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Associations between long-term dietary fatty acid intake and risk of cardiovascular disease among Chinese adults: A nationwide, population-based, prospective cohort study

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ABSTRACT: Background & Aims: Previous studies have established a significant association between dietary fatty acid intake and cardiovascular disease (CVD) risk; however, the long-term effects in China, where CVD rates are high, remain unclear. This study aims to assess the associations between long-term dietary fatty acid intake and CVD risk in Chinese populations. **Methods:** A total of 8,456 participants from the China Health and Nutrition Survey (CHNS) were enrolled. Dietary fatty acid intake was assessed using three-day 24-h dietary recalls combined with the dietary weighing method. CVD was defined as adults with myocardial infarction (MI) and/or stroke. Multivariable Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs), while restricted cubic spline (RCS) curves assessed the non-linear association. **Results:** During a median follow-up of 7 years, 418 participants developed CVD (186 MI and 251 stroke cases, including 19 with both conditions). In Chinese adults, more polyunsaturated fatty acids (PUFA) and n-6 PUFA intake was associated with an increased risk of CVD. Specifically, higher linoleic acid (C18:2n-6) intake was associated with a higher risk of CVD (HR_{Q4vsQ1}=1.80, 95% CI: 1.32-2.45), MI (HR_{Q4vsQ1}= 1.68, 95% CI: 1.06-2.68), and stroke (HR_{Q4vsQ1}=1.78, 95% CI: 1.22-2.60). Similar associations were observed between α-linolenic acid (C18:3n-3) and CVD (HR_{Q4vsQ1}=1.88, 95% CI: 1.38-2.57) and MI risk (HR_{Q4vsQ1}=3.84, 95% CI: 2.17-6.78), but no significant association was found for stroke. Furthermore, higher saturated fatty acid (SFA) intake was associated with an increased MI risk (HR_{Q4vsQ1}=1.64, 95% CI: 1.03-2.65). In contrast, the intake of marine n-3 PUFA, mainly composed of eicosapentaenoic acid and docosahexaenoic acid, was inversely linked to MI risk (HR_{Q4vsQ1}=0.51, 95% CI: 0.33-0.80). No significant correlation was detected between dietary monounsaturated fatty acid and cardiovascular event risk in Chinese adults. Similar findings for these fatty acids were also observed in RCS analyses. **Conclusion:** Higher dietary intake of marine n-3 PUFA was associated with a lower MI risk, while intakes of n-6 PUFA, C18:2n-6, and SFA were linked to a higher

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CVD risk. These findings support limiting the intake of n-6 PUFA and SFA while increasing marine n-3 PUFA consumption in the Chinese population for CVD prevention, particularly MI.

Keywords: Dietary fatty acid intake; cardiovascular diseases; Chinese adults; CHNS; stroke; myocardial infarction.

1. Introduction

Cardiovascular diseases (CVD), primarily stroke and ischaemic heart disease, remain the leading cause of mortality and a major contributor to disability worldwide [1], including in China [2]. CVD have become the most serious health concern in China, which accounts for one-fifth of the world's population [3]. According to the China Cardiovascular Health and Disease Report 2022, approximately 13 million individuals in China have suffered from strokes, while 11.39 million are affected by coronary heart disease (CHD), including myocardial infarction (MI) [4]. Notably, dietary risk factors contribute to approximately 37% of CVD-related deaths and 39% of total disability-adjusted life years associated with CVD [5]. Given that dietary fatty acids are key modifiable risk factors for CVD, most public health dietary guidelines recommend reducing saturated fatty acids (SFA) and increasing unsaturated fatty acids, particularly polyunsaturated fatty acids (PUFA), to lower CVD risk [6-8]. However, the role of different dietary fatty acids in CVD development remains controversial [9].

Numerous clinical and epidemiological studies have explored the relationship between dietary fatty acids and CVD risk, yet the findings remain inconsistent. Meta-analyses and large cohort studies in Western populations suggest that higher SFA intake is associated with an increased risk of CVD and CHD, while replacing SFA with unsaturated fatty acids appears to be protective [8, 10, 11]. A recent meta-analysis of prospective studies with 1,164,029 participants revealed a significant positive association between dietary SFA intake and CHD, while MUFA and PUFA intakes were inversely associated with stroke risk [6]. Similarly, the Danish Diet, Cancer and Health cohort study reported a lower risk of ischemic stroke with higher n-3 PUFA intake [12]. However, despite the overall trend suggesting that SFA intake increases CVD risk while PUFA intake is protective, conflicting evidence exists. Some studies have reported no significant associations between different dietary fats and CVD, MI, and stroke risk [7, 13-16], while others have even suggested an inverse relationship between SFA intake and stroke [17, 18]. These discrepancies may arise from differences in study design, dietary assessment methods, genetic predisposition, and lifestyle factors [19, 20]. Additionally, most existing studies focus on Western populations, with limited data available from China. It is well established that CVD incidence, dietary habits (e.g., food sources and intake levels), and genetic factors (e.g., polymorphisms in PUFA-related genes) differ significantly between Asian and Western populations [19, 20]. However, to date, there is very limited evidence on the association between long-term dietary fatty acid intake and CVD risk in China, where CVD rates are high.

To address this evidence gap, we analyzed data from the China Health and Nutrition Survey (CHNS), a large prospective cohort study. This study aimed to comprehensively investigate the association between long-term dietary fatty acid intake and CVD risk, particularly MI and stroke, among Chinese adults. The

findings may provide valuable insights for dietary recommendations, prevention, and treatment strategies to reduce CVD risk in China.

2. Methods

2.1 Study population

The CHNS is an ongoing cohort study employing a stratified, multistage prospective design to sample over 30,000 participants from 15 provinces or municipal cities, encompassing 288 communities across China. The survey collected data on socioeconomic status, sociodemographic factors, lifestyle, health status, dietary status, and nutritional status. Ten survey waves were conducted between 1989 and 2015. All participants provided written informed consent. The institutional review boards at the University of North Carolina (Chapel Hill, NC, United States) and the National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention (Beijing, China) reviewed and approved the studies involving human participants. The detailed procedures have been documented in prior studies [21-23] and are available on the official website (http://www.cpc.unc.edu/projects/china).

Since 2004, the CHNS has provided more accurate dietary data, which are available on its official website. Therefore, adults aged 18 years and older who participated in the survey from 2004 to 2015 were included in the study. Eligible subjects were those who had completed at least 2 survey waves and provided comprehensive demographic information as well as complete dietary data according to three-day 24-hour dietary recalls. The first survey wave was defined as the baseline. Moreover, the exclusion criteria include [24]: (1) Age < 18 years old, (2) Participants without follow-up or had a history of cancer or CVD at baseline, (3) Pregnant or lactating women, (4) With extreme energy intake (Male: < 800 kcal/day or > 6,000 kcal/day, Female: < 600 kcal/day or > 4,000 kcal/day), diastolic blood pressure > 200 mmHg or < 30 mmHg, systolic blood pressure > 300 mmHg or < 40 mmHg, without body mass index (BMI) data or BMI > 45 kg/m^2 or < 14 kg/m^2, or other unreliable observations. Finally, 8,456 individuals were included in the present analyzes (see Figure 1).

2.2 Dietary assessment and covariates

In the CHNS, dietary assessments were conducted at both individual and household levels using three-day 24-h recalls combined with a weighing inventory for household food consumption method [21, 25]. Trained field interviewers collected all dietary data, and the validity of the dietary survey method was previously confirmed in CHNS [26]. Food categories were classified using food codes recorded in the CHNS database. Dietary surveys conducted between 2004 and 2011 were primarily relied on the Chinese Food Composition Table (2002 edition), with additional data incorporated from the 2004 edition. Food consumption data were converted into the total energy and nutrient intakes using these tables. Notably, different food sources within the same category could not be directly combined. Variations in energy and nutrient content among these sources had to be accounted for when estimating food intake to enhance the accuracy of dietary data. The cumulative average dietary intake method was employed from baseline to the

latest year of the first cardiovascular event or the end of follow-up. This approach improves the weighting of individuals' baseline diet, reduces within-person variation, and more accurately reflects long-term habitual dietary intake [24, 27]. In addition, trained field investigators conducted face-to-face interviews using standardized questionnaires to collect demographic, socioeconomic, and lifestyle data. The collected information included age (years), ethnic group (Han/others), residence (urban/rural), education level (≤primary school, middle school, and ≥high school), current drinker (yes/no), history of hypertension (yes/no), current smoker (yes/no), gender (male/female), marital status (married/others), household income (Yuan), and history of diabetes (yes/no). BMI was calculated using the formula: "BMI = weight (kg)/height (m^2)". Dietary measurements included total energy intake (kcal/day), protein intake (% of energy), fat intake (% of energy), carbohydrate intake (% of energy). Fat was categorized into four types: n-3 PUFA, n-6 PUFA, MUFA, and SFA.

2.3 Case ascertainment

Stroke and MI were ascertained through telephone or face-to-face interviews. Participants' self-reported history of diagnosis and treatment was considered valid only if confirmed by a qualified physician. MI was identified based on a positive response to the question, "Has there been a MI diagnosed in the past year by a doctor?" Similarly, stroke was identified based on a positive response to the question, "Have you been diagnosed with a stroke or transient ischemic attack by a doctor?". MI and stroke were included as the major cardiovascular events. For subjects who provided inconsistent responses during the follow-up, the first recorded CVD event was used to minimize recall bias. The follow-up period was defined as the time from one year after participants' initial survey enrollment until the occurrence of the CVD outcome, loss to follow-up, or the censoring date. To minimize time-related biases, a specific method was used to estimate follow-up periods. For instance, if a participant joined the first wave in 2004, their follow-up period for cardiovascular outcomes between 2004 and 2006 was determined as: [2006-2004 year]/2. The formula is summarized as follows: Follow-up period = $[(Y_{n-1}-Y_1) + (Y_n-Y_{n-1})/2]$, $n \geq 2$ [27]. The CHNS surveys were conducted in 2015, 2011, 2009, 2006, and 2004. In the formula, n represents the number of times participated in the survey, Y_n denotes the year of n-th survey wave, Y_{n-1} represents the year of (n-1)-th survey wave, and Y_1 refers to the year of the first survey participation.

2.4 Statistical analysis

The intake of each fatty acid was represented as a percentage of total energy intake and categorized into quartiles [28]. Continuous variables were expressed as median with an interquartile range (IQR), while categorical variables were expressed as numbers and percentages. To assess differences in baseline characteristics across dietary fatty acid quartiles, the Kruskal–Wallis H test was applied to continuous variables, and the chi-square test was used for categorical variables. Multivariable Cox proportional hazards models were employed to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD risk, using the first category of fatty acids as the reference. The model was adjusted for variables such as age, gender, race, marital status, residence, education level, smoking, alcohol consumption, household income,

hypertension, diabetes, BMI, total energy intake, fat intake, protein intake, and carbohydrate intake. We assessed the linear trend using the median of each quartile as a continuous variable in the model. Furthermore, for fatty acids that showed a significant association with the risk of CVD events, a restricted cubic spline (RCS) regression was employed to explore potential nonlinear relationships. The RCS regression was applied using four knots at prespecified percentiles of the fatty acid distribution. Subgroup analyses were conducted to evaluate whether the association was influenced by various covariates, including age (<60 or ≥60 years), ethnic group (Han/others), gender (male/female), BMI (<24 or ≥24 kg/m^2), current smoker (yes/no), current drinker (yes/no), history of hypertension (yes/no), residence (urban/rural), household income (low, middle, high), history of diabetes (yes/no), marital status (married/others), and education level (≤primary school, middle school, and ≥high school). The *P*-value for interaction was determined using the likelihood-ratio test. Additionally, several sensitivity analyses were carried out by excluding participants with hypertension or diabetes at baseline, those with extreme BMI (>40 or <18.5 kg/m^2), extreme energy intake (>4000 or <500 kcal/day), or those within the first two years of follow-up [29]. All statistical analyses were conducted using R software (version 4.3.1), with a two-sided $P < 0.05$ considered statistically significant.

3. Results

Between 2004 and 2015, a total of 8,456 subjects aged 18-90 years (median=47 [37, 57]) were enrolled in this study, of whom 4,051 (47.90%) were men. Baseline demographic characteristics and dietary intake data, stratified by quartiles of total SFA, MUFA, n-6 PUFA, and n-3 PUFA intake, are presented in Table 1 and Table 2, respectively. Participants with higher intakes of SFA, MUFA, n-3 PUFA, or n-6 PUFA were more likely to be older ($P < 0.001$), women ($P < 0.001$), of Han ethnicity ($P < 0.001$), and urban residents ($P < 0.001$). Additionally, they had a higher prevalence of diabetes ($P < 0.001$) and hypertension ($P < 0.001$), greater household income ($P < 0.001$), and higher fat and protein intake ($P < 0.001$). Conversely, they smoked ($P < 0.001$) or consumed alcohol ($P < 0.001$) less frequently and had lower total energy ($P < 0.001$) and carbohydrate intake ($P < 0.001$).

Over a median follow-up of 7 years, 418 participants developed CVD, including 186 cases of MI and 251 stroke events, with 19 individuals experiencing both. The HRs and 95% CIs for the relationship between dietary SFA, MUFA, and CVD outcomes are displayed in Table 3. In Model 3, after fully adjusting for potential confounders, participants in the highest quartile of SFA intake exhibited a 64% higher risk of MI (HR_{Q4vsQ1}=1.64, 95% CI: 1.03-2.65; P_{trend}=0.015), while no significant association was observed with the risk of CVD (HR_{Q4vsQ1}=1.03, 95% CI: 0.76-1.40; P_{trend}=0.405) or stroke (HR_{Q4vsQ1}=0.75, 95% CI: 0.51-1.09; P_{trend}=0.242). A similar positive association was observed between palmitic acid (C16:0) and stearic acid (C18:0) intake and the risk of MI. Additionally, RCS regression analyses showed similar findings for these SFA (see Figures 2 and 3). Total dietary total MUFA intake, including C16:1 and C18:1, was not associated with the risk of CVD, MI, or stroke (Table 3).

Table 1 Baseline characteristics according to quintiles of dietary SFA and MUFA intake: CHNS, 2004–2015

Characteristics	SFA intake (percentage of energy, %)				*P* value	MUFA intake (percentage of energy, %)				*P* value
	Q1 (≤2.996)	Q2 (2.996-4.119)	Q3 (4.119-5.848)	Q4 (≥5.848)		Q1 (≤6.133)	Q2 (6.133-8.495)	Q3 (8.495-11.473)	Q4 (≥11.473)	
N	2114	2114	2114	2114		2114	2114	2114	2114	
Age (years)	45.00 [35.00, 54.00]	47.00 [37.00, 56.00]	48.00 [38.00, 57.00]	49.00 [39.00, 60.00]	<0.001	44.00 [34.00, 54.00]	47.00 [37.00, 56.00]	48.00 [39.00, 57.00]	49.00 [40.00, 60.00]	<0.001
Body mass index (kg/m^2)	22.69 [20.70, 25.16]	22.82 [20.71, 25.22]	22.99 [20.78, 25.50]	23.05 [20.90, 25.53]	0.008	22.82 [20.76, 25.34]	22.83 [20.83, 25.27]	22.83 [20.70, 25.43]	23.05 [20.83, 25.39]	0.359
Male (%)	57.13	49.86	44.90	39.75	<0.001	58.03	51.84	44.00	37.77	<0.001
Han (%)	84.75	87.54	88.34	89.80	<0.001	83.43	86.45	89.19	91.36	<0.001
Married (%)	87.16	87.20	85.08	85.51	0.089	87.63	87.11	85.74	84.47	0.013
Current smoker (%)	37.49	35.93	30.50	28.42	<0.001	40.42	36.36	29.84	25.73	<0.001
Current drinker (%)	38.57	34.94	31.87	30.08	<0.001	37.87	36.54	31.87	29.18	<0.001
Historty of diabetes (%)	0.90	0.71	1.75	2.12	<0.001	0.71	1.42	1.23	2.12	0.001
Historty of hypertension (%)	6.00	8.12	8.83	10.10	<0.001	6.09	7.65	8.83	10.48	<0.001
Household income (yuan)	4687.50 [2278.48, 8768.12]	5472.66 [2976.92, 9749.53]	6913.28 [3500.00, 12467.11]	8172.20 [4205.47, 14492.75]	<0.001	4833.33 [2402.86, 9148.55]	5640.07 [2832.02, 10709.26]	6536.51 [3321.89, 11838.33]	7777.78 [4185.59, 13518.52]	<0.001
Urban residence (%)	20.30	25.54	32.53	40.75	<0.001	16.86	27.57	35.08	39.61	<0.001
Education level										
≤Primary school	46.51	44.85	41.31	39.90	<0.001	45.99	42.49	40.93	43.15	<0.001
Middle school	35.08	32.58	33.76	29.75		36.12	32.67	32.58	29.79	
≥High school	18.41	22.57	24.93	30.36		17.89	24.83	26.49	27.05	
Dietary intake										
Total energy (kcal/day)	2194.63 [1867.35, 2539.62]	2140.54 [1855.11, 2463.46]	2059.84 [1801.84, 2417.70]	2001.50 [1710.80, 2342.87]	<0.001	2146.12 [1835.16, 2504.69]	2125.24 [1831.41, 2456.93]	2096.73 [1817.79, 2431.34]	2028.46 [1738.71, 2372.93]	<0.001
Fat intake (% of energy)	25.63 [20.22, 31.05]	29.21 [24.36, 33.61]	32.58 [28.11, 37.24]	34.80 [30.10, 39.66]	<0.001	24.61 [19.50, 29.73]	29.66 [24.93, 34.00]	32.35 [28.21, 36.72]	35.48 [30.74, 40.40]	<0.001
Carbohydrate intake (% of energy)	61.31 [55.59, 67.16]	57.64 [52.65, 63.13]	54.07 [48.77, 59.00]	50.96 [46.18, 56.18]	<0.001	62.15 [56.65, 67.65]	57.00 [51.91, 62.38]	54.27 [49.12, 58.76]	50.75 [45.65, 55.80]	<0.001
Protein intake (% of energy)	12.11 [11.12, 13.05]	12.16 [11.09, 13.27]	12.44 [11.33, 13.65]	12.97 [11.59, 14.34]	<0.001	12.18 [11.12, 13.14]	12.27 [11.22, 13.42]	12.43 [11.29, 13.66]	12.77 [11.41, 14.17]	<0.001

Note: Values are median [IQR] or percentages unless stated otherwise. CHNS, China Health and Nutrition Survey; Q, quartles; SFA, Saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 2 Baseline characteristics according to quintiles of dietary n-6 PUFA and n-3 PUFA intake: CHNS, 2004–2015

Characteristics	n-6 PUFA intake (percentage of energy, %)				*P* value	n-3 PUFA intake (percentage of energy, %)				*P* value
	Q1（≤4.442）	Q2（4.442-6.48）	Q3（6.48-8.886）	Q4（≥8.886）		Q1（≤0.431）	Q2（0.431-0.866）	Q3（0.866-1.311）	Q4（≥1.311）	
N	2114	2114	2114	2114		2114	2114	2114	2114	
Age (years)	46.00 [35.00, 55.00]	46.00 [36.00, 55.00]	47.00 [37.00, 57.00]	50.00 [41.00, 59.00]	<0.001	46.00 [36.00, 56.00]	47.00 [36.00, 56.00]	47.00 [37.00, 56.00]	50.00 [40.00, 59.00]	<0.001
Body mass index (kg/m^2)	22.25 [20.35, 24.57]	22.67 [20.72, 25.01]	23.04 [20.78, 25.52]	23.62 [21.41, 26.16]	<0.001	22.28 [20.37, 24.63]	22.98 [20.93, 25.40]	23.01 [20.93, 25.48]	23.24 [20.99, 25.80]	<0.001
Male (%)	56.89	52.79	45.47	36.50	<0.001	51.04	54.20	50.47	35.93	<0.001
Han (%)	74.60	89.75	92.54	93.53	<0.001	87.30	85.36	86.92	90.84	<0.001
Married (%)	85.46	86.21	86.69	86.59	0.644	84.09	85.93	88.72	86.21	<0.001
Current smoker (%)	39.00	34.61	30.26	28.47	<0.001	34.80	36.40	34.18	26.96	<0.001
Current drinker (%)	39.47	36.07	31.40	28.52	<0.001	34.18	38.29	36.17	26.82	<0.001
Historty of diabetes (%)	0.66	0.90	1.65	2.27	<0.001	0.38	1.18	1.46	2.46	<0.001
Historty of hypertension (%)	4.96	7.08	191 (9.02)	11.99	<0.001	5.15	6.56	8.97	12.37	<0.001
Household income (yuan)	4979.16 [2514.87, 9192.91]	6031.04 [3122.58, 10965.61]	6462.03 [3491.89, 11837.74]	7329.76 [3562.15, 13226.44]	<0.001	4435.50 [2302.17, 7998.50]	5552.56 [2849.78, 10608.50]	7053.19 [3669.92, 12322.77]	8105.29 [4238.10, 13883.98]	<0.001
Urban residence (%)	22.90	29.46	31.63	35.13	<0.001	20.35	26.20	33.33	39.24	<0.001
Education level										
≤Primary school	48.58	39.47	40.08	44.43	<0.001	46.55	43.11	39.38	43.53	<0.001
Middle school	32.20	34.32	33.99	30.64		33.90	33.90	33.05	30.31	
≥High school	19.22	26.20	25.92	24.93		19.55	22.99	27.57	26.16	
Dietary intake										
Total energy (kcal/day)	2162.22 [1868.08, 2482.98]	2148.92 [1859.50, 2482.16]	2058.56 [1782.05, 2420.48]	2014.89 [1716.03, 2353.90]	<0.001	2133.98 [1832.00, 2495.95]	2114.61 [1795.67, 2459.24]	2127.67 [1846.81, 2459.39]	2030.25 [1757.67, 2349.55]	<0.001
Fat intake (% of energy)	27.89 [21.97, 33.37]	29.25 [23.72, 34.48]	31.05 [26.23, 35.30]	34.46 [29.57, 39.76]	<0.001	28.74 [23.22, 33.43]	28.65 [22.31, 34.07]	30.57 [25.35, 35.22]	34.81 [30.07, 39.81]	<0.001
Carbohydrate intake (% of energy)	58.54 [53.16, 64.75]	57.21 [51.29, 63.45]	55.74 [50.22, 61.22]	52.30 [46.56, 57.54]	<0.001	58.67 [53.42, 64.41]	57.41 [51.83, 64.26]	55.62 [50.03, 61.58]	51.89 [46.64, 57.06]	<0.001
Protein intake (% of energy)	12.22 [11.08, 13.44]	12.56 [11.49, 13.64]	12.41 [11.37, 13.61]	12.32 [11.01, 13.74]	<0.001	11.86 [10.84, 12.97]	12.57 [11.56, 13.70]	12.51 [11.41, 13.81]	12.58 [11.29, 13.86]	<0.001

Note: Values are median [IQR] or percentages unless stated otherwise. CHNS, China Health and Nutrition Survey; Q, quartles; SFA, Saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 3 HR (95% CI) for CVD, stroke, and MI according to quintiles of dietary SFA and MUFA intake

	Quintiles of dietary fatty acids intake (percentage of energy, %)				*P*-trend
	Q1	Q2	Q3	Q4	
SFA					
Range	≤2.996	2.996-4.119	4.119-5.848	≥5.848	
Median	2.40	3.53	4.82	7.52	
CVD					
Cases/person-years	94/13846	86/14543	118/14394	120/14079	
Model 1	1	0.87 (0.65-1.16)	1.20 (0.92-1.58)	1.25 (0.96-1.64)	0.120
Model 2	1	0.87 (0.65-1.17)	1.13 (0.86-1.49)	1.09 (0.83-1.43)	0.242
Model 3	1	0.79 (0.58-1.06)	1.07 (0.80-1.43)	1.03 (0.76-1.40)	0.405
MI					
Cases/person-years	29/13611	33/14284	54/14120	65/13825	
Model 1	1	1.14 (0.70-1.86)	1.77 (1.13-2.75)	2.13 (1.38-3.28)	<0.001
Model 2	1	1.10 (0.68-1.79)	1.57 (1.01-2.45)	1.72 (1.11-2.66)	0.004
Model 3	1	1.03 (0.63-1.68)	1.50 (0.94-2.40)	1.64 (1.03-2.65)	0.015
Stroke					
Cases/person-years	67/13737	54/14381	67/14159	63/13856	
Model 1	1	0.76 (0.54-1.07)	0.89 (0.64-1.24)	0.83 (0.60-1.16)	0.446
Model 2	1	0.78 (0.56-1.10)	0.87 (0.63-1.21)	0.76 (0.54-1.06)	0.171
Model 3	1	0.71 (0.50-1.01)	0.85 (0.59-1.20)	0.75 (0.51-1.09)	0.242
C16:0					
Range	≤2.116	2.116-2.862	2.862-3.929	≥3.929	
Median	1.69	2.47	3.32	4.91	
CVD					
Cases/person-years	88/13896	90/14492	114/14436	126/14039	
Model 1	1	0.98 (0.73-1.31)	1.25 (0.94-1.65)	1.42 (1.08-1.86)	0.003
Model 2	1	1.01 (0.75-1.36)	1.17 (0.89-1.55)	1.24 (0.94-1.63)	0.070
Model 3	1	0.91 (0.67-1.22)	1.10 (0.82-1.48)	1.19 (0.87-1.62)	0.143
MI					
Cases/person-years	25/13662	41/14255	48/14155	67/13768	
Model 1	1	1.62 (1.00-2.63)	1.82 (1.13-2.93)	2.56 (1.62-4.02)	<0.001
Model 2	1	1.62 (1.00-2.63)	1.61 (1.00-2.60)	2.07 (1.31-3.26)	0.003
Model 3	1	1.46 (0.89-2.39)	1.49 (0.91-2.45)	1.92 (1.16-3.16)	0.015
Stroke					
Cases/person-years	64/13802	51/14304	70/14229	66/13799	
Model 1	1	0.76 (0.54-1.08)	0.97 (0.70-1.35)	0.92 (0.66-1.28)	0.946
Model 2	1	0.81 (0.57-1.14)	0.95 (0.69-1.32)	0.85 (0.61-1.19)	0.529
Model 3	1	0.73 (0.52-1.04)	0.93 (0.65-1.31)	0.86 (0.59-1.25)	0.675
C18:0					
Range	≤0.615	0.615-0.922	0.922-1.438	≥1.438	
Median	0.46	0.76	1.13	2.11	
CVD					
Cases/person-years	91/13833	91/14443	118/14385	118/14201	
Model 1	1	0.96 (0.71-1.28)	1.24 (0.95-1.63)	1.26 (0.96-1.66)	0.029
Model 2	1	0.98 (0.73-1.31)	1.19 (0.90-1.56)	1.14 (0.86-1.50)	0.191
Model 3	1	0.91 (0.68-1.23)	1.14 (0.85-1.53)	1.18 (0.87-1.59)	0.140
MI					
Cases/person-years	27/13586	35/14174	56/14132	63/13948	
Model 1	1	1.27 (0.77-2.07)	1.99 (1.27-3.12)	2.19 (1.40-3.41)	<0.001
Model 2	1	1.27 (0.77-2.07)	1.81 (1.15-2.85)	1.89 (1.21-2.95)	0.002
Model 3	1	1.21 (0.74-2.00)	1.75 (1.09-2.82)	1.95 (1.20-3.17)	0.002
Stroke					
Cases/person-years	66/13734	57/14269	68/14166	60/13964	
Model 1	1	0.79 (0.57-1.11)	0.94 (0.68-1.30)	0.80 (0.57-1.12)	0.348
Model 2	1	0.83 (0.59-1.16)	0.93 (0.67-1.28)	0.74 (0.53-1.05)	0.156
Model 3	1	0.79 (0.56-1.11)	0.93 (0.65-1.31)	0.79 (0.54-1.16)	0.390
MUFA					
Range	≤6.133	6.133-8.495	8.495-11.473	≥11.473	
Median	4.79	7.30	9.79	14.14	
CVD					
Cases/person-years	107/13814	92/14486	97/14398	122/14165	

Model 1	1	0.82 (0.62-1.08)	0.87 (0.66-1.14)	1.11 (0.86-1.44)	0.342
Model 2	1	0.73 (0.55-0.96)	0.74 (0.56-0.97)	0.87 (0.67-1.14)	0.434
Model 3	1	0.76 (0.50-1.09)	0.75 (0.58-1.00)	0.75 (0.55-1.02)	0.128
MI					
Cases/person-years	37/13546	41/14237	49/14197	54/13861	
Model 1	1	1.05 (0.68-1.62)	1.23 (0.81-1.86)	1.35 (0.90-2.04)	0.106
Model 2	1	0.91 (0.59-1.40)	0.98 (0.64-1.49)	0.98 (0.65-1.48)	0.956
Model 3	1	0.83 (0.53-1.30)	0.84 (0.53-1.33)	0.81 (0.50-1.32)	0.470
Stroke					
Cases/person-years	72/13670	53/14288	52/14207	74/13968	
Model 1	1	0.91 (0.70-1.19)	0.85 (0.66-1.12)	0.91 (0.66-1.25)	0.470
Model 2	1	0.84 (0.65-1.09)	0.77 (0.60-1.01)	0.75 (0.54-1.03)	0.073
Model 3	1	0.78 (0.61-1.02)	0.72 (0.56-1.06)	0.77 (0.56-1.08)	0.055
C16:1					
Range	≤0.157	0.157-0.275	0.275-0.43	≥0.43	
Median	0.10	0.22	0.34	0.57	
CVD					
Cases/person-years	114/13927	98/14453	95/14538	111/13944	
Model 1	1	0.83 (0.63-1.08)	0.80 (0.61-1.05)	0.97 (0.75-1.26)	0.766
Model 2	1	0.91 (0.70-1.20)	0.88 (0.67-1.15)	1.00 (0.77-1.30)	0.919
Model 3	1	0.96 (0.73-1.26)	0.91 (0.68-1.20)	0.96 (0.72-1.29)	0.706
MI					
Cases/person-years	40/13636	42/14188	43/14327	56/13689	
Model 1	1	1.06 (0.69-1.61)	1.02 (0.67-1.56)	1.36 (0.91-2.03)	0.159
Model 2	1	1.16 (0.76-1.78)	1.11 (0.72-1.70)	1.36 (0.91-2.04)	0.167
Model 3	1	1.24 (0.81-1.91)	1.12 (0.72-1.74)	1.20 (0.77-1.89)	0.535
Stroke					
Cases/person-years	76/13759	61/14293	57/14351	57/13730	
Model 1	1	0.81 (0.59-1.12)	0.69 (0.49-0.97)	0.70 (0.50-0.98)	0.020
Model 2	1	0.90 (0.66-1.24)	0.76 (0.55-1.07)	0.73 (0.52-1.03)	0.041
Model 3	1	0.97 (0.70-1.34)	0.83 (0.58-1.17)	0.77 (0.53-1.12)	0.129
C18:1					
Range	≤4.890	4.89-6.882	6.882-9.427	≥9.427	
Median	3.83	5.84	8.02	11.68	
CVD					
Cases/person-years	106/13874	88/14526	103/14415	121/14047	
Model 1	1	0.79 (0.60-1.05)	0.93 (0.71-1.22)	1.13 (0.87-1.46)	0.209
Model 2	1	0.78 (0.59-1.04)	0.83 (0.63-1.09)	0.93 (0.72-1.21)	0.763
Model 3	1	0.78 (0.51-1.01)	0.81 (0.63-1.06)	0.74 (0.54-1.02)	0.133
MI					
Cases/person-years	38/13609	35/14289	48/14167	60/13775	
Model 1	1	0.86 (0.55-1.35)	1.20 (0.79-1.82)	1.48 (0.99-2.21)	0.017
Model 2	1	0.81 (0.52-1.28)	1.01 (0.67-1.53)	1.12 (0.75-1.68)	0.353
Model 3	1	0.72 (0.45-1.13)	0.87 (0.56-1.36)	0.89 (0.55-1.42)	0.927
Stroke					
Cases/person-years	70/13727	56/14355	56/14226	69/13826	
Model 1	1	0.89 (0.70-1.17)	0.72 (0.52-1.01)	0.86 (0.62-1.18)	0.387
Model 2	1	0.90 (0.70-1.18)	0.66 (0.47-0.93)	0.75 (0.54-1.04)	0.078
Model 3	1	0.81 (0.63-1.07)	0.78 (0.40-1.04)	0.73 (0.52-1.02)	0.053

HR, hazard ratios; Q, quartile; CVD, cardiovascular disease; MI, myocardial infarction; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids.

Effect estimates were HR (95% CI) derived from multivariable Cox regressions;

Model 1: non-adjusted;

Model 2: adjusted for age, gender;

Model 3: adjusted for age, gender, race, residence, marital status, household income, body mass index, education level, smoking status, drinking status, hypertension, diabetes, energy intake, fat intake, carbohydrate intake, protein intake;

P-trend was assessed by calculating the median values in each quartile as continuous variables;

Major cardiovascular events include myocardial infarction and stroke.

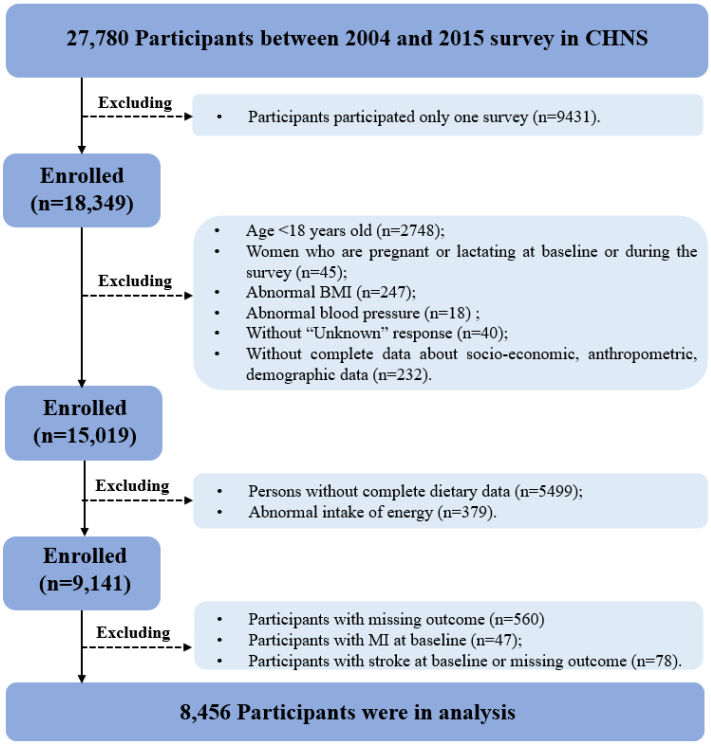

Figure 1 Flow chart of sample selection.

CHNS, China Health and Nutrition Survey; MI, Myocardial infarction.

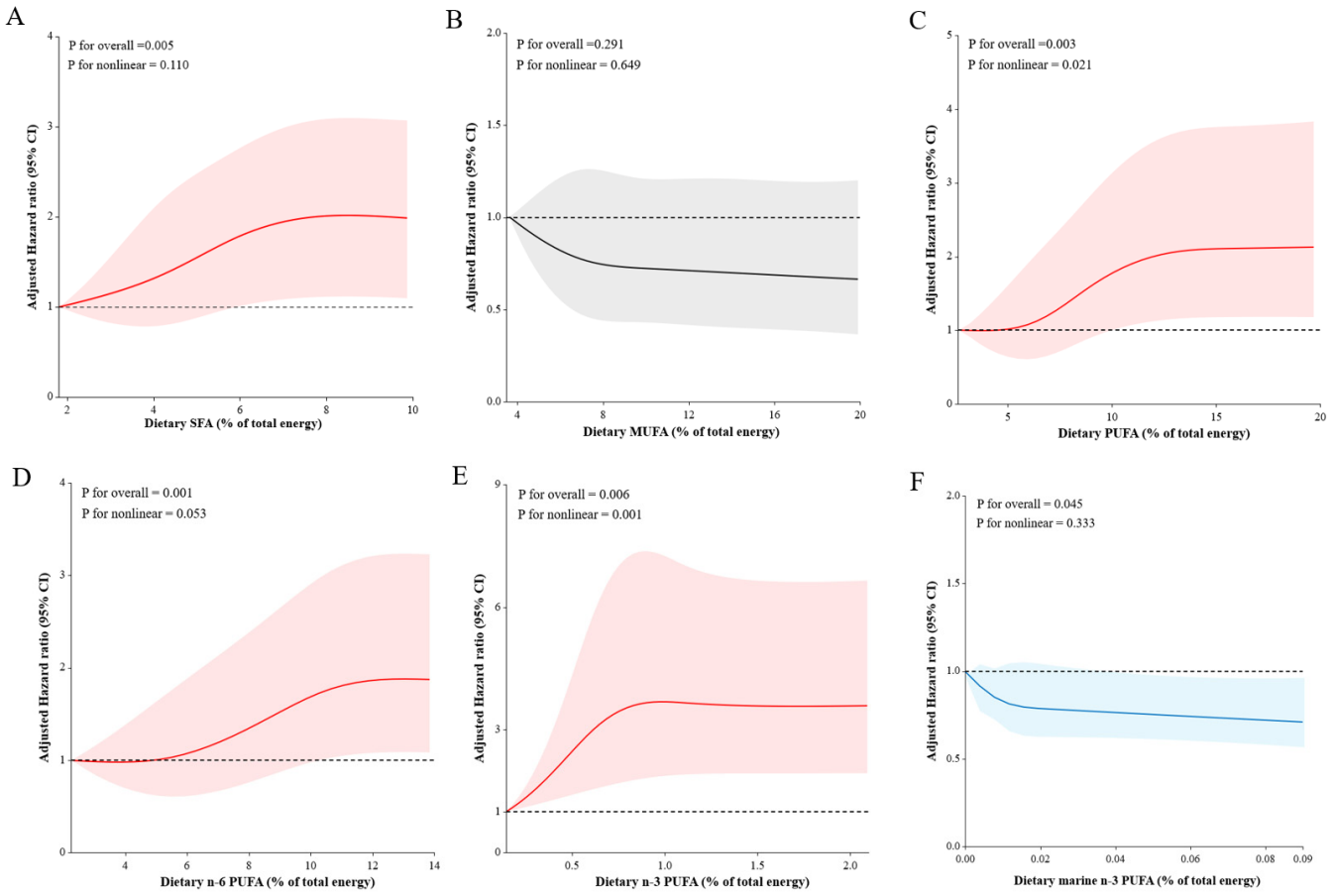

Figure 2 Potential non-linear associations between some dietary fatty acids and MI risk.

Note: Hazard risks for the CVD risk associated with dietary (A) SFA, (C) PUFA, (D) n-6 PUFA, (E) n-3 PUFA, and (F) marine n-3 PUFA intake were estimated using restricted cubic-spline regression, adjusted for age and sex, marital status, residence, body mass index, household income, nationality, education level, smoking status, drinking status, hypertension, diabetes, total energy intake, protein intake, fat intake, and carbohydrate intake. MI, myocardial infarction; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

As shown in Table 4, total dietary PUFA intake was associated with an increased risk of CVD (HR_{Q4vsQ1}=1.72, 95% CI: 1.26-2.36; P_{trend}=0.001), MI (HR_{Q4vsQ1}=1.67, 95% CI: 1.03-2.71; P_{trend}=0.017), and stroke (HR_{Q4vsQ1}=1.79, 95% CI: 1.22-2.64; P_{trend}=0.009) in the fully adjusted Model 3. Participants in the highest quartiles of n-6 PUFA and linoleic acid (C18:2n-6), but not arachidonic acid (C20:4n-6), had an increased risk of CVD, stroke, and MI compared with those in the lowest quartiles. Similarly, dietary n-3 PUFA was positively correlated with the incidence of CVD and MI, which was primarily attributable to α-linolenic acid (C18:3) (HR_{Q4vsQ1}= 1.88, 95% CI: 1.38-2.57; P_{trend}=0.001 for CVD; HR_{Q4vsQ1}= 3.84, 95% CI: 2.17-6.78; P_{trend}=0.001 for MI), whereas docosahexaenoic acid (C22:6n-3, DHA) and eicosapentaenoic acid (C20:5n-3, EPA) showed no such association. In contrast, greater intake of marine n-3 PUFA (HR_{Q4vsQ1}=0.51, 95% CI: 0.33-0.80; P_{trend}=0.003), including C20:5n-3 (HR_{Q4vsQ1}=0.62, 95% CI: 0.40-0.95; P_{trend}=0.022) and C22:6n-3 (HR_{Q4vsQ1}=0.48, 95% CI: 0.31-0.74; P_{trend}=0.001), was associated with a lower risk of MI. Similar results for these PUFA were demonstrated by RCS regression analyses (Figures 1, 2, and S1).

Table 4 HR (95% CI) for CVD, stroke, and MI according to quintiles of dietary PUFA intake

	Quintiles of dietary fatty acids intake (percentage of energy, %)				*P*-trend
	Q1	Q2	Q3	Q4	
PUFA					
Range	≤5.205	5.205-7.314	7.314-9.928	≥9.928	
Median	3.96	6.25	8.50	12.38	
CVD					
Cases/person-years	69/14172	90/14336	100/14376	159/13978	
Model 1	1	1.29 (0.94-1.77)	1.43 (1.05-1.94)	2.34 (1.77-3.11)	<0.001
Model 2	1	1.32 (0.96-1.81)	1.40 (1.03-1.90)	2.12 (1.59-2.82)	<0.001
Model 3	1	1.21 (0.88-1.68)	1.23 (0.89-1.70)	1.72 (1.26-2.36)	0.001
MI					
Cases/person-years	28/14029	33/14099	49/14128	71/13584	
Model 1	1	1.25 (0.76-2.05)	1.81 (1.14-2.88)	2.66 (1.72-4.12)	<0.001
Model 2	1	1.25 (0.76-2.05)	1.68 (1.06-2.67)	2.20 (1.42-3.41)	<0.001
Model 3	1	1.09 (0.65-1.83)	1.38 (0.84-2.26)	1.67 (1.03-2.71)	0.017
Stroke					
Cases/person-years	42/14051	63/14225	51/14144	95/13714	
Model 1	1	1.38 (0.95-2.00)	1.14 (0.77-1.68)	2.07 (1.47-2.93)	<0.001
Model 2	1	1.43 (0.99-2.08)	1.16 (0.79-1.71)	1.99 (1.40-2.82)	<0.001
Model 3	1	1.38 (0.94-2.02)	1.11 (0.74-1.67)	1.79 (1.22-2.64)	0.009
n-6 PUFA					
Range	≤4.442	4.442-6.48	6.48-8.886	≥8.886	
Median	3.25	5.5	7.55	10.95	
CVD					
Cases/person-years	70/14264	89/14262	98/14413	161/13923	
Model 1	1	1.27 (0.93-1.74)	1.39 (1.02-1.89)	2.36 (1.78-3.13)	<0.001
Model 2	1	1.34 (0.98-1.84)	1.36 (1.00-1.85)	2.17 (1.63-2.87)	<0.001
Model 3	1	1.24 (0.90-1.71)	1.18 (0.86-1.64)	1.78 (1.31-2.43)	<0.001
MI					
Cases/person-years	29/14121	32/14020	48/14173	72/13527	
Model 1	1	1.15 (0.70-1.89)	1.76 (1.11-2.77)	2.63 (1.71-4.05)	<0.001
Model 2	1	1.20 (0.73-1.98)	1.67 (1.06-2.63)	2.22 (1.44-3.43)	<0.001
Model 3	1	1.09 (0.65-1.82)	1.39 (0.86-2.26)	1.73 (1.08-2.78)	0.009
Stroke					
Cases/person-years	42/14140	62/14151	51/14194	96/13648	
Model 1	1	1.33 (0.92-1.94)	1.18 (0.81-1.74)	2.12 (1.50-2.99)	<0.001
Model 2	1	1.42 (0.97-2.06)	1.20 (0.82-1.77)	2.05 (1.45-2.91)	<0.001
Model 3	1	1.35 (0.92-1.99)	1.12 (0.75-1.68)	1.85 (1.26-2.71)	0.004
C18:2					
Range	≤4.421	4.421-6.456	6.456-8.862	≥8.862	
Median	3.23	5.49	7.52	10.94	
CVD					

Cases/person-years	70/14267	88/14264	99/14399	161/13932	
Model 1	1	1.26 (0.92-1.72)	1.40 (1.03-1.91)	2.36 (1.78-3.13)	<0.001
Model 2	1	1.33 (0.97-1.83)	1.38 (1.02-1.88)	2.18 (1.64-2.89)	<0.001
Model 3	1	1.24 (0.90-1.71)	1.20 (0.87-1.66)	1.80 (1.32-2.45)	<0.001
MI					
Cases/person-years	29/14124	32/14028	48/14153	72/13535	
Model 1	1	1.07 (0.65-1.77)	1.70 (1.08-2.67)	2.54 (1.66-3.89)	<0.001
Model 2	1	1.13 (0.69-1.86)	1.61 (1.03-2.53)	2.16 (1.41-3.31)	<0.001
Model 3	1	1.03 (0.62-1.72)	1.35 (0.83-2.17)	1.68 (1.06-2.68)	0.010
Stroke					
Cases/person-years	42/14143	61/14153	52/14180	96/13657	
Model 1	1	1.22 (0.84-1.77)	1.16 (0.79-1.69)	2.03 (1.44-2.86)	<0.001
Model 2	1	1.30 (0.90-1.89)	1.18 (0.81-1.72)	1.98 (1.41-2.79)	<0.001
Model 3	1	1.25 (0.85-1.83)	1.09 (0.73-1.62)	1.78 (1.22-2.60)	0.005
C20:4					
Range	≤0.003	0.003-0.01	0.01-0.021	≥0.021	
Median	0.00	0.01	0.01	0.03	
CVD					
Cases/person-years	112/14028	107/14461	106/14417	93/13957	
Model 1	1	0.93 (0.71-1.21)	0.92 (0.70-1.20)	0.83 (0.63-1.10)	0.209
Model 2	1	1.01 (0.78-1.32)	0.97 (0.74-1.27)	0.90 (0.69-1.19)	0.439
Model 3	1	0.96 (0.73-1.27)	0.96 (0.72-1.27)	0.85 (0.62-1.17)	0.347
MI					
Cases/person-years	41/13737	45/14173	49/14159	46/13772	
Model 1	1	1.04 (0.69-1.57)	1.13 (0.75-1.69)	1.09 (0.72-1.64)	0.618
Model 2	1	1.18 (0.78-1.78)	1.23 (0.81-1.84)	1.20 (0.79-1.82)	0.373
Model 3	1	1.11 (0.72-1.70)	1.16 (0.75-1.80)	1.05 (0.65-1.68)	0.824
Stroke					
Cases/person-years	74/13880	64/14253	63/14230	50/13771	
Model 1	1	0.88 (0.63-1.21)	0.84 (0.60-1.16)	0.67 (0.47-0.95)	0.028
Model 2	1	0.93 (0.67-1.29)	0.86 (0.62-1.20)	0.72 (0.50-1.02)	0.058
Model 3	1	0.92 (0.66-1.28)	0.92 (0.65-1.31)	0.77 (0.52-1.15)	0.248
n-3 PUFA					
Range	≤0.431	0.431-0.866	0.866-1.311	≥1.311	
Median	0.24	0.66	1.08	1.65	
CVD					
Cases/person-years	61/14295	110/13968	100/14428	147/14172	
Model 1	1	1.85 (1.35-2.53)	1.63 (1.18-2.24)	2.44 (1.81-3.29)	<0.001
Model 2	1	1.86 (1.36-2.54)	1.66 (1.21-2.29)	2.20 (1.63-2.96)	<0.001
Model 3	1	1.83 (1.33-2.51)	1.53 (1.11-2.13)	1.95 (1.42-2.67)	0.001
MI					
Cases/person-years	15/14082	52/13763	38/14155	76/13841	
Model 1	1	3.14 (1.81-5.42)	2.40 (1.37-4.23)	4.56 (2.69-7.71)	<0.001
Model 2	1	3.22 (1.86-5.56)	2.50 (1.42-4.40)	3.94 (2.33-6.67)	<0.001
Model 3	1	3.08 (1.77-5.35)	2.16 (1.22-3.85)	3.31 (1.92-5.72)	<0.001
Stroke					
Cases/person-years	47/14228	65/13765	62/14249	77/13892	
Model 1	1	1.40 (0.97-2.00)	1.37 (0.96-1.97)	1.55 (1.09-2.21)	0.025
Model 2	1	1.39 (0.97-2.00)	1.39 (0.97-1.99)	1.43 (1.01-2.04)	0.069
Model 3	1	1.42 (0.98-2.05)	1.39 (0.96-2.02)	1.37 (0.94-2.00)	0.144
C18:3					
Range	≤0.408	0.408-0.836	0.836-1.274	≥1.274	
Median	0.22	0.63	1.04	1.61	
CVD					
Cases/person-years	63/14313	111/13886	97/14452	147/14212	
Model 1	1	1.82 (1.34-2.48)	1.53 (1.11-2.10)	2.36 (1.75-3.17)	<0.001
Model 2	1	1.84 (1.35-2.50)	1.59 (1.16-2.18)	2.14 (1.59-2.88)	<0.001
Model 3	1	1.81 (1.32-2.47)	1.46 (1.05-2.02)	1.88 (1.38-2.57)	0.001
MI					
Cases/person-years	13/14088	52/13666	39/14207	77/13879	
Model 1	1	3.65 (2.06-6.47)	2.71 (1.50-4.90)	5.22 (3.00-9.08)	<0.001
Model 2	1	3.75 (2.11-6.65)	2.86 (1.58-5.17)	4.54 (2.61-7.89)	<0.001
Model 3	1	3.63 (2.04-6.48)	2.47 (1.35-4.50)	3.84 (2.17-6.78)	<0.001
Stroke					
Cases/person-years	51/14251	66/13689	58/14266	76/13928	
Model 1	1	1.36 (0.96-1.93)	1.16 (0.81-1.67)	1.42 (1.00-2.00)	0.118
Model 2	1	1.36 (0.96-1.93)	1.20 (0.84-1.72)	1.32 (0.93-1.87)	0.222

Model 3	1	1.39 (0.97-1.98)	1.20 (0.83-1.73)	1.24 (0.86-1.79)	0.425
C20:5					
Range	≤0	0-0.003	0.003-0.012	≥0.012	
Median	0.00	0.001	0.01	0.02	
CVD					
Cases/person-years	170/19484	59/8978	103/14271	86/14130	
Model 1	1	0.75 (0.56-1.01)	0.83 (0.65-1.06)	0.70 (0.54-0.90)	0.008
Model 2	1	0.84 (0.62-1.12)	0.91 (0.71-1.16)	0.70 (0.54-0.90)	0.013
Model 3	1	0.84 (0.62-1.13)	0.84 (0.64-1.08)	0.63 (0.47-0.85)	0.003
MI					
Cases/person-years	72/19101	27/8804	42/13991	40/13944	
Model 1	1	0.79 (0.51-1.23)	0.79 (0.55-1.16)	0.78 (0.53-1.13)	0.159
Model 2	1	0.91 (0.58-1.41)	0.90 (0.62-1.31)	0.79 (0.54-1.15)	0.230
Model 3	1	0.88 (0.56-1.39)	0.74 (0.50-1.11)	0.62 (0.40-0.95)	0.022
Stroke					
Cases/person-years	104/19209	33/8844	65/14096	49/13985	
Model 1	1	0.66 (0.45-0.98)	0.87 (0.64-1.18)	0.72 (0.53-1.01)	0.084
Model 2	1	0.73 (0.49-1.07)	0.94 (0.70-1.28)	0.71 (0.52-1.01)	0.084
Model 3	1	0.75 (0.51-1.13)	0.97 (0.70-1.33)	0.79 (0.55-1.14)	0.337
C22:6					
Range	≤0	0-0.002	0.002-0.017	≥0.017	
Median	0.00	0.001	0.01	0.04	
CVD					
Cases/person-years	181/21761	43/6476	96/14416	98/14209	
Model 1	1	0.80 (0.57-1.11)	0.80 (0.62-1.02)	0.83 (0.65-1.06)	0.080
Model 2	1	0.82 (0.59-1.14)	0.86 (0.67-1.11)	0.81 (0.64-1.04)	0.093
Model 3	1	0.77 (0.55-1.09)	0.80 (0.61-1.04)	0.76 (0.57-1.00)	0.039
MI					
Cases/person-years	82/21352	22/6385	44/14164	33/13939	
Model 1	1	0.88 (0.55-1.40)	0.81 (0.56-1.16)	0.64 (0.43-0.95)	0.023
Model 2	1	0.93 (0.58-1.48)	0.89 (0.62-1.28)	0.65 (0.44-0.96)	0.041
Model 3	1	0.77 (0.48-1.26)	0.71 (0.48-1.04)	0.48 (0.31-0.74)	0.001
Stroke					
Cases/person-years	107/21465	21/6363	56/14235	67/14070	
Model 1	1	0.64 (0.40-1.02)	0.80 (0.58-1.10)	1.05 (0.78-1.40)	0.972
Model 2	1	0.65 (0.40-1.03)	0.85 (0.62-1.17)	1.00 (0.75-1.34)	0.945
Model 3	1	0.66 (0.41-1.07)	0.90 (0.65-1.26)	1.18 (0.85-1.65)	0.395
Marine n-3 PUFA					
Range	≤0	0-0.003	0.003-0.021	≥0.021	
Median	0.00	0.001	0.01	0.04	
CVD					
Cases/person-years	172/21673	47/6585	99/14416	100/14189	
Model 1	1	0.90 (0.65-1.24)	0.86 (0.67-1.11)	0.89 (0.69-1.14)	0.260
Model 2	1	0.92 (0.66-1.27)	0.93 (0.73-1.20)	0.87 (0.68-1.12)	0.288
Model 3	1	0.88 (0.63-1.23)	0.88 (0.67-1.14)	0.82 (0.62-1.09)	0.165
MI					
Cases/person-years	77/21281	27/6492	44/14165	33/13903	
Model 1	1	1.12 (0.73-1.74)	0.85 (0.59-1.23)	0.68 (0.46-1.01)	0.049
Model 2	1	1.18 (0.76-1.82)	0.95 (0.66-1.37)	0.68 (0.46-1.02)	0.080
Model 3	1	0.99 (0.63-1.57)	0.77 (0.52-1.14)	0.51 (0.33-0.80)	0.003
Stroke					
Cases/person-years	103/21395	20/6456	59/14228	69/14055	
Model 1	1	0.62 (0.38-1.00)	0.87 (0.64-1.19)	1.11 (0.83-1.49)	0.564
Model 2	1	0.62 (0.39-1.01)	0.93 (0.68-1.27)	1.07 (0.80-1.43)	0.636
Model 3	1	0.65 (0.40-1.06)	0.99 (0.71-1.38)	1.28 (0.92-1.79)	0.145

HR, hazard ratios; Q, quartile; CVD, cardiovascular disease; MI, myocardial infarction; PUFA, polyunsaturated fatty acids.
Effect estimates were HR (95% CI) derived from multivariable Cox regressions;
Model 1: non-adjusted;
Model 2: adjusted for age, gender;
Model 3: adjusted for age, gender, race, residence, marital status, household income, body mass index, education level, smoking status, drinking status, hypertension, diabetes, energy intake, fat intake, carbohydrate intake, protein intake;
P-trend was assessed by calculating the median values in each quartile as continuous variables;
Major cardiovascular events include myocardial infarction and stroke.

As shown in Table S1, subgroup analyses revealed that the inverse association between dietary total MUFA intake and CVD incidence was significant only in men (*P*-interaction=0.004). Moreover, no significant association was found across stratified factors, as all *P*-interaction values were > 0.05 (Table S2). The inverse relationship between total MUFA and stroke was significant in men (*P*-interaction=0.025) and rural residents (*P*-interaction=0.027) (see Table S3). In sensitivity analyses, the relationships between dietary fatty acids and the risk of CVD, MI, and stroke remained largely unchanged after additional adjustment. These analyses excluded participants with extremely low or high BMI (<18.5 or >40 kg/m^2), those with hypertension or diabetes at baseline, individuals with extreme energy intake (<500 or >4000 kcal/day), and who experienced events within the first 2 years of follow-up (Table S4).

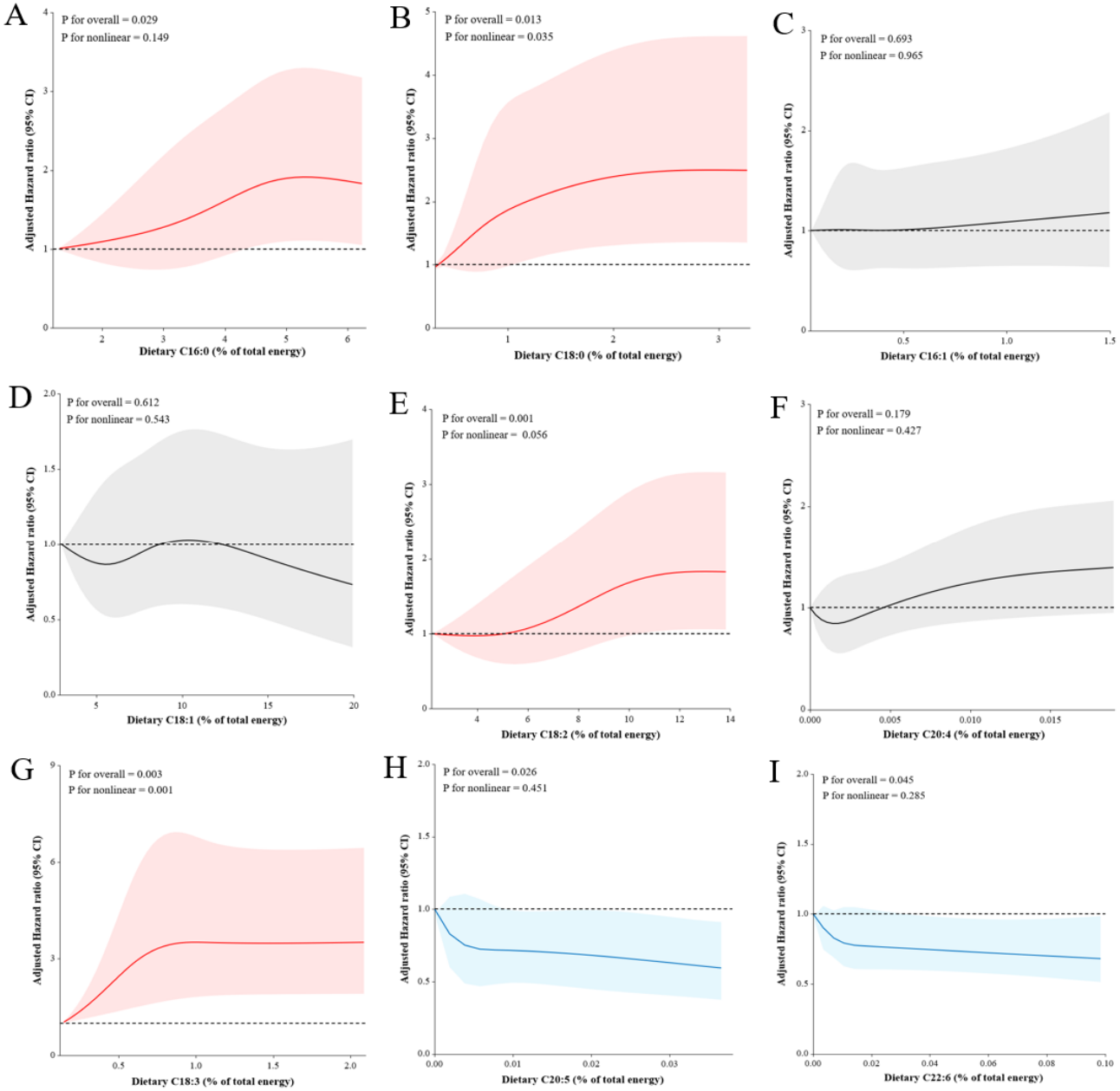

Figure 3 Potential non-linear associations between specific fatty acid intake and MI risk.

Note: Hazard risks for the MI risk associated with dietary (A) C16:0; (B) C18:0; (C) C16:1; (D) C18:1; (E) C18:2; (F) C20:4; (G) C18:3; (H) C20:5; (I) C22:6 intake were estimated using restricted cubic-spline regression, adjusted for age and sex, marital status, residence, body mass index, household income, nationality, education level, smoking status, drinking status, hypertension, diabetes, total energy intake, protein intake, fat intake, and carbohydrate intake. MI, myocardial infarction.

4. Discussion

To our knowledge, this is the first large-scale prospective cohort study to assess the associations between long-term dietary fatty acids and the risk of CVD events in Chinese adults. After adjusting for major potential risk factors, we observed that dietary n-6 PUFA and C18:2n-6 intakes were consistently and positively associated with the risks of CVD, MI, and stroke. Intake of n-3 PUFA, specifically C18:3, was positively related to CVD and MI risk but not stroke. In addition, higher intake of SFA, including C16:0 and C18:0, was linked to an increased risk of MI, whereas marine n-3 PUFA (EPA and DHA) were associated with a lower MI risk.

Previous epidemiological studies [19, 30] [31] have confirmed that a high intake of n-6 PUFA, particularly C18:2n-6, was positively correlated with the incidence of CVD, stroke, or MI that we identified. A case-control study of 628 Chinese participants found that higher C18:2n-6 levels in erythrocytes, an objective biomarker of dietary fat intake, were significantly associated with an increased CVD risk [19]. Similarly, Chen et al. (2023) [32] analyzed CHNS data and observed that increased n-6 PUFA intake correlated with CVD risk factors, including overweight and obesity (HR = 1.14; 95% CI: 1.02–1.28). Furthermore, a meta-analysis of randomized controlled trials (RCTs) [33] indicated that higher n-6 PUFA intake might increase the risk of non-fatal MI and CHD mortality. Another meta-analysis of 65 RCTs reported that an increased n-6/n-3 PUFA ratio was strongly associated with a higher risk of cardiovascular outcomes, including CVD, CHD, MI, and stroke [34]. Notably, a recent study investigated the relationship between dietary fat intake and CVD in the Chinese population over a 30-year period [35]. It reported a significant rise in the proportion of n-6 PUFA in the diet, rising from 32.8% to 40.9% [35]. This study indicates that reducing excessive n-6 PUFA intake could be crucial in lowering CVD risk in China [35]. Nevertheless, some previous studies reported an inverse association or no significant relationship between n-6 PUFA intake and CVD [11, 20, 36]. These inconsistencies might arise from differences in study design, sample size, regional dietary patterns, lifestyle factors, and participant characteristics [19].

These associations may be biologically explained by mechanistic pathways demonstrated in experimental studies. Evidence from animal models also supports the present findings, suggesting that excessive dietary intake of n-6 PUFA may promote atherosclerosis [37, 38]. The underlying mechanism involves the metabolism of C18:2n-6 into C20:4n-6, which is subsequently converted by cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes into pro-inflammatory mediators, such as prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) [39]. These mediators activate nuclear factor-kappa B (NF-κB) and MAPK signaling pathways, thereby upregulating pro-inflammatory cytokines, promoting vascular inflammation, and enhancing foam cell formation [40]. In addition, high n-6 PUFA intake may upregulate the expression of oxidative stress-related genes, including NOX2 and iNOS, leading to lipid peroxidation and the generation of oxidized low-density lipoproteins, which impair endothelial function and promote atherogenesis [41, 42]. Furthermore, peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of lipid metabolism, can be modulated by n-6 PUFA metabolites, influencing macrophage polarization and foam cell

accumulation, thereby accelerating plaque development [43]. In addition to its role in inflammation and oxidative stress, excessive n-6 PUFA intake has also been associated with increased blood viscosity, vasoconstriction, and vasospasm [44]. Given these findings, limiting the overconsumption of n-6 PUFA, particularly C18:2n-6, may help reduce CVD risk in the Chinese population.

For C20:4n-6, a previous study suggested its role in promoting atherosclerosis [45], which contradicts the current finding that C20:4n-6 intake was not associated with the risk of CVD, MI, and stroke. The inconsistency may be primarily due to the generally low C20:4n-6 consumption in the Chinese population (mean intake: 0.01% of energy). Similarly, Chen et al. (2023) [32] reported a low C20:4n-6 intake in the Chinese population (mean intake: 0.02% of energy).

α-linolenic acid (C18:3, ALA), an essential n-3 PUFA, primarily contributed to the positive association between total n-3 PUFA intake and the risk of CVD and MI in this analysis. A cohort study of 8,742 Chinese participants with a median follow-up of 7 years observed that dietary C18:3 intake was positively associated with CVD risk factors (HR_{Q4vsQ1}=1.22, 95% CI: 1.07-1.39) [32]. Similarly, Zhuang et al. (2019) [46] reported that higher C18:3 intake (≥ 1.53 g/day) was linked to increased total mortality in Chinese adults (HR_{Q4vsQ1}=1.23, 95% CI: 1.01-1.50). Additionally, a cross-sectional study from the National Health and Nutrition Examination Survey showed that the association between dietary C18:3 and CVD risk varied across sociodemographic groups, with a significant positive correlation identified in non-Hispanic Black individuals [47]. Furthermore, C18:3 in plant-based oils can be converted into potentially harmful trans-C18:3 during stir-frying [48], which could explain the observed adverse association, given that stir-frying is a prevalent cooking method for C18:3-rich vegetable oils in the Chinese diet. Moreover, C18:3-enriched diacylglycerol (C18:3-DAG) was more strongly associated with CVD risk factors (such as overweight and obesity) than C18:3-enriched triacylglycerol (C18:3-TAG) [49]. Nonetheless, our study did not differentiate C18:3 into C18:3-TAG and C18:3-DAG, which may partially explain the observed adverse association with C18:3. Although our findings suggested a positive association between higher C18:3 intake and increased CVD risk, the potential health benefits of C18:3 should not be overlooked. Previous studies have indicated that moderate C18:3 intake may help improve vascular function, lower blood pressure, and reduce low-density lipoprotein levels, particularly when consumed in appropriate amounts and processed correctly [50, 51]. Therefore, our results are more likely to reflect the adverse effects of excessive intake, improper processing methods, or dietary habits specific to the Chinese population (e.g., stir-frying) on the health effects of C18:3.

In contrast to plant-derived C18:3, marine n-3 PUFA intake, particularly EPA and DHA, exhibited significant cardiovascular protective effects in the present study, notably reducing the risk of CVD and MI. This finding was consistent with many previous epidemiological studies [19, 44, 52, 53]. A meta-analysis conducted by Hu et al. (2019) [54], which included 13 RCTs with 127,477 participants, demonstrated that marine n-3 PUFA supplementation was strongly associated with a lower risk of MI, CHD, and total CVD. Similarly, Von Schacky et al. (2020) [55] confirmed an inverse association between marine n-3 PUFA levels in erythrocytes and the risk of MI, CHD and CVD. A prospective study involving 14,117 participants also found

that higher marine n-3 PUFA consumption was significantly associated with lower all-cause mortality in CHNS (HR_{Q4vsQ1}=0.74, 95% CI: 0.61-0.89) [46]. Nevertheless, according to the China National Nutrition Surveys, the overall dietary intake of PUFA was high (8.6% of daily energy), but the marine n-3 PUFA intake was low (3.6 mg/day) among Chinese adults [56]. This finding aligns with our study. Hence, marine n-3 PUFA consumption should be increase, especially among the Chinese population, to meet the international dietary guidelines, which recommend a total DHA and EPA intake of ≥250 mg/day [46].

The cardiovascular protective effects of marine n-3 PUFA may be explained by several interrelated biological mechanisms. Experimental studies have demonstrated that EPA and DHA are readily incorporated into cell membranes, enhancing membrane fluidity and modulating lipid rafts that influence signal transduction and gene expression [57, 58]. This membrane remodeling facilitates the generation of specialized pro-resolving mediators, such as resolvins and protectins, which have been shown to suppress NF-κB activity and inhibit the production of pro-inflammatory cytokines [59]. These anti-inflammatory effects are considered central to the cardioprotective properties of marine n-3 PUFA. In addition, marine n-3 PUFA improve endothelial function by enhancing nitric oxide bioavailability and reducing oxidative stress; they also inhibit platelet aggregation, lower triglyceride levels, stabilize cardiac electrophysiology, and reduce heart rate and blood pressure [57, 58]. These pleiotropic actions contribute to their beneficial effects on atherosclerosis progression and cardiovascular event prevention. Notably, EPA and DHA may differ in their cardiovascular actions: EPA appears to exert stronger anti-inflammatory and endothelial-protective effects, whereas DHA is more effective in lowering blood pressure, heart rate, and platelet aggregation [60, 61]. These distinct effects likely stem from their structural and metabolic differences, and support more tailored approaches to CVD prevention.

In the Chinese population, higher dietary SFA intake was positively associated with an increased risk of MI but showed no significant association with stroke. Higher intakes of C18:0 and C16:0 markedly elevated MI risk by approximately 1.92-fold and 1.95-fold, respectively. These results are consistent with previous findings from a Chinese case-control study conducted by Wang et al. (2024) [19]. While earlier meta-analyses, such as those by Mazidi et al. (2020) [6], Zong et al. (2016) [10], and Siri-Tarino et al. (2010) [62], highlighted the complexity of the relationship between SFA and CVD risk, recent Mendelian randomization evidence by Wang et al. (2024) [63] has further supported a causal relationship between higher circulating SFA levels and increased CHD risk. In addition, a recent NHANES-based cohort study [64] found that higher dietary SFA intake was associated with increased cardiovascular mortality among older adults. Overall, the current body of evidence continues to support a positive association between high SFA intake and CAD risk. Notably, this association may be influenced by dietary patterns in China, particularly the increasing consumption of animal-based foods and the high intake of SFA [35]. The primary dietary sources of SFA include red meat, animal fats such as lard, lamb, and beef, as well as plant-based oils (e.g., palm oil, coconut oil). Previous investigations have demonstrated that excessive SFA intake, especially C18:0 and C16:0, may contribute to lipid metabolism disorders, promote inflammatory responses, and impair insulin sensitivity as well as vascular

endothelial function [19, 29]. Mechanistically, these fatty acids can elevate low-density lipoprotein cholesterol levels, a key factor in atherosclerosis and MI development [65]. Additionally, they may activate inflammatory signaling pathways, such as NF-κB, inducing the expression of pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin-6, which play critical roles in chronic inflammation and MI progression [66]. These findings suggest that limiting dietary SFA intake, particularly from C16:0- and C18:0-rich sources, may help reduce MI risk in Chinese individuals.

No significant associations were found among total dietary MUFA, C18:1, and C16:1 intake and the risk of CVD, MI, or stroke in the Chinese population. This finding aligns with the Prospective Urban Rural Epidemiology study [18], a large cohort study involving 18 countries, which reported no association between MUFA intake and CVD, MI, or stroke risk. Similarly, a meta-analysis of 11 cohort studies found no significant relationship between MUFA intake and CHD risk [67]. However, conflicting evidence remains. A prospective study by Virtanen et al. (2014) [68] suggested that high MUFA intake may increase CHD risk. Additionally, a study analyzing three population-based cohorts reported that elevated blood MUFA levels were associated with increased cardiovascular risk [69]. In contrast, Wang et al (2024) found a negative association between erythrocyte total MUFA and CAD risk in Chinese adults (OR_{T3vsT1} = 0.50, 95% CI: 0.33-0.77) [19]. Furthermore, a meta-analysis incorporating 32 cohort studies (including 841,211 subjects) indicated that long-term consumption of MUFA-rich olive oil was associated with a reduced risk of cardiovascular events (9%), and stroke (17%) [70]. These inconsistent findings may stem from differences in study design, sample size, population characteristics, regional dietary patterns, dietary assessment methods, and MUFA sources, including plant- and animal-based foods [13]. Therefore, caution is warranted when interpreting these results, and further research is needed to clarify the relationship between MUFA intake and CVD risk in Chinese adults.

In subgroup analyzes, a significant association between CVD risk and total dietary MUFA intake was found only in men, while the link between stroke risk and MUFA intake was observed among rural residents. These interactions may be attributed to a higher MUFA intake among individuals with these traits. Other identified interactions remain to be elucidated in future studies.

Our research has important public health implications for reducing CVD through dietary modifications in the Chinese population. To our knowledge, this is the first nationwide study to assess the association between dietary fatty acids and CVD risk in China. The present study has the following advantages. The prospective design, large population, and long duration of follow-up with detailed covariate collection could reduce the probability of reverse causation. Furthermore, we adopted the cumulative average intake of nutrients method to represent long-term diet, which helps to minimize within-individual heterogeneity and dietary assessment errors. Additionally, RCS analyses were implemented to explore the potential non-linear relationships between dietary fatty acid intake and the risk of cardiovascular events.

Nevertheless, certain limitations must be acknowledged when interpreting our findings. First, although we adjusted for a wide range of demographic, lifestyle, and clinical covariates, the observational nature of this

study makes it susceptible to residual confounding from unmeasured factors, such as health-conscious behaviors, physical activity, and access to healthcare, which could influence both dietary intake and CVD risk. Additionally, the possibility of reverse causality and recall bias cannot be fully excluded. Second, stroke and MI cases in the CHNS were based on self-reports, and CVD was defined solely based on these two diseases. Third, dietary trans-fatty acids were not included in the study due to a lack of available data. Nonetheless, given the reported very low intake of trans-fatty acids in China [71], their exclusion is unlikely to have a significant impact on our findings. Fourth, a 3-day 24-hour recall period may not fully reflect an individual's long-term dietary habits, as it can be affected by factors such as temporary dietary changes, seasonal variations, and special occasions [24]. Even so, the cumulative average of the 3-day recall data remains a reasonable method for long-term dietary assessment [26, 32]. Fifth, although this study focused on individual dietary fatty acids, it did not incorporate analyses of overall dietary patterns. Since fatty acids are consumed as part of complex food matrices, interactions with other dietary components may influence their effects. Future research incorporating dietary pattern analysis could provide additional insights. Sixth, the study did not distinguish between different food sources or cooking methods of dietary fatty acids. However, the physiological effects of fatty acids may differ depending on their sources (e.g., dairy vs. red meat) and cooking methods (e.g., frying vs. boiling) [48, 72]. Some high-quality studies suggest saturated fats from certain sources, such as dairy products, may not be significantly associated with increased cardiovascular risk [7, 72]. Further studies are needed in the future to explore these aspects in more detail. Finally, caution is needed when generalizing our findings to other populations, as Chinese dietary patterns and cooking styles are distinct.

5. Conclusion

In conclusion, our findings support an inverse association between marine n-3 PUFA intake, including EPA and DHA, and the risk of MI. In contrast, higher dietary intake of PUFA, n-6 PUFA, C18:2n-6, C18:3n-3, and SFA was positively associated with an increased risk of CVD, particularly MI, in the Chinese population. Moreover, similar results for these fatty acids were observed in RCS regression analyses. These findings highlight the critical role of promoting marine n-3 PUFA intake while limiting n-6 PUFA and SFA consumption in CVD prevention. Collectively, our results may provide valuable insights for future intervention studies designed to develop effective prevention and treatment strategies to alleviate the burden of CVD among Chinese adults.

Data availability statement

All datasets utilized in present study are available in online repositories. The repository names or accession numbers can be accessed at: https://www.cpc.unc.edu/projects/china.

Ethics statement

The institutional review boards at the University of North Carolina (Chapel Hill, NC, United States) and the National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention (Beijing,

China) reviewed and approved the studies involving human participants. All participants provided written informed consent.

Conflicts of interest

The authors declare no competing interests.

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