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Association between saturated and polyunsaturated fatty acid proportions in total fat intake and mortality risk: mediation by the neutrophil percentage-to-albumin ratio

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Abstract

Background For over half a century, dietary guidelines have consistently advocated for the substitution of saturated fatty acids (SFA) with monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) as a cornerstone strategy for health life, but evidence on independent associations between specific fatty acids and mortality remains inconsistent.

Methods This prospective cohort study from the National Health and Nutrition Examination Survey (NHANES) 2007–2018 analyzed 21,823 participants aged 20–80 years. Survey-weighted Cox regression assessed associations between SFA, MUFA, PUFA intake, and their ratios to the total fat (TFAT) intake quantity, and all-cause mortality. Mediation analyses examined whether the neutrophil percentage-to-albumin ratio (NPAR) mediated the effects of fatty acid-related parameters on mortality risk.

Results In multivariable-adjusted models, no significant trends were observed for all-cause mortality across tertiles of SFA, MUFA, or PUFA intake. In multivariable-adjusted Cox models, the highest tertile of SFA/TFAT ratio was significantly associated with elevated mortality risk (HR = 1.23, p for trend < 0.01). Conversely, the highest PUFA/TFAT tertile demonstrated a protective association (HR = 0.86, p for trend < 0.01). However, the MUFA/TFAT ratio showed no significant mortality association across tertiles (p for trend = 0.137). Mediation analysis revealed that NPAR mediated 9.8% and 11.8% of SFA/TFAT and PUFA/TFAT effects on mortality risk, suggesting partial mediation through a shared inflammatory pathway.

Conclusion This study provides the novel evidence that the proportional composition of dietary fatty acids within total fat intake—rather than their absolute intake levels—is a critical determinant of longevity. By demonstrating

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that replacing SFA with PUFA reduces mortality risk through NPAR-mediated inflammatory pathways, our findings inform the World Health Organization's 2023 guidelines on dietary fat modification. These results shift the paradigm from isolated nutrient restrictions to balanced fatty acid ratios, offering a novel mechanistic basis for public health strategies aimed at extending healthy lifespan.

Keywords Saturated fatty acid, Monounsaturated fatty acid, Polyunsaturated fatty acid, Mortality, NHANES

Introduction

Since 1961, the American Heart Association has advocated for reduced dietary intake of SFA while promoting their substitution with unsaturated fatty acids. This dietary recommendation was a cornerstone of global nutritional guidelines [1, 2]. Biochemically classified by hydrocarbon chain saturation, fatty acids comprise three categories: saturated (SFA, single bonds), monounsaturated (MUFA, one double bond), and polyunsaturated (PUFA, multiple double bonds), each exhibiting distinct health-related properties [3, 4]. Evidence from several studies substantiated this paradigm's efficacy in primary prevention and clinical management of metabolic syndrome-related comorbidities [5–8].

However, current evidence revealed that conclusions from studies investigating the impact of saturated and unsaturated fats on survival outcomes remain conflicting. Prospective cohort studies and meta-analyses have generally reported inverse associations between increased intake of total fat (TFAT), MUFA, and PUFA with all-cause mortality. SFA has been consistently associated with elevated mortality risk in multiple large-scale observational studies and contemporary meta-analyses [9–11]. However, conflicting evidence persists regarding SFA's association with mortality risk, as demonstrated by non-significant associations reported in earlier meta-analyses and selected cohort studies [12, 13]. While most epidemiological analyses indicated a protective effect of PUFA intake, null associations with mortality risk reduction have been documented in specific cohort studies [12, 14]. Of particular interest is the multinational Prospective Urban Rural Epidemiology (PURE) study, which revealed inverse associations between mortality and SFA [15], suggesting potential variations in these associations across populations or dietary contexts.

The World Health Organization (WHO) has recently issued updated dietary guidelines recommending the substitution of SFA with PUFA and MUFA as an evidence-based strategy for mitigating the risk of diet-related non-communicable diseases across adult and pediatric populations [16]. The guideline proposes a dietary modification strategy that adjusts the relative proportions of fatty acid subtypes while maintaining constant total fat-derived energy intake. However, there remains a paucity of studies investigating the association between proportional intake of different fatty acid subtypes within total fat consumption and all-cause mortality. This cohort study analyzed the independent intake of different fatty acids and their relative proportions in total fat intake to all-cause mortality risk. Dietary replacement of SFA with unsaturated fatty acids might modulate inflammatory responses by suppressing pro-inflammatory pathways and mediators, thereby reducing the risks of inflammation-related diseases [17–19]. The neutrophil percentage-to-albumin ratio (NPAR), an emerging prognostic biomarker integrating inflammatory and nutritional status, has been established as an independent predictor of all-cause mortality across a spectrum of common chronic disorders [20–23]. We pioneer investigating whether NPAR mediates the association between specific fatty acids and mortality risk.

To our knowledge, this is the first study to comprehensively assess the all-cause mortality risk associated with the proportional balance of three major fatty acid subtypes within total fat intake, rather than evaluating individual subtypes in isolation. Furthermore, we examined the mediating role of NPAR in these associations. The findings provide novel insights into the interrelationships among dietary fatty acid composition, inflammatory regulation, and mortality outcomes, offering robust evidence for preventive medicine.

Materials and methods

Study design and participants

Six survey cycles in the National Health and Nutrition Examination Survey (NHANES) 2007–2018 were integrated, with subsequent tracking until December 31, 2019. This timeframe aligns with enhanced NHANES data collection protocols implemented since 2007, which ensured standardized acquisition of core variables including physical activity metrics-critical for controlling potential confounding in mortality analyses. Initially, the 59,842 participants were enrolled in this cohort study. Then, participants aged < 20 years or > 80 years were excluded. Subsequent exclusions were applied to individuals with unavailable dietary fatty acid intake data, those lacking survival outcome documentation, and cases with incomplete covariate information, as delineated in Fig. 1. The remaining 21,823 participants were enrolled in the final cohort.

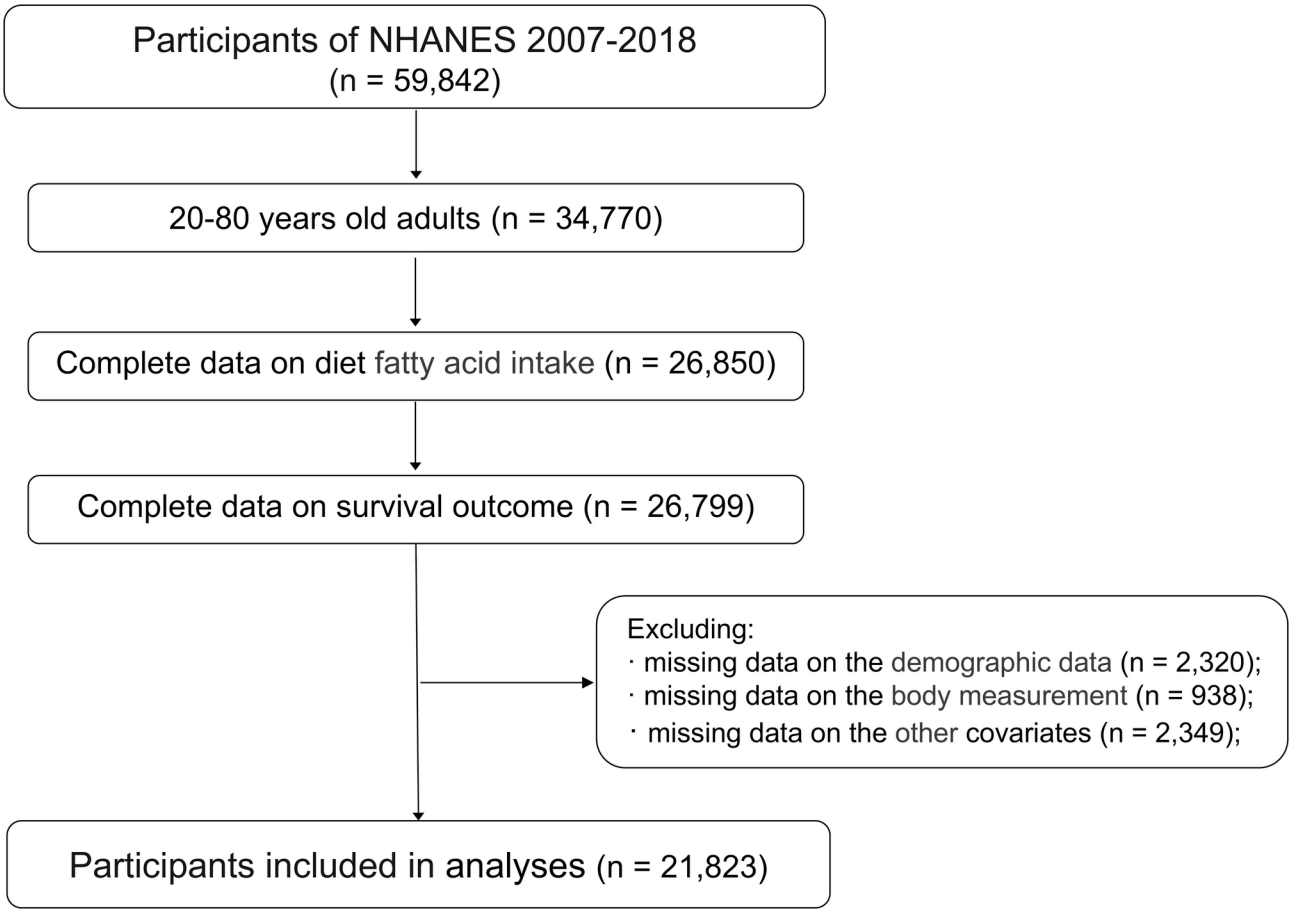

Fig. 1 Flowchart for participant recruitment in the NHANES 2007–2018

Assessment of fatty acid-related parameters in dietary intake

The primary 24-hour dietary interview was carried out by trained interviewers at a mobile examination facility, whereas the second interview was by telephone 3–10 days later. Subjects failing to complete both interviews were excluded prior to nutrient calculations to ensure data completeness, with all analyses restricted to participants providing two valid 24-hour recalls. Nutrient values were derived from the US Department of Agriculture National Nutrient Database for Standard Reference [24]. Dietary intake levels of energy (kcal/day), protein, total fat, and three fatty acid subtypes (total SFA, MUFA, and PUFA) were quantified as daily values using averaged data from both interviews, with protein and fat-related components expressed in grams per day (g/day). Specifically, the ratios of SFA, MUFA, and PUFA to total fat intake (expressed as SFA/TFAT, MUFA/TFAT, and PUFA/TFAT, respectively) were calculated by dividing the absolute intake (in grams/day) of each fatty acid subtype by the total daily fat consumption (in grams/day). These ratios reflect the relative contribution of individual fatty acid subtypes to overall fat intake.

Survival outcome

Participant mortality was ascertained through linkage with the National Death Index, specifically capturing all-cause mortality. The follow-up duration was calculated from the baseline interview date until the occurrence of death or the censoring date of 31 December 2019, whichever occurred first.

Mediators of NPAR

Potential mediators were considered the factors hypothesized to affect the path from exposure to outcome. The hematology analyzer was the Beckman Coulter, and the whole blood count differential used VCS technology. Neutrophil percentage was calculated using the ratio of segmented neutrophils to white blood cell count. The serum albumin levels were assessed using Roche Modular P and Roche Cobas 6000 chemical analyzers. NPAR was calculated as a neutrophil percentage (%) × 100/Albumin (g/dL).

Assessment of covariates

The present study collected covariate data including demographic characteristics, physical examination

measurements, laboratory blood test results, and medical histories [1]. Demographic data included age, gender, ethnicity, education, family poverty-to-income ratio (FMPIR), and smoking [2]. Physical examination included body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). BMI was the ratio of weight (kg) to height (m) squared. SBP and DBP were calculated as the average of four measurements [3]. Clinical indicators, including glycosylated hemoglobin (HbA1c), total cholesterol (TC), alanine aminotransferase (ALT), and serum creatinine were collected. TC levels were measured on a Roche Modular P or Roche Cobas 6000 chemical analyzer in different NHANES cycles. A Beckman 5,800 automatic biochemical analyzer was utilized to measure HbA1c, ALT, and serum creatinine levels. The estimated glomerular filtration rate (eGFR) was calculated using the collaboration of chronic kidney disease epidemiology. (4) The questionnaire data included physical activity levels and diagnoses of hypertension and diabetes. The 2018 Physical Activity Guidelines for Americans suggested that the total weekly PA duration was calculated as minutes of the vigorous intensity multiplied by 2 and added to minutes of the moderate intensity for each PA. Hypertension was defined as average SBP ≥ 140 mmHg or DBP ≥ 90 mmHg measured on MEC vehicles or current use of antihypertensive medications. Diabetes was identified as antihyperglycemic therapy, diagnosed by a doctor, a blood HbA1c level ≥ 6.5%, FBG level ≥ 7.0 mmol/L, or random plasma glucose level ≥ 11.1 mmol/L.

Statistical analysis

The baseline characteristics were examined by classifying participants according to survival state. Continuous variables were initially assessed for normality using the Shapiro-Wilk test combined with quantile-quantile plots. Based on the distributional characteristics, the non-normally distributed variables were presented as medians with interquartile ranges (25th-75th percentiles). Cox proportional hazards models were constructed using survival time calculated from the baseline survey date to the date of death or study cutoff (December 31, 2019). The Cox proportional hazards regression models were constructed to assess the associations between tertiles of fatty acid-related variables (stratified by SFA/TFAT, MUFA/TFAT, and PUFA/TFAT ratios) and all-cause mortality risk. Three models were constructed: Model 1 was unadjusted; Model 2 included covariates such as age, gender, ethnicity, education, FMPIR, smoking, physical activity, and the total energy, protein, and fat from dietary intake. Model 3 was adjusted for all the variables in Model 2 and BMI, SBP, DBP, HbA1c, TC, ALT, eGFR, hypertension, and diabetes. To address violations of the proportional hazards (PH) assumption, age was stratified into three categories (20–39, 40–59, ≥ 60 years) using the strata function. Additionally, eGFR was categorized into five groups based on chronic kidney disease staging guidelines: ≥ 90 (Stage 1), 60–89 (Stage 2), 30–59 (Stage 3), 15–29 (Stage 4), and < 15 mL/min/1.73 m^2 (Stage 5). Model assumptions were verified via Schoenfeld residual tests, with a global p-value > 0.05 indicating adherence to the PH assumption. Overall model significance was assessed using likelihood ratio tests and Wald tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were derived from the Cox regression analyses to quantify associations between fatty acid-related parameters and mortality risk. Additionally, weighted linear regression models assessed the relationship between fatty acid-related variables and NPAR. To explore nonlinear relationships after controlling for confounders, restricted cubic splines (RCS) were applied to determine trends between fatty acid-related parameters and mortality. The subgroup analyses were performed using the fully adjusted Model 3 to evaluate potential effect modifications. Specifically, likelihood ratio tests (LRT) were applied to assess interactions between fatty acid ratios (SFA/TFAT and PUFA/TFAT) and prespecified subgroup variables (age, gender, ethnicity, smoking status, BMI, physical activity and baseline comorbidities). The LRT compared two nested Cox proportional hazards models: the null model (without interaction terms) and the alternative model (with interaction terms). The test statistic followed a chi-squared distribution with degrees of freedom equal to the difference in the number of parameters between the two models. A significant interaction ($P < 0.05$) indicated heterogeneity in the exposure-outcome association across subgroups.

To investigate whether the observed effects of fatty acid-related parameters on mortality could be mediated via NPAR, causal mediation analyses were conducted using the 'mediation' package in R. SFA/TFAT and PUFA/TFAT were analyzed as continuous variables scaled by their interquartile ranges (IQRs). Weibull survival regression models were used to estimate log-time ratios, with effects expressed per IQR increase in fatty acid percentages. Mediation analyses compared effects between the 25th and 75th percentiles of fatty acid distributions. Statistical computations were performed using R version 4.4.2, with p-values < 0.05 considered statistically significant (two-tailed).

Results

Descriptive statistics

The characteristics of 21,823 participants were grouped by survival outcome (Table 1). Deceased individuals demonstrated a higher prevalence of older age, male, non-Hispanic White ethnicity, smoking, and lower socioeconomic indicators (education and income levels). The

Table 1 Descriptive statistics of participants

Characteristic	Overall (*N* = 21,823)	Survivor (*N* = 19,850)	Mortality (*N* = 1,973)
Age (years)	47.0 (33.0, 60.0)	45.0 (32.0, 58.0)	70.0 (58.0, 80.0)
Gender			
Male	10,479 (48.1%)	9312 (47.6%)	1167 (55.4%)
Female	11,344 (51.9%)	10,538 (52.4%)	806 (44.6%)
Ethnicity			
Mexican American	3136 (8.5%)	2997 (8.8%)	139 (3.6%)
Other Hispanic	2141 (5.5%)	2030 (5.7%)	111 (2.1%)
Non-Hispanic White	9816 (68.2%)	8538 (67.3%)	1278 (81.1%)
Non-Hispanic Black	4379 (10.2%)	4008 (10.2%)	371 (9.4%)
Other race	2351 (7.7%)	2277 (7.9%)	74 (3.8%)
Education			
Less than High school	4729 (14.0%)	4095 (13.3%)	634 (24.8%)
High school	4987 (22.8%)	4446 (22.5%)	541 (26.6%)
College or more	12,107 (63.2%)	11,309 (64.2%)	798 (48.6%)
FMPIR			
< 1	4511 (14.3%)	4100 (14.2%)	411 (16.1%)
1-1.99	5781 (20.4%)	5072 (19.6%)	709 (32.0%)
2-3.99	5817 (27.9%)	5287 (27.9%)	530 (28.2%)
≥ 4	5714 (37.3%)	5391 (38.3%)	323 (23.6%)
Smoking			
Never	12,167 (56.4%)	11,409 (57.6%)	758 (38.6%)
Former	5416 (24.9%)	4610 (24.0%)	806 (38.8%)
Current	4240 (18.7%)	3831 (18.5%)	409 (22.6%)
SBP (mmHg)	119.3 (110.0, 130.0)	118.7 (110.0, 129.3)	130.0 (118.0, 144.0)
DBP (mmHg)	70.7 (64.0, 78.0)	71.3 (64.0, 78.0)	66.7 (58.7, 75.3)
BMI (kg/m^2)	28.0 (24.3, 32.7)	28.0 (24.3, 32.7)	28.1 (24.3, 33.0)
HbA1c (%)	5.4 (5.2, 5.8)	5.4 (5.2, 5.7)	5.7 (5.4, 6.2)
TC (mmol/L)	4.9 (4.3, 5.7)	4.9 (4.3, 5.7)	4.9 (4.1, 5.7)
ALT (U/L)	21.0 (16.0, 28.0)	21.0 (16.0, 29.0)	19.0 (15.0, 25.0)
eGFR ($mL/min/1.73m^2$)	98.5 (83.4, 111.5)	99.4 (85.0, 112.2)	78.1 (59.8, 94.9)
NPAR	13.6 (12.1, 15.3)	13.5 (12.0, 15.2)	14.9 (13.2, 16.7)
Energy (kcal/day)	1,977.0 (1,537.0, 2,532.0)	1,994.0 (1,550.0, 2,549.5)	1,814.5 (1,380.5, 2,257.5)
Protein (g/day)	77.0 (58.7, 100.1)	77.5 (59.1, 100.7)	69.2 (53.2, 88.4)
TFAT (g/day)	75.2 (55.2, 100.7)	75.7 (55.7, 101.4)	67.6 (48.0, 89.8)
SFA (g/day)	24.1 (17.0, 33.5)	24.3 (17.0, 33.7)	22.1 (15.5, 30.1)
MUFA (g/day)	26.3 (18.9, 35.7)	26.5 (19.0, 35.9)	23.7 (16.9, 32.0)
PUFA (g/day)	16.8 (11.8, 23.3)	17.0 (12.0, 23.5)	14.6 (10.0, 20.5)
SFA/TFAT (%)	32.3 (28.4, 36.5)	32.3 (28.4, 36.4)	33.0 (28.9, 37.5)
MUFA/TFAT (%)	35.0 (32.4, 37.7)	35.0 (32.4, 37.7)	35.5 (32.5, 38.1)
PUFA/TFAT (%)	22.6 (19.0, 26.8)	22.7 (19.1, 26.9)	21.7 (18.2, 25.8)
Physical activity (minutes/week)	360.0 (60.0, 1,150.0)	400.0 (75.0, 1,200.0)	60.0 (0.0, 420.0)
Hypertension	7854 (31.2%)	6596 (29.2%)	1258 (61.5%)
Diabetes	2924 (9.7%)	2377 (8.7%)	547 (25.0%)

Based on the distributional characteristics, non-normally distributed variables were presented as medians with interquartile ranges (25th-75th percentiles). Abbreviations: FMPIR, family poverty-to-income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NPAR, neutrophil percentage-to-albumin ratio; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; TFAT, total fat; SFA/TFAT, SFA-to-TFAT ratio; MUFA/TFAT, MUFA-to-TFAT ratio; PUFA/TFAT, PUFA-to-TFAT ratio

deceased group also exhibited the elevated SBP, HbA1c, and NPAR and reduced DBP, TC, ALT, and eGFR. Notable changes in lifestyle variables included lower physical activity levels and decreased dietary intake of total energy, protein, TFAT, MUFA, and PUFA in the deceased group. Notably, this group showed a higher SFA/TFAT but lower PUFA/TFAT than survivors.

Association between fatty acid-related variables and mortality

Over the median follow-up period of 6.5 years, 1,973 deaths were ascertained. Unadjusted Cox proportional hazards models demonstrated that individuals in the highest tertile of SFA, MUFA, PUFA, and PUFA/TFAT exhibited significantly lower all-cause mortality risk compared to those in the lowest tertile, with HRs of 0.71, 0.63, 0.66, and 0.85, respectively. Conversely, the highest tertile of the SFA/TFAT ratio was associated with a 26% increased mortality risk (all $p < 0.05$). The proportional hazards assumptions were validated through Schoenfeld residual tests. Both global ($p > 0.05$ for all models) and variable-specific tests ($p > 0.05$ for all covariates) confirmed no violations of the PH assumption, supporting the effectiveness of age-stratified Cox models in addressing time-dependent bias. Likelihood ratio tests further indicated robust model fit across all analyses ($p < 0.05$). After multivariable adjustment in Model 3, only SFA/TFAT and PUFA/TFAT ratios maintained significant associations with mortality risk (all p for trend < 0.05). Specifically, the PUFA/TFAT ratio exhibited a dose-response protective relationship, with the middle tertile showing a 12% risk reduction (HR = 0.88, 95% CI = 0.79–0.98) and the highest tertile demonstrating a 14% lower risk (HR = 0.86, 95% CI = 0.77–0.95) compared to the reference tertile. Conversely, the highest SFA/TFAT tertile was associated with a 23% increased mortality risk (HR = 1.23, 95% CI = 1.10–1.37), as visualized in the dose-response patterns of Fig. 2.

In the full model as showed in Fig. 3, the RCS with 4 internal knots (placed at the 5th, 35th, 65th, and 95th percentiles) and 2 boundary knots (minimum and maximum values) indicated a linear association between three fatty acid-related parameters and mortality (all p for non-linearity > 0.05). The overall effects of SFA/TFAT, MUFA/TFAT and PUFA/TFAT on mortality risk remained significant (p for overall < 0.05). Subgroup analyses revealed distinct interaction patterns for PUFA/TFAT across age strata. While neither SFA/TFAT nor PUFA/TFAT showed significant interaction effects with other subgroup variables (all p for interaction > 0.05 for gender, ethnicity, smoking, BMI, and comorbidities), a notable age-specific interaction emerged for PUFA/TFAT (p for interaction = 0.03). Each 1% increase in PUFA/TFAT was associated with differential mortality risk: 7% lower risk

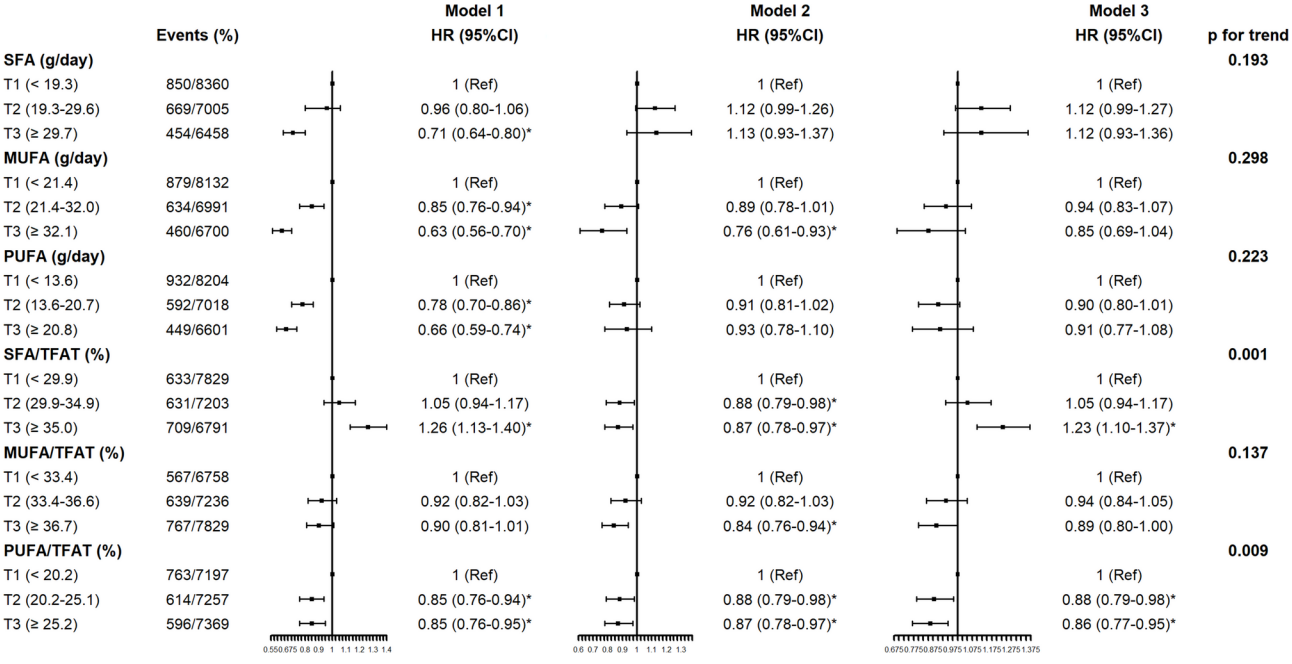

Fig. 2 The COX regression between tertiles of fatty acids-related variables and mortality risk. Model 1 was unadjusted; Model 2 was adjusted for age, gender, ethnicity, education, FMPIR, smoking, physical activity, and the total energy, protein, and fat from dietary intake; Model 3 was adjusted for all the variables in Model 2 and BMI, SBP, DBP, HbA1c, TC, ALT, eGFR, hypertension, and diabetes. *$P < 0.05$. Abbreviations: FMPIR, family poverty-to-income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; TFAT, total fat; SFA/TFAT, SFA-to-TFAT ratio; MUFA/TFAT, MUFA-to-TFAT ratio; PUFA/TFAT, PUFA-to-TFAT ratio

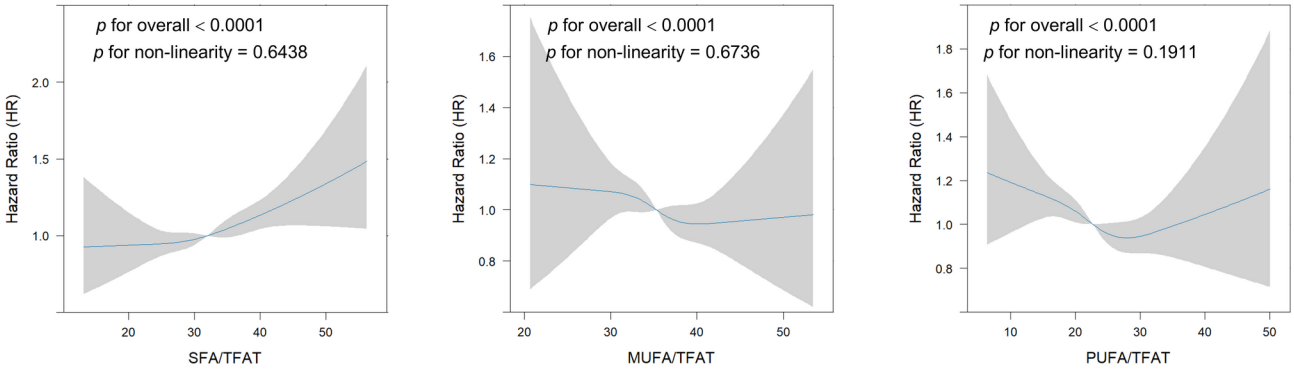

Fig. 3 Restricted cubic splines between specific fatty acid proportions in total fat and mortality risk. Solid lines represent hazard ratios, and shaded areas indicate 95% confidence intervals. Knots were placed at the 5th, 35th, 65th, and 95th percentiles. The confounding factors were adjusted for age, gender, ethnicity, education, FMPIR, smoking, physical activity, and the total energy, protein, and fat from dietary intake, BMI, SBP, DBP, HbA1c, TC, ALT, eGFR, hypertension, and diabetes. *$P < 0.05$. Abbreviations: FMPIR, family poverty-to-income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; TFAT, total fat; SFA/TFAT, SFA-to-TFAT ratio; MUFA/TFAT, MUFA-to-TFAT ratio; PUFA/TFAT, PUFA-to-TFAT ratio

in young adults (20–44 years: HR = 0.93, 95% CI = 0.87–0.99; $p = 0.028$), non-significant association in middle-aged (45–64 years: HR = 1.00, 95% CI = 0.97–1.03) and 2% risk reduction in elderly (65–80 years: HR = 0.98, 95% CI = 0.97–0.99; $p = 0.009$). These findings suggest that the protective effect of PUFA/TFAT exhibits age-dependent potency, as visualized by the modified dose-response curves in Fig. 4.

Relationship of fatty acid-related variables with NPAR

In the unadjusted Model 1, NPAR demonstrated a significant positive association with the SFA/TFAT (β = 0.018; 95% CI = 0.010–0.026) and a negative association with the PUFA/TFAT (β = -0.013; 95% CI = -0.021 - -0.005). Both SFA/TFAT and PUFA/TFAT retained statistically significant associations with NPAR following covariate adjustment in Model 2. Notably, in the fully adjusted Model 3, SFA/TFAT (β = 0.013; 95% CI = 0.005–0.021) and PUFA/TFAT (β = -0.014; 95% CI = -0.023 - -0.005) retained their statistical significance even after full covariate adjustment (Table 2).

Mediating roles of NPAR

The overall effects of SFA/TFAT and PUFA/TFAT on all-cause mortality were −9.3 (95% CI = -15.0 to -3.8) and 7.0 (95% CI = 1.6 to 13.3), respectively. These values represent log-time ratios per IQR increase in SFA/TFAT or PUFA/TFAT (expressed as percentages of total fatty acids), derived from Weibull survival regression models. Specifically, SFA/TFAT was found to mediate approximately 9.8% (95% CI = 4.5 −23.9%) of its total effect on mortality risk via NPAR. PUFA/TFAT showed a higher mediated proportion (11.8%, 95% CI = 4.6 −42.6%), suggesting that reliance on NPAR was also involved in its survival risk. These findings emphasize that NPAR might serve as a common pathway for SFA/TFAT and PUFA/TFAT to influence the risk of all-cause mortality (Fig. 5).

Discussion

This study pioneers in revealing a linear dose-response relationship between the proportional contributions of SFA and PUFA within total fat intake and longevity, thereby transcending the limitations of conventional single-subtype assessment paradigms. Multivariable-adjusted Cox models revealed that the highest SFA/TFAT tertile conferred a 23% elevated mortality risk versus the lowest tertile. Conversely, PUFA/TFAT exhibited a dose-dependent protective association, with mortality risk progressively decreasing by 12% (middle tertile: HR = 0.88, 0.79–0.98) and 14% (highest tertile: HR = 0.86, 0.77–0.95) across ascending tertiles (both p for trend < 0.05). Mediation analysis identified that the inflammation and nutrition-related marker NPAR partially mediated the effects of both SFA/TFAT (9.8% mediation proportion) and PUFA/TFAT (11.8% mediation proportion) on mortality outcomes.

Existing evidence on dietary fatty acids and mortality remains inconsistent. While PUFA and MUFA generally exhibit inverse associations with mortality risk in cohort studies—with PUFA intake showing 19–23% risk reduction in extreme intake comparisons [9, 10, 15]—the effects of SFA are contradictory. Some studies report 8% elevated mortality risk with high SFA intake [9, 10], whereas others find nonsignificant or even inverse associations [12, 13, 15]. This heterogeneity likely stems from methodological limitations in observational studies, where confounding by coexisting dietary components (e.g., antagonistic effects between SFA and unsaturated fats) obscures independent associations [25]. In our study, baseline analysis revealed that the deceased group

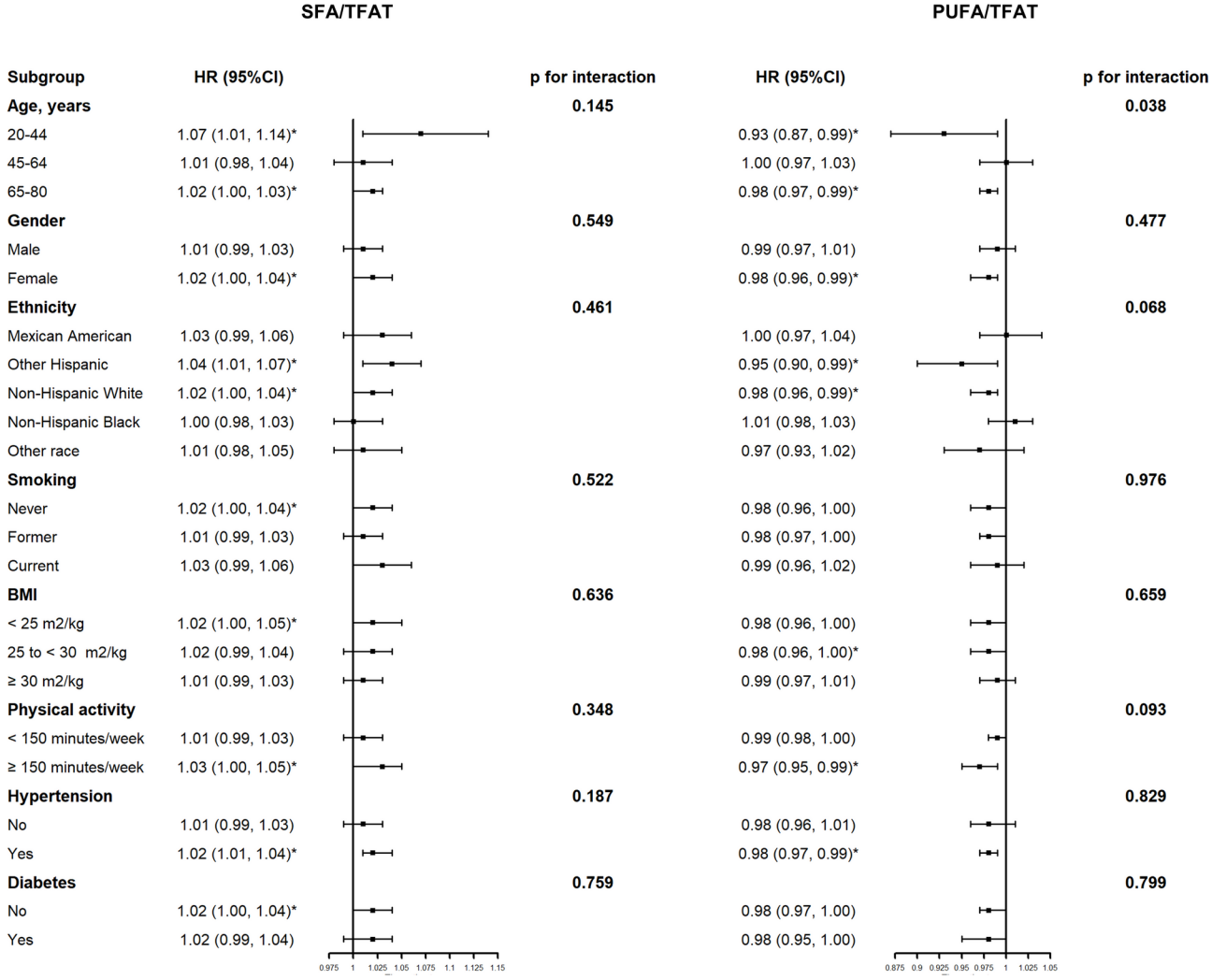

Fig. 4 Subgroup analysis of SFA/TFAT and PUFA/TFAT with all-cause mortality risk. The confounding factors were adjusted for age, gender, ethnicity, education, FMPIR, smoking, physical activity, and the total energy, protein, and fat from dietary intake, BMI, SBP, DBP, HbA1c, TC, ALT, eGFR, hypertension, and diabetes. *$P < 0.05$. Abbreviations: FMPIR, family poverty-to-income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; TFAT, total fat; SFA/TFAT, SFA-to-TFAT ratio; PUFA/TFAT, PUFA-to-TFAT ratio

Table 2 Survey-weighted linear regression between fatty acid-related variables with NPAR

	Model 1		Model 2		Model 3	
	β (95%CI)	*p*	β (95%CI)	*p*	β (95%CI)	*p*
SFA (g/day)	-0.002 (-0.005-0.002)	> 0.05	0.011 (0.002–0.020)	**< 0.05**	0.010 (0.002–0.019)	**< 0.05**
MUFA (g/day)	-0.005 (-0.008–0.002)	**< 0.05**	-0.012 (-0.023-0.000)	> 0.05	-0.005 (-0.017-0.006)	> 0.05
PUFA (g/day)	-0.007 (-0.011–0.002)	**< 0.05**	-0.010 (-0.019–0.001)	**< 0.05**	-0.010 (-0.019–0.001)	**< 0.05**
SFA/TFAT (%)	0.018 (0.010–0.026)	**< 0.05**	0.014 (0.006–0.023)	**< 0.05**	0.013 (0.005–0.021)	**< 0.05**
MUFA/TFAT (%)	-0.012 (-0.023–0.001)	**< 0.05**	-0.007 (-0.014-0.004)	> 0.05	-0.001 (-0.012-0.009)	> 0.05
PUFA/TFAT (%)	-0.013 (-0.021–0.005)	**< 0.05**	-0.015 (-0.023–0.006)	**< 0.05**	-0.014 (-0.023–0.005)	**< 0.05**

Model 1 was unadjusted; Model 2 was adjusted for age, gender, ethnicity, education, FMPIR, smoking, physical activity, and the total energy, protein, and fat from dietary intake; Model 3 was adjusted for all the variables in Model 2 and BMI, SBP, DBP, HbA1c, TC, ALT, eGFR, hypertension, and diabetes. *$p < 0.05$. Abbreviations: FMPIR, family poverty-to-income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NPAR, neutrophil percentage-to-albumin ratio; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; TFAT, total fat; SFA/TFAT, SFA-to-TFAT ratio; MUFA/TFAT, MUFA-to-TFAT ratio; PUFA/TFAT, PUFA-to-TFAT ratio

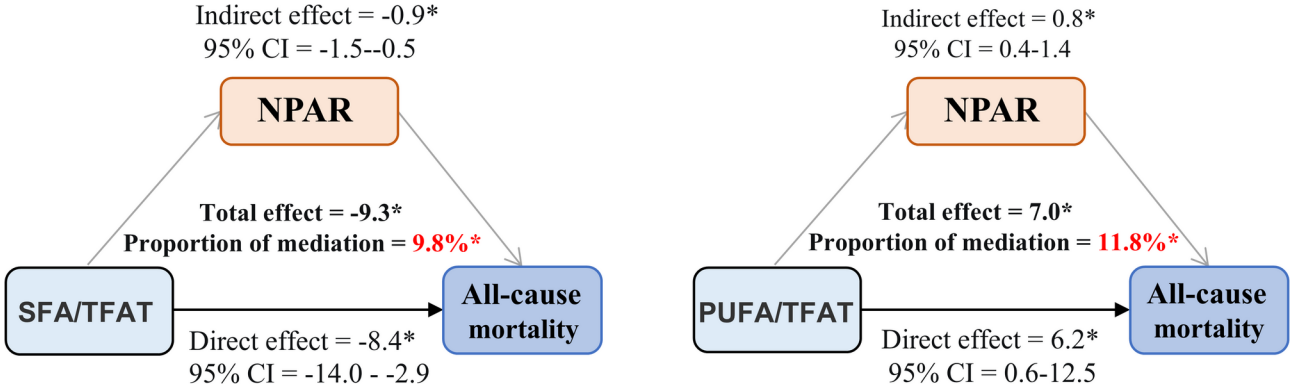

Fig. 5 Mediation roles of NPAR in the associations of SFA/TFAT and PUFA/TFAT with mortality risk. Direct, indirect, and total effects are expressed as log-time ratios per interquartile range (IQR) increase in SFA/TFAT or PUFA/TFAT (units: %), derived from Weibull survival regression models. Error bars represent 95% confidence intervals. The confounding factors were adjusted for age, gender, ethnicity, education, FMPIR, smoking, physical activity, and the total energy, protein, and fat from dietary intake, BMI, SBP, DBP, HbA1c, ALT, eGFR, hypertension, and diabetes. *$P < 0.05$. Abbreviations: FMPIR, family poverty-to-income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; TC, total cholesterol; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NPAR, neutrophil percentage-to-albumin ratio; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; TFAT, total fat; SFA/TFAT, SFA-to-TFAT ratio; PUFA/TFAT, PUFA-to-TFAT ratio

had lower baseline levels of total energy intake, protein, fat, three types of fatty acids (SFA, MUFA, PUFA), and the PUFA/TFAT ratio compared to the survival group. Notably, the SFA/TFAT ratio was higher in the deceased group. After adjusting for demographic characteristics, lifestyle factors, and clinical indicators, the Cox regression analysis showed that the highest tertile group of SFA, MUFA, and PUFA intake had no significant association with all-cause mortality compared to the lowest tertile group (p for trend > 0.05). In summary, the evidence remains inconclusive regarding the definitive impact of independent intake levels of three fatty acid subtypes on mortality outcomes. Mechanistic studies employing animal models have demonstrated clearer causal relationships through precise control of fatty acid types and dosages, effectively circumventing confounding effects from other lipid species [26]. In observational population-based studies, analyzing the impact of independent intake levels of specific fatty acids on survival outcomes may introduce bias due to inadequate consideration of synergistic or antagonistic interactions among different fatty acids, particularly when SFA and unsaturated fatty acids might exhibit potential opposing directions of effect on the outcome of interest.

Multivariable Cox proportional hazards regression analysis further revealed that the highest tertile of SFA/TFAT ratio was associated with a 23% increased mortality risk (HR: 1.23, 95% CI = 1.10–1.37, p for trend < 0.05), while the highest PUFA/TFAT tertile demonstrated a 14% risk reduction (HR: 0.86, 95% CI = 0.77–0.95, p for trend < 0.05) after adjusting the confounding factors. In contrast, no significant association emerged for MUFA/TFAT (p for overall > 0.05). The RCS analyses identified significant linear associations between mortality risk and SFA/TFAT and PUFA/TFAT ratios (p for overall < 0.05). Subgroup analyses revealed a significant age interaction for PUFA/TFAT effects (p for interaction = 0.038), with differential mortality associations per 1% increment: 7% risk reduction in young adults (20–44 years: HR = 0.93, 95% CI = 0.87–0.99), null effect in middle-aged (45–64 years: HR = 1.00, 95% CI = 0.97–1.03), and 2% reduction in elderly (65–80 years: HR = 0.98, 95% CI = 0.97–0.99). Crucially, no significant interactions emerged with gender, ethnicity, smoking, BMI, or comorbidities (all p for interaction > 0.05), reinforcing that the proportion of fatty acid intake, rather than the absolute level of fat consumption drives mortality associations– a mechanistic insight corroborating WHO's 2023 unsaturated fat substitution guidelines [16]. The attenuated middle-aged association likely reflects unmeasured confounders (e.g., chronic stress, sleep deprivation) prevalent in this demographic, suggesting future studies should incorporate psychosocial stress biomarkers when modeling diet-mortality relationships.

The neutrophil percentage-to-albumin ratio (NPAR), a biomarker integrating inflammatory and nutritional status, has been associated with mortality across cardiometabolic disorders. Our analyses revealed that the relative proportions of saturated (SFA) and polyunsaturated fatty acids (PUFA) within total fat intake, rather than their absolute amounts, differentially correlated with NPAR (SFA/TFAT: $\beta = 0.013$, $p < 0.05$; PUFA/TFAT: $\beta = -0.014$, $p < 0.05$). Mechanistically, SFA promotes inflammation through TLR4/NF-κB activation and oxidative stress, while PUFA counteracts these effects via AMPK and SIRT1 pathways [27, 28]. Mediation analysis demonstrated NPAR partially explains the mortality associations, accounting for 9.8% (SFA/TFAT) and 11.8% (PUFA/TFAT) of the effects. These findings position NPAR as a pro-inflammatory mediator linking dietary

fat composition to mortality risk. Specifically, the 9.8% mediation by NPAR for SFA/TFAT indicates that higher SFA intake exacerbates all-cause mortality risk through NPAR-related pro-inflammatory pathways, explaining ~ 10% of the total effect. The 11.8% mediation for PUFA/TFAT suggests that PUFA intake may reduce mortality risk partially by suppressing NPAR activity. These findings highlight NPAR's role as a pro-inflammatory mediator, though its pathway-specific contributions require further validation.

This study presents several notable strengths. First, a nationally representative cohort of 21,823 non-institutionalized U.S. adults was prospectively analyzed using robust NHANES data, ensuring generalizability to the broader population. Methodologically, the implementation of validated 24-hour dietary recalls conducted by trained professionals, with averaged measurements from two assessments [29], minimized recall bias and enhanced dietary data accuracy. Comprehensive adjustment for confounders was achieved through meticulous documentation of demographic characteristics, lifestyle factors (including diet and physical activity), clinical parameters, and laboratory biomarkers. Analytically, the dual-strategy approach combining tertile-based categorization of fatty acid intake with RCS models for continuous exposure analysis, complemented by extensive subgroup analyses, ensured both clinical interpretability and statistical robustness. The study makes a seminal contribution to nutritional epidemiology by being the first to demonstrate that the relative proportions of SFA and PUFA within total fat intake, rather than their independent consumption levels, exhibit significant associations with all-cause mortality.

However, there are still some limitations. First, dietary assessment relying on 24-hour recall questionnaires introduces recall bias and measurement errors. While our primary analysis employed complete-case exclusion to maximize data quality, we acknowledge that missing covariate data could theoretically introduce bias. Future studies with more complete covariate ascertainment are warranted to confirm these associations. Dietary substitution effects might confound the calculated nutrient intakes. Second, the absence of longitudinal dietary pattern tracking limits insights into temporal exposure-outcome relationships. Third, external validity is constrained by the U.S.-centric cohort lacking other population validation and insufficient consideration of dietary practices. Fourth, the relatively short follow-up duration may restrict the detection of long-term dietary effects on mortality outcomes. Fifth, the limited number of recorded deaths could reduce statistical power to identify significant associations, particularly for subgroup analyses. Sixth, residual confounding from unmeasured factors may persist despite comprehensive adjustment. Finally, the single timepoint assessment of dietary patterns and NPAR levels at baseline limits the ability to account for potential temporal variations in these exposures during follow-up. Although reverse causation is less likely in this prospective cohort given the temporal sequence of exposure-outcome measurement, residual confounding from unmeasured time-varying factors cannot be excluded. These methodological constraints highlight the necessity for future multinational cohorts incorporating biomarker-validated dietary assessments, Mendelian randomization approaches, and ethnically stratified analyses with extended follow-up periods and larger sample sizes to enhance causal inference and generalizability.

This longitudinal cohort study yields novel insights into the complex relationship between dietary fat composition and mortality risk. Our findings demonstrate that the relative proportions of SFA and PUFA within total fat intake exhibit statistically significant associations with long-term all-cause mortality. In contrast, the independent intake levels of either fatty acid subtype show no independent correlation with survival outcomes. Mechanistically, the nutrition-inflammatory index NPAR emerges as a potentially crucial mediating pathway through which SFA/TFAT and PUFA/TFAT influence mortality risk. These findings suggest that the substitution of SFA with PUFA strategy may confer survival benefits by reducing all-cause mortality risk, potentially contributing to enhanced lifespan extension in aging populations.

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Author contributions
Yanyan Liu and Jiaxuan Wang conducted the research and served as the primary author of the manuscript. Xiaona Chang analyzed the data collection process. Xiaoying Ren interpreted the data. Guang Wang and Jia Liu designed and supervised the manuscript's development. All authors reviewed and approved the final manuscript..

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Data availability
These datasets are publicly available at the following link: https://wwwn.cdc.gov/nchs/nhanes/default.aspx.

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics' Ethics Review Board approved the survey plan and protocol. All participants provided written informed consent.

Consent for publication
All participants provided written informed consent in this study.

Competing interests
The authors declare no competing interests.

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