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Association of Pro-Inflammatory Diet with Long-Term Risk of All-Cause and Cardiovascular Disease Mortality: NIPPON DATA80

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Aim: A pro-inflammatory diet may increase the risk of cardiovascular disease (CVD) and all-cause mortality. However, this remains inconclusive as there is yet no study using a dietary record method that has been conducted in a large general population. Furthermore, an underestimation of the pro-inflammatory diet may exist due to the unmeasured effect of salt intake. Thus, in this study, we aimed to examine how pro-inflammatory diet is associated with the long-term risk of all-cause and CVD mortality in a representative Japanese population.

Methods: A national nutrition survey was conducted throughout Japan in 1980. After considering the exclusion criteria, 9284 individuals (56% women aged 30–92 years) were included in this study. In total, 20 dietary parameters derived from 3-day weighed dietary records were used to calculate the dietary inflammatory index (DII). The causes of death were monitored until 2009. The Cox proportional hazards model was used to determine multivariable-adjusted hazard ratios (HRs). Stratified analysis according to salt intake level was also performed.

Results: Compared with the lowest quartile of DII, multivariable-adjusted HRs (95% confidence intervals) in the highest quartile were 1.28 (1.15, 1.41), 1.35 (1.14, 1.60), 1.48 (1.15, 1.92), 1.62 (1.11, 2.38), and 1.34 (1.03, 1.75) for all-cause mortality, CVD mortality, atherosclerotic CVD mortality, coronary heart disease mortality, and stroke mortality, respectively. Stratified analysis revealed stronger associations among individuals with higher salt intake.

Conclusions: As per our findings, a pro-inflammatory diet was determined to be positively associated with the long-term risk of all-cause and CVD mortality in a representative Japanese population. Thus, considering both salt intake and pro-inflammatory diet is deemed crucial for a comprehensive assessment of CVD risk.

Key words: Dietary Inflammatory Index, Cardiovascular disease mortality, Salt intake, Cohort study

Introduction

Chronic inflammation is known to contribute to the development of cardiovascular diseases (CVDs) and other non-communicable diseases[1]. Diet may exert a pro- or anti-inflammatory effect[2]. Hence, dietary inflammatory potential may amplify all-cause and CVD mortality[3-6]. However, the association of a

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pro-inflammatory diet with all-cause and CVD mortality remains inconclusive as there is yet no study conducted using a dietary record method in a large general population. In addition, underestimation of pro-inflammatory diet for all-cause and CVD mortality may exist due to the unmeasured effect of salt intake because no previous study has considered how salt intake affects the association between pro-inflammatory diet and all-cause and CVD mortality. Salt intake is an important risk factor for all-cause and CVD mortality[7] and is considered the main component of any diet.

Furthermore, the association of a pro-inflammatory diet with coronary heart disease (CHD) and stroke mortality is yet to be elucidated[3, 8]. In addition, how a pro-inflammatory diet affects atherosclerotic cardiovascular disease (ASCVD) mortality in the general population remains unknown. There is only one study that has associated pro-inflammatory diet with atherosclerotic vascular disease mortality in women aged ≥ 70 years[9]. The effects of a pro-inflammatory diet may differ according to the pathological basis of CVD mortality.

Thus, in this present study, we aimed to investigate how a pro-inflammatory diet is associated with the long-term risk of all-cause and CVD mortality and how this association is influenced by salt intake. We used a 29-year follow-up data from the National Nutrition Survey of Japan (NNSJ), in which nutrient intake was assessed using a 3-day weighed dietary record method.

Methods

Study Participants

The National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, 1980 (NIPPON DATA80), is a prospective cohort study of the National Survey of Circulatory Disorders and the NNSJ conducted by the Japanese Ministry of Health and Welfare. Participants were 10546 adults aged ≥ 30 years from 300 districts randomly selected throughout Japan and enrolled in the baseline survey. Further details are described elsewhere[10]. For this study, the participants were excluded if they had missing information in terms of their diet (n=124), demographics, lifestyle factors, and CVD risk factors (n=113); had history of myocardial infarction or stroke (n=161); had total energy intake of <500 kcal/day or >5,000 kcal/day (n=15) at baseline; or had lost to follow-up (n=849) owing to incomplete residential address at the baseline survey. In total, 9284 participants were included in the analysis **(Supplementary Fig. 1)**. This current study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and it was approved by the Institutional Review Board of Shiga University of Medical Science (R2005-021).

Dietary Assessment

Estimates of food groups and nutrient intakes were calculated using the weighed dietary record method for each household from the NNSJ 1980. Participants weighed and recorded all foods and beverages consumed by any family member on three consecutive days (excluding weekends and national holidays), as per the instructions of a trained dietitian. Accuracy of the data was reviewed and confirmed during and after the survey. The intakes of food groups and nutrients were coded and calculated for each household using the Modified Standards Tables for Food Composition in Japan (3rd edition). For individual-based data, estimates of food groups and nutrient intakes were calculated by dividing household data proportionally by the average consumption ratio by sex and age groups because individual data were not measured in the NNSJ that was conducted before 1995. Further details on the estimation and validation of this method are reported elsewhere[11, 12]. Salt intake (g) was calculated from dietary sodium (mg) using the molar mass equation[13]. β-Carotene (μg) was converted from vitamin A (RE) based on interconversion equivalency[14].

Dietary Inflammatory Index

The inflammatory potential of a diet was assessed using the dietary inflammatory index (DII). In a previous study, 45 dietary parameters of DII were identified based on their effects on 6 inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and C-reactive protein (CRP)), and a global standard database was created to compare the DII scores in diverse populations. A more detailed description of the DII is provided elsewhere[15]. Briefly, DII is known to provide the overall inflammatory effect score, global daily mean intake, and standard deviation (SD) for each dietary parameter. The estimates of the global daily mean intake and SD for each parameter were derived from 11 datasets, which represent a wide range of diets across diverse populations living in different regions of the world. First, the Z-score was obtained by subtracting the global daily mean intake from the individual's intake and then dividing it by the SD. To minimize "right skewing," each Z-score was converted to a percentile value, which was then doubled, and 1 was subtracted from the doubled percentile value.

Next, the centered value was multiplied by its respective overall inflammatory effect score. Finally, all dietary parameter-specific DII scores were added to obtain the overall DII score for each participant. A positive DII score was representative of a pro-inflammatory diet, whereas a negative DII score indicated an anti-inflammatory diet. Given that the overall consumption of energy in the diet has been associated with inflammation, and many studies have shown a strong association between DII score and total energy intake, a method accounting for energy intake, that is, the energy-adjusted DII (E-DII), was later developed[16]. In this study, the energy adjustment of the dietary parameters of DII (including salt) was performed using the residual method[17]. In total, 20 dietary parameters were utilized to calculate the DII, and these are as follows: protein, fat, carbohydrate, vitamin A, vitamin B1, vitamin B2, vitamin C, niacin, vitamin E, magnesium, fiber, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega-6 fatty acids, omega-3 fatty acids, total trans fatty acids, β-carotene, and iron. Only foods, not supplements, were found to have contributed to the DII score in this study.

Covariates

Information on age, sex, smoking and drinking status, work strength, body mass index (BMI), serum total cholesterol, hypertension status, and diabetes history was assessed by physical examination and questionnaires, including medical history information and casual blood samples from the participants at baseline. Salt intake was measured using a dietary survey. Body height and weight were measured with the participants wearing light clothing and no shoes. BMI was defined as weight (kg) divided by height squared (m^2). Smoking and drinking status, work strength, and diabetes history were assessed using self-administered questionnaires during the face-to-face interviews with trained public health nurses. Blood pressure (BP) was measured using a standard mercury sphygmomanometer. Hypertension status was defined as systolic BP of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mm Hg and/or taking antihypertensive medicine[18]. Casual blood samples were collected and centrifuged within 60 min of collection. The total cholesterol concentration (mg/dL) was measured using enzyme assays[19, 20].

Follow-Up and Outcomes

The participants of this study were followed up from 1980 to 2009. The vital status of the participants was confirmed every 5 years, and the last year of confirmed survival was censored. The primary outcomes were all-cause and CVD mortality. The secondary outcomes were ASCVD, CHD, stroke, and non-CVD mortality. The National Vital Statistics database of Japan was used to identify the cause of death in the deceased participants, with permission from the Management and Coordination Agency of the Government of Japan. Causes of death were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) until the end of 1994 and the Tenth Revision (ICD-10) from 1995 to the end of 2010. Details of this classification have been described previously[21]. Cause-specific mortality was coded for CVD (ICD-9: 393–459 or ICD-10: I00–I99); ASCVD included CHD and cerebral infarction (ICD-9: 410–414, 433, 434, 437.7a, 437.7b or ICD-10: I20–I25, I63, I69.3), CHD (ICD-9: 410–414 or ICD-10: I20–I25), stroke (ICD-9: 430–438 or ICD-10: I60–I69), and non-CVD (except for ICD-9: 393–459 or ICD-10: I00–I99).

Statistical Analysis

The participants were divided into quartiles (Q) of equal size based on their DII scores. The baseline characteristics of the participants across the DII quartiles were compared using the Cochran–Mantel–Haenszel test for categorical variables and analysis of variance or Kruskal–Wallis for continuous variables. The intake of nutrients or food groups across the DII quartiles, which was adjusted for age, sex, and total energy consumption, was compared using a general linear regression test. To determine the association between DII and all-cause and CVD mortality risk, Cox proportional hazards model was used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Five models were used to assess the associations. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, BMI, smoking and drinking status, and work strength. Model 4 was adjusted for the variables mentioned in Model 3, with energy-adjusted salt intake as the main model. In Model 5, total cholesterol, hypertension status, and diabetes history were further adjusted. Moreover, analyses were further stratified by salt intake (< 13.2 g/day [median] and ≥ 13.2 g/day), sex (men and women), age at baseline (aged < 65 years and ≥ 65 years), and BMI (< 25 kg/m^2 and ≥ 25 kg/m^2). The interactions between the DII score and salt intake, age, sex, and BMI for all-cause and CVD mortality were also assessed. *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Analysis Systems software package (version 9.4; SAS Institute, Cary, NC, USA).

Table 1. Baseline characteristics of participants according to DII quartiles (NIPPON DATA80, 1980, Japan)

Characteristics	Overall (n = 9284)	Q1 (n = 2321)	Q2 (n = 2321)	Q3 (n = 2321)	Q4 (n = 2321)	p value
DII score	-0.44 ± 1.14	-1.91 ± 0.50	-0.82 ± 0.23	-0.05 ± 0.23	1.02 ± 0.51	<0.001
(range)	(-3.94, 3.24)	(-3.94, -1.24)	(-1.24, -0.44)	(-0.44, 0.36)	(0.36, 3.24)	
Age, years	50.0 ± 13.2	52.8 ± 12.0	49.9 ± 13.3	48.9 ± 13.7	48.4 ± 13.3	<0.001
Sex, n (%)						
Men	4078 (43.9)	693 (29.9)	824 (35.5)	1100 (47.4)	1461 (63.0)	<0.001
Women	5206 (56.1)	1628 (70.1)	1497 (64.5)	1221 (52.6)	860 (37.1)	
BMI, kg/m^2	22.7 ± 3.2	23.0 ± 3.2	22.8 ± 3.2	22.5 ± 3.1	22.5 ± 3.1	<0.001
SBP, mmHg	136 ± 21	137 ± 21	136 ± 21	135 ± 21	136 ± 22	<0.001
Total cholesterol, mg/dL	189 ± 34	193 ± 34	190 ± 34	187 ± 34	186 ± 32	<0.001
Salt, g/day	13.2 (10.4, 16.6)	14.8 (12.0, 18.6)	13.0 (10.4, 16.5)	12.4 (9.9, 15.6)	12.3 (9.7, 15.6)	<0.001
Total energy, kcal/d	2140 ± 492	2156 ± 481	2089 ± 472	2104 ± 487	2209 ± 517	<0.001
Smoking status, n (%)						
Current smoker	3045 (32.8)	509 (21.9)	614 (26.5)	853 (36.8)	1069 (46.1)	<0.001
Ex-smoker	855 (9.2)	186 (8.0)	189 (8.1)	214 (9.2)	266 (11.5)	
Never smoker	5384 (58.0)	1626 (70.1)	1518 (65.4)	1254 (54.0)	986 (42.5)	
Drinking status, n (%)						
Current drinker	4082 (44.0)	780 (33.6)	929 (40.0)	1083 (46.7)	1290 (55.6)	<0.001
Ex-drinker	296 (3.2)	68 (2.9)	50 (2.2)	79 (3.4)	99 (4.3)	
Never drinker	4906 (52.8)	1473 (63.5)	1342 (57.8)	1159 (49.9)	932 (40.2)	
Work strength, n (%)						
Hard	2409 (26.0)	517 (22.3)	538 (23.2)	614 (26.5)	740 (31.9)	<0.001
Moderate	3348 (36.1)	832 (35.9)	803 (34.6)	878 (37.8)	835 (36.0)	
Light	3527 (38.0)	972 (41.9)	980 (42.2)	829 (35.7)	746 (32.1)	
Diabetes history, n (%)						
Yes	283 (3.1)	78 (3.4)	72 (3.1)	64 (2.8)	69 (3.0)	0.683
Hypertension status[§], n (%)						
Yes	4196 (45.2)	1142 (49.2)	1041 (44.9)	977 (42.1)	1036 (44.6)	<0.001

Continuous variables are expressed as mean ± standard deviation and median (interquartile range) for variables with a skewed distribution. Analysis of Variance/Kruskal–Wallis test was used to analyze continuous variables. Categorical variables are expressed as numbers (%). The Cochran–Mantel–Haenszel test was used to analyze categorical variables.

[§]Hypertension status was defined as systolic blood pressure 140 (mmHg) or greater and/or diastolic blood pressure 90 (mmHg) or greater and/or taking antihypertensive medicine.

DII, Dietary Inflammatory Index; BMI, Body Mass Index; SBP, systolic blood pressure; Q, quartile.

Results

In total, 9284 participants were included in this analysis. Their overall mean age was 50 years, with a minimal difference between sexes (56.1% women). The average DII was determined to be −0.44 (range −3.94, 3.24). With regard to the baseline characteristics of participants according to DII quartiles, the most anti-inflammatory diet-consuming group (Q1) was older; had higher BMI, total cholesterol, and salt intake; and had a greater proportion of hypertension status. In contrast, the most pro-inflammatory diet-consuming group (Q4) was more likely to be men, current smokers, current drinkers, and those whose workload is heavy. Systolic BP and total energy were observed to have a U-shaped association with DII quartiles. The proportion of participants with a history of diabetes was similar across the DII quartiles **(Table 1)**.

The adjusted intake of nutrients according to DII quartiles is shown in **Table 2**. Only carbohydrate intake was found to be positively associated with the DII score, whereas the remaining nutrients were determined to be inversely associated with DII scores. For the adjusted intake of food groups, increase in cereal and rice intake has resulted in higher DII scores **(Supplementary Table 1)**. Compared with global daily mean intake, there were lower intake of fat, saturated fatty acids, and total trans fatty acids and higher intake of vitamin E, omega-3 fatty acids, and β -carotene. The dietary parameter-specific DII scores for these nutrients were negative and thus were added

Table 2. Adjusted intake[§] of nutrients according to DII quartiles

Nutrients	Q1 (n = 2321)	Q2 (n = 2321)	Q3 (n = 2321)	Q4 (n = 2321)	p value
Protein (g/day)	86.7 (86.3, 87.2)	82.3 (81.8, 82.7)	79.8 (79.4, 80.2)	76.2 (75.8, 76.6)	<0.001
Total fat (g/day)	54.0 (53.5, 54.5)	51.5 (51.0, 52.0)	48.6 (48.1, 49.1)	43.4 (42.9, 43.9)	<0.001
Carbohydrate (g/day)	314 (313, 316)	322 (320, 323)	329 (328, 330)	341 (340, 342)	<0.001
Vitamin A (RE/day)	726 (720, 733)	531 (524, 537)	434 (427, 440)	316 (309, 322)	<0.001
Vitamin B1 (mg/day)	1.29 (1.28, 1.31)	1.17 (1.15, 1.18)	1.10 (1.09, 1.12)	1.03 (1.01, 1.04)	<0.001
Vitamin B2 (mg/day)	1.22 (1.21, 1.23)	1.06 (1.05, 1.07)	0.98 (0.97, 0.99)	0.88 (0.87, 0.89)	<0.001
Vitamin C (mg/day)	162 (161, 163)	120 (118, 121)	100 (98, 101)	77 (76, 78)	<0.001
Niacin (mg/day)	19.9 (19.7, 20.1)	19.1 (18.9, 19.3)	18.9 (18.7, 19.1)	18.6 (18.4, 18.8)	<0.001
Vitamin E (mg/day)	11.7 (11.6, 11.7)	10.2 (10.2, 10.3)	9.3 (9.2, 9.3)	7.7 (7.6, 7.8)	<0.001
Magnesium (mg/day)	342 (341, 344)	307 (306, 309)	290 (289, 292)	270 (269, 272)	<0.001
Total dietary fiber (g/day)	22.1 (22.0, 22.2)	18.5 (18.4, 18.6)	16.7 (16.6, 16.8)	14.6 (14.5, 14.7)	<0.001
Cholesterol (mg/day)	393 (388, 398)	379 (374, 384)	356 (352, 361)	327 (323, 332)	<0.001
Saturated fatty acids (g/day)	14.6 (14.5, 14.8)	14.5 (14.3, 14.6)	13.8 (13.7, 14.0)	13.0 (12.8, 13.1)	<0.001
MUFA (g/day)	20.2 (20.1, 20.4)	19.3 (19.1, 19.5)	18.2 (18.0, 18.3)	16.0 (15.8, 16.1)	<0.001
PUFA (g/day)	15.0 (14.9, 15.1)	13.8 (13.6, 13.9)	12.8 (12.6, 12.9)	10.8 (10.6, 10.9)	<0.001
Omega-6 fatty acids (g/day)	11.5 (11.4, 11.6)	10.6 (10.4, 10.7)	9.8 (9.7, 9.9)	8.3 (8.2, 8.4)	<0.001
Omega-3 fatty acids (g/day)	1.94 (1.92, 1.96)	1.74 (1.72, 1.76)	1.57 (1.55, 1.60)	1.23 (1.20, 1.25)	<0.001
Total trans fatty acids (g/day)	0.83 (0.81, 0.85)	0.84 (0.83, 0.86)	0.78 (0.76, 0.80)	0.69 (0.67, 0.71)	<0.001
β-carotene (μg/day)	8715 (8634, 8796)	6369 (6289, 6448)	5204 (5125, 5283)	3787 (3707, 3868)	<0.001
Iron (mg/day)	16.4 (16.3, 16.5)	14.5 (14.4, 14.6)	13.5 (13.4, 13.6)	12.3 (12.2, 12.4)	<0.001
Salt (g/day)	15.7 (15.6, 15.9)	14.2 (14.0, 14.4)	13.4 (13.3, 13.6)	12.6 (12.4, 12.8)	<0.001

Continuous variables are expressed as least-squares means and 95% confidence intervals (95% CIs). A general linear regression test was used to analyze the estimates of least-squares means, 95% CIs, and p-values.
[§]Adjusted for age, sex, and total energy consumption.
DII, Dietary Inflammatory Index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; Q, quartile.

to the overall DII score as an anti-inflammatory dietary parameter **(Supplementary Table 2)**.

Table 3 shows the multivariable-adjusted HRs (95% CIs) by DII quartiles for all-cause, CVD, and non-CVD mortality. In age- and sex-adjusted model (Model 2), all-cause, CVD, ASCVD, and non-CVD mortality were determined to be positively associated with DII score across consecutive quartiles. In the same model, the highest HR was found in the third quartile for stroke mortality. These associations have remained significant with further adjustment for BMI and lifestyle factors (Model 3). In the main model (Model 4), HRs (95% CIs) for the highest, in comparison to the lowest quartile of DII were 1.28 (1.15, 1.41), 1.35 (1.14, 1.60), 1.48 (1.15, 1.92), 1.62 (1.11, 2.38), and 1.23 (1.09, 1.39) for all-cause mortality, CVD mortality, ASCVD mortality, CHD mortality, and non-CVD mortality, respectively. For stroke mortality, the third quartile and the highest quartile of DII were indicated to be 1.49 (1.17, 1.91) and 1.34 (1.03, 1.75), respectively (Model 4). These results were similar after additional adjustment for CVD risk factors was conducted (Model 5). Similar results were obtained in the analysis using the continuous DII score, as shown in **Supplementary Table 3** and **Supplementary Fig. 2**. DII score per 1 SD increase was found as a significant determinant for each event across models 2 to 5.

Table 4 shows the multivariable-adjusted HRs (95% CIs) by DII quartiles for all-cause and CVD mortality according to salt intake level. In the group with higher salt intake, increased DII score was associated with higher HRs for all-cause, CVD, ASCVD, CHD, and stroke mortality. Pro-inflammatory diet was determined to be associated with all-cause and stroke mortality in the lower salt intake group, although the trend was deemed insignificant for stroke mortality (p trend=0.226). However, there was no significant interaction between DII score and salt intake for all-cause and CVD mortality, except for ASVCD mortality (p for interaction =0.024). Furthermore, among the most anti-inflammatory diet-consuming group, higher HRs were observed in the strata of younger age and normal weight **(Supplementary Table 4)**. The significant interaction was observed between DII score and age or BMI for all-cause mortality (p for interaction <0.001 and 0.002, respectively). For CVD mortality, a

Table 3. Multivariable-adjusted HRs and 95% CIs by DII quartiles for all-cause, cardiovascular disease and non-cardiovascular disease mortality

	Q1 (n = 2321)	Q2 (n = 2321)	Q3 (n = 2321)	Q4 (n = 2321)	p for trend
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Person-years	56401	56501	56425	55994	
All-cause mortality					
Deaths, n	863	802	835	881	
Model 1	1.00 (ref.)	0.93 (0.84, 1.02)	0.96 (0.88, 1.06)	1.03 (0.94, 1.13)	0.389
Model 2	1.00 (ref.)	1.11 (1.01, 1.23)	1.18 (1.07, 1.30)	1.27 (1.15, 1.40)	<0.001
Model 3	1.00 (ref.)	1.12 (1.02, 1.23)	1.15 (1.04, 1.26)	1.24 (1.13, 1.37)	<0.001
Model 4	1.00 (ref.)	1.13 (1.03, 1.25)	1.17 (1.06, 1.29)	1.28 (1.15, 1.41)	<0.001
Model 5	1.00 (ref.)	1.12 (1.02, 1.24)	1.18 (1.07, 1.30)	1.27 (1.15, 1.41)	<0.001
CVD mortality					
Deaths, n	300	273	286	290	
Model 1	1.00 (ref.)	0.91 (0.77, 1.07)	0.95 (0.81, 1.12)	0.98 (0.83, 1.15)	0.916
Model 2	1.00 (ref.)	1.10 (0.93, 1.29)	1.19 (1.01, 1.41)	1.28 (1.09, 1.51)	0.002
Model 3	1.00 (ref.)	1.10 (0.93, 1.30)	1.16 (0.98, 1.37)	1.26 (1.07, 1.49)	0.006
Model 4	1.00 (ref.)	1.13 (0.96, 1.33)	1.21 (1.02, 1.43)	1.35 (1.14, 1.60)	0.001
Model 5	1.00 (ref.)	1.11 (0.94, 1.31)	1.24 (1.05, 1.46)	1.36 (1.15, 1.62)	<0.001
ASCVD mortality					
Deaths, n	128	130	143	138	
Model 1	1.00 (ref.)	1.01 (0.79, 1.29)	1.11 (0.88, 1.41)	1.09 (0.86, 1.38)	0.367
Model 2	1.00 (ref.)	1.23 (0.96, 1.57)	1.38 (1.09, 1.75)	1.39 (1.09, 1.78)	0.005
Model 3	1.00 (ref.)	1.22 (0.96, 1.56)	1.34 (1.05, 1.70)	1.38 (1.08, 1.77)	0.009
Model 4	1.00 (ref.)	1.26 (0.98, 1.61)	1.40 (1.10, 1.79)	1.48 (1.15, 1.92)	0.002
Model 5	1.00 (ref.)	1.25 (0.97, 1.60)	1.45 (1.13, 1.85)	1.52 (1.17, 1.96)	0.001
CHD mortality					
Deaths, n	60	55	57	62	
Model 1	1.00 (ref.)	0.91 (0.63, 1.32)	0.95 (0.66, 1.36)	1.04 (0.73, 1.49)	0.777
Model 2	1.00 (ref.)	1.12 (0.78, 1.62)	1.21 (0.84, 1.74)	1.40 (0.97, 2.02)	0.066
Model 3	1.00 (ref.)	1.12 (0.78, 1.62)	1.18 (0.82, 1.70)	1.40 (0.97, 2.02)	0.077
Model 4	1.00 (ref.)	1.20 (0.83, 1.73)	1.30 (0.89, 1.88)	1.62 (1.11, 2.38)	0.014
Model 5	1.00 (ref.)	1.21 (0.84, 1.76)	1.36 (0.94, 1.98)	1.71 (1.17, 2.51)	0.006
Stroke mortality					
Deaths, n	123	112	149	125	
Model 1	1.00 (ref.)	0.91 (0.70, 1.17)	1.21 (0.95, 1.54)	1.03 (0.80, 1.32)	0.368
Model 2	1.00 (ref.)	1.08 (0.84, 1.40)	1.48 (1.16, 1.88)	1.28 (0.99, 1.65)	0.011
Model 3	1.00 (ref.)	1.08 (0.83, 1.39)	1.43 (1.12, 1.82)	1.25 (0.97, 1.62)	0.021
Model 4	1.00 (ref.)	1.11 (0.86, 1.43)	1.49 (1.17, 1.91)	1.34 (1.03, 1.75)	0.006
Model 5	1.00 (ref.)	1.08 (0.83, 1.40)	1.52 (1.19, 1.94)	1.33 (1.02, 1.74)	0.005
Non-CVD mortality					
Deaths, n	563	529	549	591	
Model 1	1.00 (ref.)	0.94 (0.83, 1.05)	0.97 (0.86, 1.09)	1.06 (0.94, 1.19)	0.257
Model 2	1.00 (ref.)	1.12 (0.99, 1.26)	1.16 (1.03, 1.31)	1.25 (1.11, 1.41)	<0.001
Model 3	1.00 (ref.)	1.12 (1.00, 1.27)	1.13 (1.00, 1.27)	1.22 (1.09, 1.38)	0.002
Model 4	1.00 (ref.)	1.13 (1.00, 1.27)	1.14 (1.01, 1.28)	1.23 (1.09, 1.39)	0.002
Model 5	1.00 (ref.)	1.12 (0.99, 1.26)	1.14 (1.01, 1.29)	1.22 (1.08, 1.38)	0.002

The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).
Model 1 was unadjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for age, sex, BMI, smoking status, drinking status, and work strength.
Model 4 was adjusted for the variables in Model 3 plus energy-adjusted salt intake.
Model 5 was adjusted for the variables in Model 4 plus serum total cholesterol, hypertension status, and diabetes history.
DII, Dietary Inflammatory Index; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; Q, quartile; ref, reference.

Table 4. Multivariable-adjusted HRs[§] and 95% CIs by DII quartiles for all-cause and cardiovascular disease mortality according to salt intake level

	Q1 (n = 2321)	Q2 (n = 2321)	Q3 (n = 2321)	Q4 (n = 2321)	p for trend
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Salt intake					
≥ 13.2 g/day (n = 4642)					
Person-years	28305	28020	28431	27821	
All-cause mortality					
n	415	424	417	452	
HR (95% CI)	1.00 (ref.)	1.12 (0.98, 1.29)	1.19 (1.04, 1.37)	1.33 (1.15, 1.53)	<0.001
CVD mortality					
n	148	144	147	154	
HR (95% CI)	1.00 (ref.)	1.11 (0.88, 1.40)	1.29 (1.02, 1.63)	1.50 (1.18, 1.91)	<0.001
ASCVD mortality					
n	59	69	70	72	
HR (95% CI)	1.00 (ref.)	1.36 (0.95, 1.93)	1.58 (1.11, 2.25)	1.88 (1.30, 2.71)	0.001
CHD mortality					
n	28	30	29	33	
HR (95% CI)	1.00 (ref.)	1.28 (0.76, 2.15)	1.41 (0.83, 2.40)	1.93 (1.13, 3.32)	0.018
Stroke mortality					
n	68	62	71	71	
HR (95% CI)	1.00 (ref.)	1.01 (0.71, 1.43)	1.31 (0.93, 1.83)	1.41 (0.99, 2.01)	0.025
< 13.2 g/day (n = 4642)					
Person-years	28298	28338	28196	27910	
All-cause mortality					
n	429	393	407	444	
HR (95% CI)	1.00 (ref.)	1.18 (1.03, 1.35)	1.14 (0.99, 1.30)	1.23 (1.07, 1.41)	0.009
CVD mortality					
n	145	127	143	141	
HR (95% CI)	1.00 (ref.)	1.16 (0.91, 1.47)	1.19 (0.94, 1.51)	1.23 (0.97, 1.56)	0.099
ASCVD mortality					
n	70	64	64	71	
HR (95% CI)	1.00 (ref.)	1.21 (0.86, 1.71)	1.08 (0.77, 1.52)	1.20 (0.85, 1.68)	0.443
CHD mortality					
n	33	25	24	32	
HR (95% CI)	1.00 (ref.)	0.97 (0.58, 1.64)	0.88 (0.52, 1.50)	1.21 (0.73, 1.99)	0.580
Stroke mortality					
n	54	56	71	56	
HR (95% CI)	1.00 (ref.)	1.36 (0.94, 1.99)	1.56 (1.09, 2.23)	1.23 (0.84, 1.80)	0.226

The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).
[§]Adjusted for age, sex, BMI, smoking status, drinking status, and work strength.
DII, Dietary Inflammatory Index; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular diseases; CHD, coronary heart disease; Q, quartile; ref., reference.

significant interaction was observed between DII score and age (p for interaction =0.003). No significant interaction was observed between DII score and sex for all-cause and CVD mortality.

Discussion

In this cohort study that examined a representative Japanese population, we assessed the long-term effects of a pro-inflammatory diet on all-cause and CVD mortality risk using the weighed dietary record method. As per our findings, participants who consumed a pro-inflammatory diet had a 35% higher risk of CVD mortality than those who consumed an anti-inflammatory diet. The association between a pro-inflammatory diet and long-

term CVD mortality risk was more apparent after adjusting for salt intake. A significant interaction was observed between salt intake and pro-inflammatory diet for ASCVD mortality risk.

During this era, the population in Japan exhibited an overall anti-inflammatory diet, as evidenced by a baseline DII score average of −0.44. Only carbohydrate intake was higher in a pro-inflammatory diet, which is consistent with another study from Japan[12]. In contrast, lower intake of fat, saturated fatty acids, and total trans fatty acids as compared to their respective global daily mean intakes was observed, resulting in an anti-inflammatory effect on the overall diet in the current population. Meanwhile, the Multiethnic Cohort Study reported that Japanese Americans were more likely to have an anti-inflammatory diet than other ethnic groups[22]. However, anti-inflammatory diets have been replaced by pro-inflammatory diets in the general Japanese population. The Japanese National Health and Nutrition Survey (NHNS) 2003–2015 has attributed this to the trend of Westernization in Japanese diet[23]. Similarly, a Japanese cohort study of the NHNS in 2010 (NIPPON DATA2010)[24] reported an average DII score of 0.82, which was higher than the present NIPPON DATA80. This indicates that the overall diet has become pro-inflammatory in the representative Japanese population after 30 years. Food intake patterns and dietary parameter-specific DII scores in association with DII quartiles reported in the NIPPON DATA2010 study were consistent with our results[24].

With regard to the association between a pro-inflammatory diet and long-term risk of all-cause and CVD mortality, our findings appear to be similar to those of studies using a food frequency questionnaire (FFQ) conducted in the general population with a follow-up period of 12–19 years[22, 25, 26]. However, the JACC study from Japan[26] confirmed this finding only in Japanese men. In terms of ASCVD mortality, our findings were consistent with that of a previous study demonstrating that a higher DII score was associated to an increased risk of subclinical atherosclerosis and 15-year ASCVD mortality among postmenopausal women[9]. There has been a weak or null association between DII score and CHD or stroke mortality in previous studies[26-29]. This may be related to the lack of salt intake control. The association between DII scores and stroke mortality was found to be nonlinear, as observed in other two studies[26, 28]. In the strata with higher salt intake, the DII score was determined to be linearly associated with stroke mortality. In contrast to our findings, several studies have reported no association between a pro-inflammatory diet and CVD mortality[27, 29, 30]. This may be attributed to factors such as different settings, different dietary survey methods, or residual effects of salt intake on the association between a pro-inflammatory diet and CVD mortality.

The association between a pro-inflammatory diet and CVD mortality remained constant even after adjusting for CVD risk factors. Possible mechanism underlying this association could be low-grade inflammation that contributes to atherogenesis[31, 32]. In people with and without known CVD risk factors, a diet rich in fish, fruit, and vegetables and low in dairy products and meat with moderate alcohol consumption has been associated with decreased levels of endothelial dysfunction and inflammation[33-35]. Inflammation is known to be a key driver of atherosclerotic plaque formation along with serum cholesterol, which is involved in all stages of atherosclerosis, from endothelial dysfunction to plaque rupture[32, 36]. Regardless of cholesterol level, low-grade inflammation can predict the risk of CVD events. In low-risk men, those with elevated CRP levels consistently exhibit a high ischemic risk, even in the absence of hyperlipidemia[37]. The synergistic effect of healthier food combinations, such as an anti-inflammatory diet, can have a beneficial impact on endothelial function, as estimated by a decrease in the circulating levels of biomarkers[33]. In general, dietary habits are inclined to be unhealthy as compared with individuals without smoking and alcohol drinking habits[38]. However, the effect of DII score on all-cause and CVD mortality showed minimal difference between models with and without adjustment for smoking and drinking status. In addition, the DII score was independently associated with the outcomes regardless of smoking and drinking status in our population.

The association between a pro-inflammatory diet and CVD mortality was more evident in the higher salt intake group, as increased dietary salt intake may induce inflammation[6, 39]. In a cross-sectional study, higher CRP levels in hypertensive patients with increased urinary sodium and potassium ratios indicated the role of inflammation as a pathogenic mechanism of vascular damage associated with excess salt intake[40]. In addition, a pro-inflammatory diet can have significant effects on all-cause mortality in the low and high salt intake groups. This may be due to excessive salt consumption, which is traditionally high among Japanese population. According to the NHNS in Japan, in 1973, the average salt intake was 14.5 g/day[41]. This high intake of salt has been attributed to Japanese dietary habit, which includes consuming miso soup and pickles and using soy sauce as an

additional seasoning in the 1980s[42]. In this study, the median salt intake was found to be 10.4 g/day even in the low salt intake group, which is higher than the current World Health Organization (WHO) recommendation (5 g/day)[43]. Therefore, confirming this observation in populations identified to have lower salt consumption is required.

The effect of a pro-inflammatory diet on the risk of CVD mortality was observed only in younger individuals, which can be attributed to differences in the prevalence of hypertension, which is a strong risk factor between younger and older age groups. The risk of high BP for CVD mortality may be more significant in older individuals as compared to the risk associated with a pro-inflammatory diet[44]. Additionally, the effect of DII score on all-cause and CVD mortality was significant in individuals with normal weight, which is consistent with a previous study[26]. Several reasons need to be mentioned for it. Firstly, given the low percentage of overweight participants in this current study, the number of CVD events in this group may be insufficient to observe the effect of a pro-inflammatory diet. Secondly, adipose mass correlates with BMI, which is known to increase the secretion of pro-inflammatory adipokines[45]. Because of the high levels of pro-inflammatory adipokines, the diet-induced inflammatory effect may be less pronounced for obese individuals as compared to those of normal weight. No significant interaction was determined between DII score and sex for all-cause and CVD mortality. The DII score was derived from household dietary survey, and individual-based data was calculated proportionally in this study, which may have resulted in minimal differences between men and women.

Our study has its strong points with regard to external and internal validity. First, dietary information was collected using a 3-day weighed dietary record method, which is known to provide a more precise estimation than the FFQ[22, 26] or dietary recall[25, 46, 47] methods that were mostly used in previous studies. This is the only current study that confirmed the significant association between a pro-inflammatory diet and long-term CVD mortality using the dietary record method. Second, our study's follow-up duration was longer than those reported in previous studies. Third, the study population was randomly selected across Japan, with a wide spectrum of characteristics and dietary habits, which allowed for the generalizability of our findings in the country. Lastly, yet importantly, our study is the first to examine how the association between a pro-inflammatory diet and long-term risk of all-cause and CVD mortality is affected by one's salt intake, which is a potential confounder or modifier of this association.

However, several limitations should be noted when interpreting our results. First, only 20 dietary parameters were used to estimate the DII scores. It should be noted, however, that no previous study used all 45 dietary parameters to calculate the DII score for all-cause and CVD mortality. In previous studies, 25–29 dietary parameters were used to calculate for DII scores[12, 22, 25, 27, 28, 30, 46-50]. Furthermore, a construct validation study reported that the reduction in available dietary parameters would not lead to a large drop-off in the predictive ability of the DII score[51]. Second, dietary habits and CVD risk factors were assessed only once in the baseline survey, and changes during the follow-up period were not considered. Third, inflammatory biomarkers were not assessed in our study. However, NIPPON DATA2010 study has validated that higher DII scores were associated with higher CRP levels in the general Japanese population[24], which used a similar dietary survey method with NIPPON DATA80 study. Elevated levels of triglyceride-rich lipoproteins have been found to increase inflammation[52, 53]. However, the residual effect of triglyceride-rich lipoproteins was undetermined. Lastly, information on medications for dyslipidemia remains lacking because these medications were not popular in Japan in this era.

Conclusions

A significant association between pro-inflammatory diet and long-term all-cause and CVD mortality risk among the general Japanese population was observed in our study. It is thus important to consider both salt intake and a pro-inflammatory diet for a comprehensive assessment of CVD mortality risk. Regulating inflammation with an anti-inflammatory diet at an earlier age may prevent all-cause and CVD mortality risks.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Author Contributions

The authors contributed to the study as follows. Study conception and design by GG, YO, AK and KM. Material preparation, data collection by AK, KK, NO, KY, TO, AO, HU and KM. Analysis were performed by GG and NG. Manuscript drafting and reviewing by GG, YO, AK, YY, AH and KM. All authors read and approved the final manuscript.

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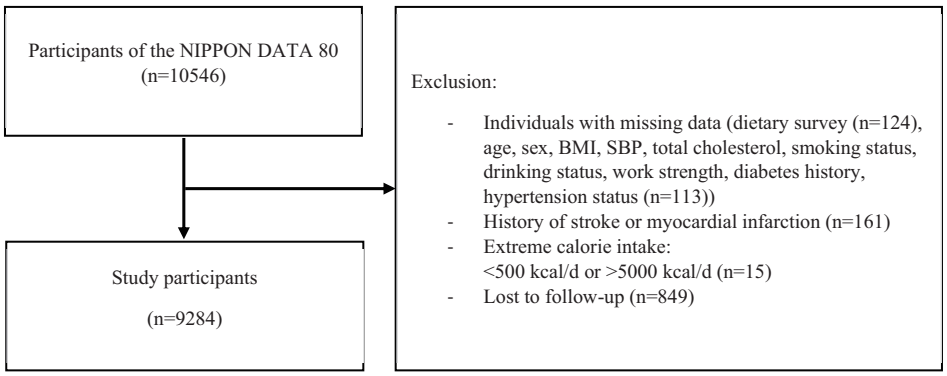


Supplementary Fig. 1. Flow diagram of study participants (NIPPON DATA 80, 1980, Japan)

Supplementary Table 1. Adjusted intake[§] of food groups according to DII quartiles

Food groups	Q1 (*n* = 2321)	Q2 (*n* = 2321)	Q3 (*n* = 2321)	Q4 (*n* = 2321)	*p* value
Cereals (g/day)	299 (297, 302)	325 (323, 327)	344 (342, 347)	371 (369, 373)	<0.001
Potatoes (g/day)	79.0 (77.1, 80.8)	66.2 (64.4, 68.0)	61.4 (59.6, 63.2)	56.7 (54.9, 58.6)	<0.001
Sugar and sweeteners (g/day)	13.8 (13.4, 14.2)	13.7 (13.3, 14.1)	13.4 (13.0, 13.8)	12.8 (12.4, 13.2)	0.007
Soybean and legume (g/day)	91.8 (90.0, 93.5)	78.0 (76.2, 79.7)	72.3 (70.6, 74.0)	64.2 (62.4, 65.9)	<0.001
Nuts (g/day)	2.45 (2.23, 2.67)	1.63 (1.42, 1.84)	1.38 (1.17, 1.59)	0.88 (0.66, 1.09)	<0.001
Fruits (g/day)	227 (223, 232)	177 (173, 181)	147 (143, 151)	118 (114, 123)	<0.001
Mushrooms (g/day)	12.2 (11.7, 12.7)	9.9 (9.4, 10.4)	8.7 (8.2, 9.2)	7.0 (6.5, 7.5)	<0.001
Sea algae (g/day)	9.37 (9.04, 9.70)	6.88 (6.55, 7.20)	5.20 (4.88, 5.52)	3.93 (3.60, 4.26)	<0.001
Meats (g/day)	61.5 (60.1, 62.9)	61.6 (60.2, 63.0)	60.8 (59.5, 62.2)	60.1 (58.7, 61.5)	0.438
Eggs (g/day)	40.1 (39.2, 40.9)	39.3 (38.5, 40.1)	36.7 (35.9, 37.5)	33.4 (32.6, 34.2)	<0.001
Milk and dairy products (g/day)	92.7 (90.1, 95.4)	86.6 (84.0, 89.2)	77.7 (75.1, 80.3)	68.9 (66.3, 71.6)	<0.001
Fats and oils (g/day)	19.4 (19.0, 19.8)	17.9 (17.5, 18.3)	15.8 (15.4, 16.2)	11.2 (10.8, 11.6)	<0.001
Sweets and snacks (g/day)	21.6 (20.6, 22.6)	22.9 (21.9, 23.8)	21.3 (20.3, 22.3)	22.2 (21.2, 23.2)	0.130
Fish and shellfish (g/day)	122 (119, 124)	113 (111, 115)	106 (104, 108)	95 (93, 97)	<0.001
Green and yellow vegetable (g/day)	95.5 (94.2, 96.8)	60.8 (59.5, 62.0)	45.9 (44.6, 47.1)	28.0 (26.7, 29.3)	<0.001
Other vegetable (g/day)	270 (266, 273)	225 (221, 228)	205 (202, 209)	177 (174, 180)	<0.001
Rice (g/day)	216 (213, 219)	241 (238, 243)	262 (260, 265)	292 (289, 295)	<0.001
Flour product (g/day)	82.2 (80.0, 84.4)	84.9 (82.8, 87.1)	84.0 (81.9, 86.1)	81.8 (79.7, 84.0)	0.139

Continuous variables are expressed as least-squares means and 95% confidence intervals (95% CIs). A general linear regression test was used to analyze the estimates of least-squares means, 95% Cis, and *p*-values.
[§]Adjusted for age, sex, and total energy consumption.
DII, Dietary Inflammatory Index; Q, quartile.

Supplementary Table 2. Dietary parameter-specific DII scores and mean intake included in DII

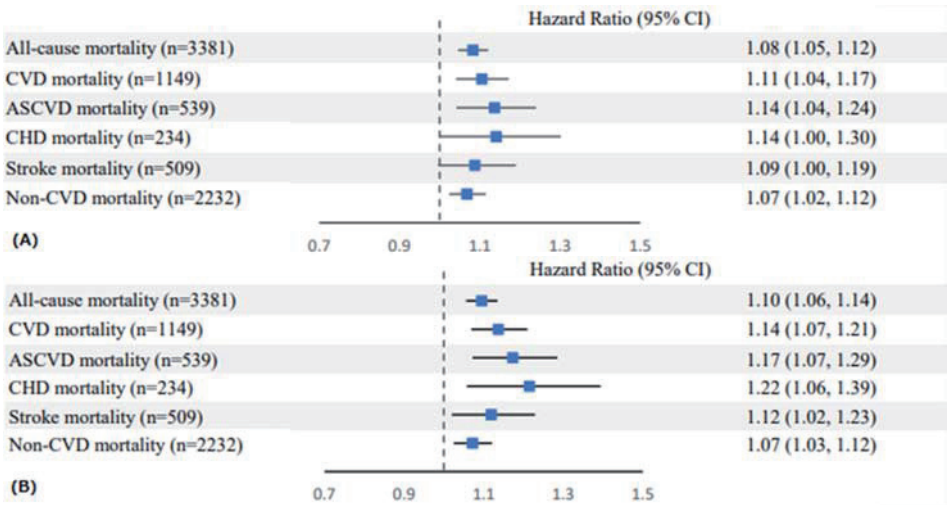
Dietary parameters	Overall inflammatory effect score[§]	Global daily mean intake, units/day[§]	SD[§]	NIPPON DATA80 mean intake, units/day	NIPPON DATA80 dietary parameter-specific DII score[†]
Total energy (kcal/day)	0.180	2056	338.0	2139	0.014
Protein (g/day)	0.021	79.4	13.9	81.3	0.001
Total fat (g/day)	0.298	71.4	19.4	49.4	-0.195
Carbohydrate (g/day)	0.097	272.2	40.0	326.5	0.068
Vitamin A (RE/day)	-0.401	983.9	518.6	501.6	0.246
Vitamin B1 (mg/day)	-0.098	1.7	0.7	1.1	0.053
Vitamin B2 (mg/day)	-0.068	1.7	0.8	1.0	0.039
Vitamin C (mg/day)	-0.424	118.2	43.5	114.5	0.040
Niacin (mg/day)	-0.246	25.9	11.8	19.1	0.103
Vitamin E (mg/day)	-0.419	8.7	1.5	9.7	-0.119
Magnesium (mg/day)	-0.484	310.1	139.4	302.5	0.021
Total dietary fiber (g/day)	-0.663	18.8	4.9	18.0	0.085
Cholesterol (mg/day)	0.110	279.4	51.2	363.9	0.054
Saturated fatty acids (g/day)	0.373	28.6	8.0	14.0	-0.336
MUFA (g/day)	-0.009	27.0	6.1	18.4	0.007
PUFA (g/day)	-0.337	13.9	3.8	13.1	0.052
Omega-6 (g/day)	-0.159	10.8	7.5	10.0	0.013
Omega-3 (g/day)	-0.436	1.1	1.1	1.6	-0.150
Total trans fatty acids (g/day)	0.229	3.2	3.8	0.8	-0.107
β-carotene (μg/day)	-0.584	3718	1720	6019	-0.317
Iron (mg/day)	0.032	13.4	3.7	14.2	0.004

[§]Corresponding values of overall inflammatory effect score, global daily mean intake, and standard deviation (SD) were obtained from Shivappa *et al* [15].
[†]Dietary parameter-specific DII score calculated using method by Shivappa *et al* [15].
DII, Dietary Inflammatory Index; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; RE, retinol equivalent.

Supplementary Table 3. Multivariable-adjusted HRs and 95% CIs per 1 SD increase of DII score for all-cause and cardiovascular disease mortality

	HR (95% CI)
All-cause mortality	
Deaths, n	3381
Model 1	1.02 (0.99, 1.06)
Model 2	1.10 (1.06, 1.13)
Model 3	1.08 (1.05, 1.12)
Model 4	1.10 (1.06, 1.14)
Model 5	1.10 (1.06, 1.14)
CVD mortality	
Deaths, n	1149
Model 1	1.01 (0.96, 1.08)
Model 2	1.12 (1.05, 1.18)
Model 3	1.11 (1.04, 1.17)
Model 4	1.14 (1.07, 1.21)
Model 5	1.14 (1.07, 1.22)
ASCVD mortality	
Deaths, n	539
Model 1	1.06 (0.97, 1.15)
Model 2	1.15 (1.05, 1.25)
Model 3	1.14 (1.04, 1.24)
Model 4	1.17 (1.07, 1.29)
Model 5	1.19 (1.08, 1.30)
CHD mortality	
Deaths, n	234
Model 1	1.04 (0.91, 1.18)
Model 2	1.15 (1.01, 1.31)
Model 3	1.14 (1.00, 1.30)
Model 4	1.22 (1.06, 1.39)
Model 5	1.24 (1.08, 1.42)
Stroke mortality	
Deaths, n	509
Model 1	1.03 (0.94, 1.12)
Model 2	1.10 (1.01, 1.21)
Model 3	1.09 (1.00, 1.19)
Model 4	1.12 (1.02, 1.23)
Model 5	1.12 (1.02, 1.23)
Non-CVD mortality	
Deaths, n	2232
Model 1	1.03 (0.99, 1.07)
Model 2	1.08 (1.04, 1.13)
Model 3	1.07 (1.02, 1.12)
Model 4	1.07 (1.03, 1.12)
Model 5	1.07 (1.02, 1.12)

The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).
Model 1 was unadjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for age, sex, BMI, smoking status, drinking status, and work strength.
Model 4 was adjusted for the variables in Model 3 plus energy-adjusted salt intake.
Model 5 was adjusted for the variables in Model 4 plus serum total cholesterol, hypertension status, and diabetes history.
DII, Dietary Inflammatory Index; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease.



Supplementary Fig. 2. Forest plot for multivariable-adjusted HRs and 95% CIs per 1 SD increase of DII score for all-cause and cardiovascular disease mortality

Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs). A represents model 3, which adjusted for age, sex, BMI, smoking status, drinking status, and work strength. B represents model 4, which adjusted for Model 3 plus energy-adjusted sodium intake.

Supplementary Table 4. Multivariable-adjusted HRs and 95% CIs by DII quartiles for all-cause and cardiovascular disease mortality according to subgroups

	Q1 (n = 2321)	Q2 (n = 2321)	Q3 (n = 2321)	Q4 (n = 2321)	p for trend
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Sex[§]					
Men (n = 4078)					
Person-years	23323	24023	23940	23920	
All-cause mortality					
n	463	435	431	442	
HR (95% CI)	1.00 (ref.)	1.18 (1.03, 1.35)	1.20 (1.05, 1.37)	1.30 (1.13, 1.49)	<0.001
CVD mortality					
n	148	130	121	150	
HR (95% CI)	1.00 (ref.)	1.19 (0.94, 1.52)	1.13 (0.89, 1.45)	1.55 (1.22, 1.97)	0.001
ASCVD mortality					
n	77	59	63	74	
HR (95% CI)	1.00 (ref.)	1.05 (0.75, 1.48)	1.16 (0.82, 1.63)	1.50 (1.07, 2.09)	0.018
CHD mortality					
n	32	19	27	31	
HR (95% CI)	1.00 (ref.)	0.83 (0.47, 1.48)	1.27 (0.75, 2.16)	1.67 (0.99, 2.84)	0.023
Stroke mortality					
n	71	59	66	66	
HR (95% CI)	1.00 (ref.)	1.11 (0.78, 1.58)	1.29 (0.92, 1.82)	1.38 (0.97, 1.97)	0.049
Women (n = 5206)					
Person-years	32503	32499	32462	32651	
All-cause mortality					
n	432	391	396	391	
HR (95% CI)	1.00 (ref.)	1.12 (0.97, 1.29)	1.22 (1.06, 1.40)	1.19 (1.03, 1.37)	0.010
CVD mortality					
n	159	138	146	157	
HR (95% CI)	1.00 (ref.)	1.07 (0.85, 1.35)	1.23 (0.97, 1.55)	1.29 (1.02, 1.62)	0.017
ASCVD mortality					
n	63	64	69	70	
HR (95% CI)	1.00 (ref.)	1.26 (0.89, 1.80)	1.49 (1.04, 2.12)	1.47 (1.03, 2.09)	0.023
CHD mortality					
n	27	36	26	36	
HR (95% CI)	1.00 (ref.)	1.72 (1.04, 2.86)	1.37 (0.79, 2.39)	1.86 (1.11, 3.14)	0.052
Stroke mortality					
n	67	49	75	56	
HR (95% CI)	1.00 (ref.)	0.90 (0.62, 1.30)	1.50 (1.07, 2.11)	1.12 (0.77, 1.61)	0.160
Age[†]					
≥ 65 years (n = 1504)					
Person-years	5878	5358	5265	5167	
All-cause mortality					
n	342	346	348	359	
HR (95% CI)	1.00 (ref.)	1.06 (0.91, 1.23)	1.10 (0.94, 1.28)	1.14 (0.97, 1.33)	0.100
CVD mortality					
n	142	143	148	143	
HR (95% CI)	1.00 (ref.)	1.05 (0.83, 1.33)	1.15 (0.91, 1.46)	1.15 (0.90, 1.47)	0.213
ASCVD mortality					
n	65	72	75	72	
HR (95% CI)	1.00 (ref.)	1.15 (0.82, 1.62)	1.24 (0.88, 1.75)	1.25 (0.87, 1.79)	0.196
CHD mortality					
n	26	27	25	30	
HR (95% CI)	1.00 (ref.)	1.20 (0.69, 2.07)	1.20 (0.68, 2.12)	1.69 (0.96, 2.98)	0.087
Stroke mortality					
n	57	64	78	62	
HR (95% CI)	1.00 (ref.)	1.11 (0.77, 1.59)	1.39 (0.98, 1.98)	1.09 (0.75, 1.60)	0.416

(Cont. Supplementary Table 4)

	Q1 (n = 2321)	Q2 (n = 2321)	Q3 (n = 2321)	Q4 (n = 2321)	p for trend
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
< 65 years (n = 7780)					
Person-years	51051	50951	51248	50402	
All-cause mortality					
n	493	465	476	552	
HR (95% CI)	1.00 (ref.)	1.17 (1.03, 1.34)	1.19 (1.04, 1.35)	1.34 (1.17, 1.53)	< 0.001
CVD mortality					
n	146	126	143	158	
HR (95% CI)	1.00 (ref.)	1.15 (0.91, 1.47)	1.34 (1.06, 1.70)	1.54 (1.21, 1.97)	< 0.001
ASCVD mortality					
n	56	57	70	72	
HR (95% CI)	1.00 (ref.)	1.37 (0.94, 1.98)	1.74 (1.21, 2.51)	1.84 (1.26, 2.68)	0.001
CHD mortality					
n	31	28	31	36	
HR (95% CI)	1.00 (ref.)	1.20 (0.72, 2.02)	1.44 (0.86, 2.40)	1.73 (1.03, 2.92)	0.032
Stroke mortality					
n	61	48	74	65	
HR (95% CI)	1.00 (ref.)	1.06 (0.72, 1.55)	1.68 (1.18, 2.39)	1.53 (1.05, 2.24)	0.005
BMI‡					
≥ 25.0 kg/m^2 (n = 1962)					
Person-years	11888	11975	12385	12088	
All-cause mortality					
n	191	186	158	184	
HR (95% CI)	1.00 (ref.)	0.96 (0.78, 1.18)	0.98 (0.79, 1.22)	1.24 (1.00, 1.55)	0.056
CVD mortality					
n	67	60	58	66	
HR (95% CI)	1.00 (ref.)	0.92 (0.64, 1.31)	1.10 (0.76, 1.58)	1.41 (0.97, 2.03)	0.043
ASCVD mortality					
n	31	27	27	29	
HR (95% CI)	1.00 (ref.)	0.91 (0.53, 1.54)	1.18 (0.69, 2.01)	1.39 (0.80, 2.42)	0.158
CHD mortality					
n	15	14	9	11	
HR (95% CI)	1.00 (ref.)	1.01 (0.48, 2.14)	0.80 (0.34, 1.88)	1.12 (0.48, 2.60)	0.936
Stroke mortality					
n	29	21	28	26	
HR (95% CI)	1.00 (ref.)	0.76 (0.43, 1.36)	1.28 (0.75, 2.19)	1.33 (0.75, 2.36)	0.140
< 25.0 kg/m^2 (n = 7322)					
Person-years	44597	44293	44206	43887	
All-cause mortality					
n	657	634	671	700	
HR (95% CI)	1.00 (ref.)	1.22 (1.09, 1.36)	1.20 (1.08, 1.34)	1.30 (1.16, 1.46)	< 0.001
CVD mortality					
n	230	213	227	228	
HR (95% CI)	1.00 (ref.)	1.20 (0.99, 1.45)	1.22 (1.01, 1.47)	1.36 (1.11, 1.65)	0.004
ASCVD mortality					
n	95	102	116	112	
HR (95% CI)	1.00 (ref.)	1.41 (1.06, 1.87)	1.47 (1.11, 1.95)	1.57 (1.17, 2.10)	0.003
CHD mortality					
n	43	43	48	51	
HR (95% CI)	1.00 (ref.)	1.38 (0.90, 2.12)	1.50 (0.98, 2.30)	1.88 (1.21, 2.91)	0.005
Stroke mortality					
n	95	89	118	103	
HR (95% CI)	1.00 (ref.)	1.18 (0.88, 1.58)	1.47 (1.11, 1.94)	1.37 (1.02, 1.85)	0.016

The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs).
§Adjusted for age, BMI, smoking status, drinking status, work strength, and energy-adjusted salt intake.
†Adjusted for age, sex, BMI, smoking status, drinking status, work strength and energy-adjusted salt intake
‡Adjusted for age, sex, smoking status, drinking status, work strength and energy-adjusted salt intake
DII, Dietary Inflammatory Index; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; BMI, body mass index; Q, quartile; ref., reference