed from the National Health and Nutrition Examination Survey (NHANES) at the following link: https://www.cdc.gov/nchs/nhanes/index.htm.

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Author contributions

Yu Huang designed the study, wrote the R code, and drafted the manuscript. Xianfeng Zhu collected and cleaned the data. Liang Han conducted secondary analysis and correction of the R code, and reanalyzed the data. Hulan Hu reviewed and revised the manuscript.All authors reviewed the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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