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Field report

Relationship between daily eating habits and occurrence of stroke in the O City Cohort I survey: a 26-year follow-up of residents in rural Japan

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Abstract

Objective: This study aimed to elucidate the relationship between daily eating habits and stroke risk factors in O City, Ehime Prefecture, Japan, using stroke registry data collected over a 26-year follow-up period based on standardized national criteria.
Materials and Methods: Overall, 1,793 middle-aged Japanese participants (446 men and 1,347 women) who completed a 33-item Food Frequency Questionnaire (FFQ) and had no history of stroke were matched to those from O City in a stroke registry from 1996 to 2022. Stroke diagnosis for each person was used to determine whether this was their first documented stroke, and we classified strokes as either a cerebral infarction (CI) or a hemorrhagic stroke (HS), the latter which included an intracerebral hemorrhage (ICH) or a subarachnoid hemorrhage (SAH). A Cox proportional hazard regression model was used to examine the association between habitual dietary intake and the occurrence of stroke, using the following covariates: age, body mass index, elevated blood pressure/hypertension, dyslipidemia, prediabetes/diabetes, alcohol consumption, and smoking.
Results: During the 26 years of follow-up, 45 men (10.1%) and 76 women (5.6%) had stroke. The CI rate was 70.2% (n=85; 38 men, 47 women). The HS rate was 29.8% (n=36; 7 men and 29 women); of these patients, 26 and 10 had ICH and SAH, respectively. In men, orange intake showed a significant inverse correlation with CI. In women, fresh fish intake showed a significant inverse correlation with CI, while yogurt intake showed a significant inverse correlation with HS.
Conclusion: Our results indicated that fresh fish intake was significantly associated with the prevention of CI among women in a Japanese cohort survey.

Key words: daily eating habits, occurrence of stroke, cohort survey, rural Japan

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Introduction

When a person experiences a stroke, the emergence of conditions such as post-stroke paralysis leads to impairment in the ability to conduct daily activities. Residual poststroke disability imposes a burden on patients and their families. Since people who have experienced a stroke require nursing care[1)], it is of vital importance for Japan's aging society to establish strategies for stroke prevention.

Recently, the mortality rate of patients after stroke has been decreasing[2)] due to developments in clinical medicine. Stroke is considered a lifestyle-related disease and is influenced by several unhealthy lifestyle factors such as hypertension, type 2 diabetes mellitus, and dyslipidemia. Recently, advancements in hospital-based emergency stroke care and the early detection of lifestyle-related diseases have primarily focused on the prevention of hypertension[3] through health guidance disseminated by public health nurses in regional health centers, which has played an influential role in the decline in mortality from stroke. However, as not all stroke patients die, stroke incidence does not always coincide with stroke mortality[4].

Some studies have reported a relationship between daily eating habits such as high salt and stroke[5–7]. However, few cohort studies have surveyed participants not only about their incidence of stroke but also about lifestyle habits, including dietary intakes[8–11]. Excluding certain well-known nutrients and foods, considerable scope remains for investigation into the relationships between many types of nutrients and foods and the occurrence of stroke. The study aimed to elucidate the relationship between daily eating habits and risk factors for stroke in O City, Ehime Prefecture, Japan, using stroke registry data collected over a 26-year follow-up period based on standardized national criteria[12].

Materials and Methods

Survey participants

To elucidate the risk factors of stroke, we conducted the O City Cohort I Survey between 1996 and 1998. The baseline population consisted of residents who underwent an annual medical examination in O City (before the municipal merger in 2005) based on the Geriatric Health and Medical Service Law (GHMSL). Residents aged 20–94 years who belonged to the National Health Insurance scheme were able to undergo annual medical examinations based on the GHMSL. The local government of O City sent an annual medical examination letter to inform residents who had undergone a medical examination at either a district meeting place or a health center in O City.

Based on data derived from the Basic Resident Register of the former O City, the total population comprised 39,224 people (18,728 men and 20,496 women). Of the people in the 1996 National Health Insurance scheme in the former O City aged 20–94 years, the total population was 10,730 (5,012 men and 5,718 women).

The participants in our O City Cohort I Survey represented 46.3% (n=4,972 respondents out of a total of 10,730 people) of those aged 29–94 years who were enrolled in the National Health Insurance scheme of the former O City.

Of the 4,972 participants in the O City Cohort I Survey, we used data from 1,793 participants (446 men and 1,347 women) who fully responded to the Food Frequency Questionnaire (FFQ) and had no history of stroke. The 1,793 participants aged 29–77 years represented approximately 16.7% of the total 10,730 people aged 20–94 years who belonged to the National Health Insurance scheme in the former O City.

Ethical considerations that arose from privacy issues in this epidemiological study

To use confidential information from medical examinations, health-related questionnaires, and registration data for cerebrocardiovascular events, we obtained written consent from individuals, as required under the Japanese Privacy Protection Law. We received permission from the Research Ethics Committee of the Faculty of Education at Ehime University (approval no. R4-34-1).

Disclosure of information from the O City Basic Resident Register and access to this information as digital data stored on portable media

The survey was approved by the Research Ethics Committee of the Faculty of Education at Ehime University (approval no. R4-34-1) to access the electronically stored personal information in the Basic Resident Register maintained by the local government of O City.

Ethical considerations related to registries for cerebro-cardiovascular events (stroke or myocardial infarction) in O City

Cerebrocardiovascular events were also registered after obtaining approval from the Research Ethics Committee of the Faculty of Education, Ehime University (Approval No. R4-34-1) and submitted documentation to each hospital. Patients who were accurately recorded by the hospital as having experienced a stroke were assigned a research ID. When analyzing the registry data involving personal information connected to a research ID, we deleted personal information and used only the research ID. Furthermore, each hospital notified participants of their opt-out rights regarding epidemiological studies and provided them with the opportunity to withdraw their consent for registration in the database.

Identification of the onset of stroke

The emergency medical care system in O City consists of four core medical institutions with computed tomography (CT) and magnetic resonance imaging (MRI) equipment, in addition to surgical facilities, and one specialized cardiovascular hospital with cardiac intervention facilities. These hospitals were staffed by several neurosurgeons and cardiovascular disease specialists, and accepted patients transported in emergency circumstances from O City and surrounding cities; over 90% of early stage stroke patients in the area were treated at these facilities. We used medical records from surveys, based on a prescribed form completed for patients who had confirmed a stroke and had been domiciled in O City since 1994. Individuals with traumatic brain cerebrovascular disease were excluded. Stroke diagnosis standards from the Ministry of Education and Science were used for each person, and we determined whether this appeared to have been their first stroke and classified the event as cerebral infarction (CI), intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH).

Terminology underpinning cerebrovascular events

Collectively, we defined CI or hemorrhagic stroke (HS), including ICH and SAH, as a cerebrovascular event (CVE).

In cases with CT and MRI findings, classification was aided by identifying the site of the lesion as either a high- or low-density area on the CT and/or MRI scan based on CT and MRI classifications derived from epidemiological studies.

Some stroke incidents that could not be ascertained in the hospital survey were included as stroke occurrences in our survey based on the certificate of death. For all deaths, we applied to the Ministry of Health, Labour and Welfare for special permission to use statistics related to population movement. Using death certificate data and the International Classification of Disease (ICD) code ICD-10, we determined the cause of death for cases in which the cause was previously unknown. When the ICD-10 code for the cause of death was I60-I69, it was defined as stroke. When the codes were I60–I61, I69.0, and I69.1, we defined the event as HS (SAH and ICH). When the codes were I63 and I63.9, the event was defined as a CI.

Follow-up period

Participants were tracked annually until December 31, 2022, and information regarding whether the cohort participants had left O City was verified. By referencing the Basic Resident Register, we documented whether the person was still alive, had resided in or moved out of the area, or had died.

For people who had a CVE, the relevant dates (years) were from the date of the medical examination between 1996 and 1998 until the date of onset of the CVE. For those who did not have a CVE, the relevant dates (years) were from the date of the medical examination between 1996 and 1998 until December 31, 2022, or the date of death. For those who relocated from O City, the relevant dates (years) were from the date of the medical examination between 1996 and 1998 until the date of departure from O City.

Medical examination information for survey subjects

The baseline data of the 1,793 participants consisted of sex, age, height, weight, systolic and diastolic blood pressure, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and blood glucose. Furthermore, we collected blood postprandially, and when the collection was performed after over 8 h had elapsed since eating, we considered the sample to be representative of fasting blood samples.

We used body mass index (BMI)[13] as a measure to determine if a person was underweight (<18.5 kg/m^2), within a normal weight (18.5 to <25.0 kg/m^2), or overweight (≥25.0 kg/m^2).

The following four established risk factors are correlated with the occurrence of a CVE: BMI, elevated blood pressure/hypertension (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg), dyslipidemia (serum triglycerides ≥150 mg/dL or HDL cholesterol <40 mg/dL), and prediabetes/diabetes (fasting glucose ≥110 mg/dL). In the case of a non-fasting blood sample[14], dyslipidemia (blood triglycerides ≥175 mg/dL), and the prediabetes/diabetes criterions (glucose ≥140 mg/dL) were used instead.

Participants who had been receiving medication for hypertension, dyslipidemia, or diabetes mellitus were classified into the respective abnormal category.

Health questionnaire items and analysis

Our health questionnaire consisted of the following items: work history, medical history, physical symptoms, smoking, alcohol consumption, dietary lifestyle, health consciousness, and the FFQ. From the eight components of the questionnaire, we analyzed smoking, alcohol consumption, and the FFQ items.

Dietary assessment

We used 33 items derived from the FFQ of the Japan Public Health Center-based prospective study (JPHC) Cohort II baseline questionnaire[15] which included five frequency categories. The JPHC study was conducted in collaboration with 11 Japan Public Health Centers, National Cancer Centers, National Cardiovascular Centers, universities, research institutes, and medical institutions using a common questionnaire and medical examination.

The FFQ consisted of the following items: chicken, beef, pork, ham, sausage, bacon, liver, fresh fish (*sashimi*, boiled fish, grilled fish), dried fish, dried salted salmon, minced fish products, canned fish, pickled fish, small fish (whitebait, *zyako*, *mezashi*, *tsukudani*), seaweed (kelp, *wakame*, etc.), green vegetables, carrots, tomatoes, potatoes, bean curd, *natto*, *tsukemono*, *nozawana*, other types of *tsukemono*, apples, oranges, eggs, milk, cheese, yogurt, butter, margarine, bread, noodles (except instant noodles), instant noodles, dessert, and Japanese dessert. To determine the frequency of weekly food intake, we used the following classifications: a1=almost never, a2=seldom, a3=1–2 days per week, a4=3–4 days per week, and a5=almost every day. We divided the five answers (a1–a5) into the "no intake" group and the "intake" group. The answers a1 and a2 were classified into the "no intake" group, and the answers a3, a4, and a5 were classified into the “intake” group.

There was a single question in the alcohol consumption section. Q1: “Do you drink alcohol, including occasional drinking?” and the three possible answers were a1=“I do not drink alcohol” (meaning the respondent only drinks alcohol once a month at most), a2=“I used to drink but have given up alcohol”, and a3=“Yes, I drink alcohol”. We divided the three answers (a1–a3) into the “no intake” group and the “intake” group. The answers a1 and a2 were classified into the “no intake” group, and the answer a3 was classified into the “intake” group.

There was also one question in the smoking habit section. Q1: “Do you smoke?” and the three possible answers were a1=“No, I have never smoked”, a2=“I used to smoke but I gave up”, meaning the respondent had not been smoking for ≥3 consecutive months, and a3=“Yes, I smoke”. We divided the three answers (a1–a3) into the “no smoking” group and the “smoking” group. The answers a1 and a2 were classified into the “no smoking” group, and the answer a3 was classified into the “smoking” group.

Statistical methods

The means, medians, and proportions of baseline characteristics were calculated for those who had or did not have a CVE. Comparisons between groups were assessed using the t-test, Wilcoxon test, or either the χ^2 or Fisher’s exact test.

We used the Kaplan–Meier method for the “no intake” groups according to the 33-item FFQ and used them as the standard against which we compared the “intake” groups for the same FFQ items; this was done to determine the influence of eating habits on the occurrence of a CVE in men and women. The log-rank test was used to test for differences based on occurrence curves.

The hazard ratio (HR) and 95% confidence intervals (CI) were calculated for occurrence of stroke in the “intake” group by each food separately compared with the Cox proportional hazard regression model being used for the “no intake” after the following adjustments for model 1: age (continuous), BMI category (underweight, normal weight, and overweight), elevated blood pressure/hypertension (yes or no), dyslipidemia (yes or no), prediabetes/diabetes (yes or no), alcohol consumption (yes or no), and smoking (yes or no). For model 2, we further adjusted for food items that were significantly associated with the occurrence of CVEs in model 1.

The CVEs were further classified into two disease categories: CI and HS. Using the same Cox proportional hazard regression approach for Models 1 and 2, we analyzed the relationship between the frequency of food intake and the occurrence of CI and HS, respectively. A Cox proportional hazards regression model was used to examine the association between habitual dietary intake and the occurrence of CI or HS using the following covariates: age, BMI, elevated blood pressure/hypertension, dyslipidemia, prediabetes/diabetes, alcohol consumption, and smoking. For Model 2, we further adjusted for food items that were significantly associated with the occurrence of CI or HS in Model 1. Statistical significance was set at $P<0.05$. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Japan).

Results

A total of 4,972/10,730 people (46.3%) underwent an annual medical examination; this rate was >29.1% of people who underwent an annual medical examination based on the GHMSL in O City, Ehime Prefecture, in 1995. This higher percentage was due to the Department of Public Health at the Public Health Center at Ehime University School of Medicine, Ehime Prefecture, and O City’s Health Center encouraging residents to undergo medical examinations between 1996 and 2014.

In the O City Cohort I survey, there were 1,793 survey respondents. During the 26-years follow-up (totaling 43,301 person-years), 121 subjects had a CVE at a crude incidence rate of 2.8 per 1,000 person-years. During the 26-year observational period, 45 men (10.1%) and 76 women (5.6%) had CVE. The CI rate was 70.2% (n=85; 38 men, 47 women). The rate of HS was 29.8% (n=36; seven men and 29 women); of these patients, 26 had ICH and 10 had SAH.

The baseline characteristics of patients with and without CVE are shown in Table 1. In the univariate analysis in men, a significant relationship was identified between the occurrence of CVE and age, systolic blood pressure, and elevated blood pressure/hypertension. In women, there was a significant relationship between the occurrence of CVE and age, BMI, systolic blood pressure, diastolic blood pressure, blood glucose, alcohol consumption, elevated blood pressure/hypertension, and dyslipidemia.

Table 2 shows the significant food items associated with CVE in men by CI and HS using Model 1. For the CVE, the HR and 95% confidence were associated with the habitual intake of each food group by men, none of which was statistically significant. Orange consumption showed a significant inverse correlation with the occurrence of CI (HR=0.48, 95% confidence interval: 0.24–0.97). Conversely, there were too few cases of HS in men to be analyzed, and the HR and 95% confidence interval were associated with the habitual intake of each food group.

Table 3 shows the significant food items associated with CVE in women by CI and HS using Model 1. We detected significant inverse associations with the intake of fresh fish (HR=0.46, 95% confidence interval: 0.29–0.75), yogurt (HR=0.43, 95% confidence interval: 0.23–0.82), and Japanese dessert (HR=0.59, 95% confidence interval: 0.36–0.96)

Table 1 Baseline characteristics of participants who had and did not have cerebrovascular events[#]

Characteristic	Study participants, N=1,793					
	Men n=446			Women n=1,347		
	Cerebrovascular events	No cerebrovascular events	*P*-value	Cerebrovascular events	No cerebrovascular events	*P*-value
Participants (%)	45 (10.1)	401 (89.9)		76 (5.6)	1,271 (94.4)	
Age, years	59.4 ± 8.0	53.6 ± 9.4	**<0.001**[*]	58.9 ± 7.1	49.5 ± 10.5	**<0.001**[*]
Body mass index, kg/m^2	22.9 ± 2.3	23.4 ± 2.7	0.156[*]	23.8 ± 3.5	22.8 ± 3.1	**0.014**[*]
Body weight category						
Underweight, number (%)	1 (2.2)	10 (2.5)		4 (5.3)	61 (4.8)	
Normal weight, number (%)	34 (75.6)	284 (70.8)		47 (61.8)	949 (74.7)	
Overweight, number (%)	10 (22.2)	107 (26.7)		25 (32.9)	261 (20.5)	
Blood pressure						
Systolic, mm Hg	136.5 ± 18.8	129.2 ± 16.7	**0.016**[*]	134.9 ± 17.1	122.4 ± 17.6	**<0.001**[*]
Diastolic, mm Hg	81.4 ± 12.5	80.0 ± 11.0	0.47[*]	79.7 ± 9.8	73.7 ± 10.9	**<0.001**[*]
Abnormal[†]	33 (73.3)	215 (53.6)	**0.012**[***]	56 (73.7)	480 (37.8)	**<0.001**[***]
HDL Cholesterol, mg/dL	52.6 ± 12.3	56.2 ± 16.8	0.074[*]	60.5 ± 17.3	62.6 ± 15.4	0.309[*]
Triglyceride, median (IQR), mg/dL	94 (73–142)	110 (71–157)	0.452[**]	98 (68–146)	88 (64–123)	0.112[**]
Serum lipid abnormality[§]	12 (26.7)	120 (29.9)	0.65[***]	19 (25.0)	187 (14.7)	**0.016**[***]
Blood glucose, median (IQR), mg/dL	96 (93–104)	94 (88–104)	0.229[**]	95 (89–105)	92 (87–101)	**0.038**[**]
Serum glucose abnormality[‖]	5 (11.1)	40 (10.0)	0.486[***]	6 (7.9)	59 (4.6)	0.155[***]
Lifestyle factors						
Alcohol consumption	32 (71.1)	280 (69.8)	0.858[***]	2 (2.6)	161 (12.7)	**0.009**[***]
Smoker	33 (73.3)	275 (68.6)	0.513[***]	2 (2.6)	73 (5.7)	0.935[***]

All data are n (%) or mean ± standard deviation, unless indicated otherwise. Significant differences (of 5% or less) between means, medians and percentages were calculated using a: [*]t-test, [**]Wilcoxon test, or either a [***]χ^2 or Fisher's exact test, respectively. [#]Cerebrovascular events included cerebral infarctions and hemorrhagic strokes. [†]Body weight categories were underweight (<18.5 kg/m^2), normal weight (18.5 to <25.0 kg/m^2), and overweight (≥25.0 kg/m^2). [‡]Abnormal blood pressure was defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg. If participants had been receiving medication for hypertension, they were classified as being within the abnormal category. [§]Serum lipid abnormality was defined as serum triglycerides ≥150 mg/dL or HDL cholesterol <40 mg/dL. In the case of a non-fasting blood sample, blood triglycerides ≥175 mg/dL was used instead. If participants had been receiving medication for dyslipidemia, they were classified as being within the abnormal category. [‖]Serum glucose abnormality was defined as fasting glucose ≥110 mg/dL. In the case of a non-fasting blood sample, glucose ≥140 mg/dL was used instead. If participants had been receiving medication for diabetes mellitus, they were classified as being within the abnormal category. HDL: high density lipoprotein; IQR: interquartile range.

Table 2 Food items significantly associated with cerebrovascular events in men using model 1[#, *]

		Male participants, n=446				
		Cerebrovascular events		No cerebrovascular events		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Non		–	–	–	–	–
		Cerebral infarction		No cerebral infarction		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Oranges	–	19 (9.1)	275.8	191 (91.0)	4,594.9	1.00
	+	19 (8.1)	276.9	217 (92.0)	5,101.9	0.48 (0.24–0.97)
		Hemorrhagic stroke		No hemorrhagic stroke		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Not calculated		–	–	–	–	–

[#]Cerebrovascular events included cerebral infarctions and hemorrhagic strokes. [*]Adjusted by age, BMI (according to "underweight", "normal weight", and "overweight"), abnormal blood pressure, serum lipid abnormality, serum glucose abnormality, alcohol consumption, and smoking at baseline. –: no intake; +: intake; BMI: body mass index; HR: hazard ratio.

Table 3 Food items significantly associated with cerebrovascular events in women using model 1[#,*]

		Female participants, n=1,347				
		Cerebrovascular events		No cerebrovascular events		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Fresh fish (*sashimi*,	–	24 (9.8)	378.6	222 (90.2)	5,589.3	1.00
boiled fish, fried fish)	+	52 (4.7)	862.7	1,049 (95.3)	26,220.6	0.46 (0.29–0.75)
Yogurt	–	65 (7.2)	1,066.7	842 (92.8)	21,018.9	1.00
	+	11 (2.5)	174.5	429 (97.5)	10,791.0	0.43 (0.23–0.82)
Japanese dessert	–	51 (6.3)	840.4	755 (93.7)	18,931.0	1.00
	+	25 (4.6)	400.8	516 (95.4)	12,878.9	0.59 (0.36–0.96)
		Cerebral infarction		No cerebral infarction		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Fresh fish (*sashimi*,	–	15 (6.1)	251.4	231 (93.9)	5,716.4	1.00
boiled fish, fried fish)	+	32 (2.9)	525.3	1,069 (97.1)	26,558.1	0.46 (0.25–0.85)
Japanese dessert	–	32 (4.0)	530.2	774 (96.0)	19,241.2	1.00
	+	15 (2.8)	246.4	526 (97.2)	13,033.3	0.53 (0.29–0.99)
		Hemorrhagic stroke		No hemorrhagic stroke		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Yogurt	–	26 (2.9)	412.7	881 (97.1)	21,673.0	1.00
	+	3 (0.7)	51.9	437 (99.3)	10,913.6	0.29 (0.09–0.96)

[#]Cerebrovascular events included cerebral infarctions and hemorrhagic strokes. [*]Adjusted by age, BMI (according to "underweight", "normal weight", and "overweight"), abnormal blood pressure, serum lipid abnormality, serum glucose abnormality, alcohol consumption, and smoking at baseline. –: no intake; +: intake; BMI: body mass index; HR: hazard ratio.

with the occurrence of a CVE. For women, the 30 food items, excluding the following three items of fresh fish, yogurt, and Japanese dessert, were not significantly correlated with the prevention of CVEs (data are not shown). The inverse correlation with either the intake of fresh fish (HR=0.46, 95% confidence interval: 0.25–0.85) or Japanese dessert (HR=0.53, 95% confidence interval: 0.29–0.99) with the occurrence of a CI was found to be statistically significant. The intake of yogurt (HR=0.29, 95% confidence interval: 0.09–0.96) showed a significant inverse correlation with the occurrence of HS. Using the Kaplan–Meier method, Figure 1 shows the cumulative probability of CVE in women related to the same three foods: (A) fresh fish, (B) yogurt, and (C) the Japanese desert. The log-rank test showed that those consuming fresh fish or yogurt were significantly less likely to have CVE than those who did not consume them; however, Japanese desert made no difference. Moreover, when using Model 2 for women, we mutually adjusted for food items that were significantly associated with the occurrence of CI in Model 1.

When we further mutually adjusted for fresh fish, yogurt, and Japanese desert using Model 2, the HR for the intake of Japanese desert was attenuated and lacked significance. In women, the intake of fresh fish and yogurt showed a significant inverse correlation with the occurrence of CVE. The multivariable-adjusted HR for fresh fish intake was 0.53 (95% confidence interval: 0.33–0.87), and for yogurt intake it was 0.50 (95% confidence interval: 0.26–0.96). Using Model 2 in a multivariable-adjusted model for women, the intake of fresh fish showed a significant inverse correlation with the occurrence of CI (HR=0.50, 95% confidence interval: 0.27–0.92).

Table 4 shows the final adjusted food items associated with CI in men using Model 1. Orange consumption was significantly inversely correlated with CI occurrence. However, for CVEs in men, the HR and 95% confidence interval associated with the habitual intake of each food group were not statistically significant, and cases of HS were too few cases of HS to be analyzed to determine the association with the habitual intake of each food group.

Table 5 shows the final adjusted food items associated with the CVE of CI and HS for women using either model 1 or model 2. In model 2, either the intake of fresh fish or yogurt showed a significant inverse correlation with the occurrence of a CVE. Furthermore, the inverse correlation of fresh fish intake with the occurrence of a CI and the inverse correlation of yogurt intake with the occurrence of a HS were found to be statistically significant.

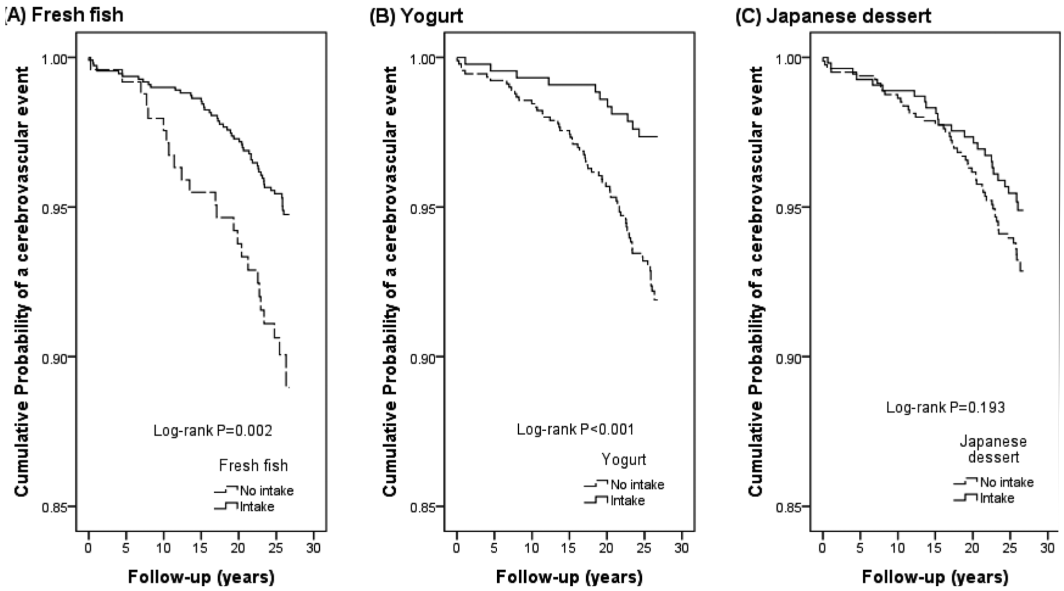

Figure 1 Cumulative probability of cerebrovascular events in relation to the intake of (A) fresh fish, (B) yogurt, and (C) Japanese desserts in women. Cerebrovascular events included cerebral infarctions and hemorrhagic strokes. *P*-value based on the log-rank test.

Table 4 Final adjusted food items associated with cerebrovascular events in men, using model 1[#, *]

		Male participants, n=446				
		Cerebral infarction		No cerebral infarction		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Oranges[b]	–	19 (9.1)	275.8	191 (91.0)	4,594.9	1.00
	+	19 (8.1)	276.9	217 (92.0)	5,101.9	0.48 (0.24–0.97)

[#]Cerebrovascular events included cerebral infarctions and hemorrhagic strokes. [*]Adjusted by age, BMI (according to "underweight", "normal weight", and "overweight"), abnormal blood pressure, serum lipid abnormality, serum glucose abnormality, alcohol consumption, and smoking at baseline. [b]A significant food item in Model 1. –: no intake; +: intake; BMI: body mass index; HR: hazard ratio.

Discussion

Our survey documented the responses of participants in a 26-year-long prospective cohort study and examined the relationship between the frequency of food intake and stroke risk.

For men, the frequency of food consumption was not significantly related to the occurrence of CVE, except for a low intake of oranges, which was significantly correlated with the occurrence of CI. Conversely, our results suggest that in women, either a low intake of fresh fish or the low intake of yogurt showed a significant inverse correlation with the occurrence of CI, and a low intake of yogurt was significantly associated with HS.

In 2014, Hu *et al.*[16] performed a meta-analysis of 20 independent medical articles that consisted of prospective cohort studies published before 2014 and described the relationship between the intake of fruits and vegetables and the risk of stroke among approximately 760,629 participants. Hu *et al.*[16] reported that the intake of oranges negatively impacted the risk of stroke. In 2004, He *et al.*[17] performed a meta-analysis (N=200,575 people from eight independent medical articles published between 1966 and 2003) to assess the relationship between fish intake and stroke. After performing a meta-analysis of nine cohort studies, He *et al.*[17] reported that fish intake had a negative impact on the risk of stroke. In 2022, Chen *et al.*[18] performed a meta-analysis of 20 independent medical articles (covering 21 cohort studies) published between 1966 and 2020 that described the relationship between dairy product intake and stroke in approximately 100,000 participants. Chen *et al.*[18] revealed that dairy product intake has a negative impact on the risk of stroke. Weseler *et al.*[19] reported that the flavonoids found in oranges exhibit the following effects: (1)

Table 5 Final adjusted food items associated with cerebrovascular events in women, using either model 1 or model 2[#, *]

		Female participants, n=1,347				
		Cerebrovascular events		No cerebrovascular events		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Fresh fish (*sashimi*,	–	24 (9.8)	378.6	222 (90.2)	5,589.3	1.00
boiled fish, fried fish)	+	52 (4.7)	862.7	1,049 (95.3)	26,220.6	0.53 (0.33–0.87)
Yogurt	–	65 (7.2)	1,066.7	842 (92.8)	21,018.9	1.00
	+	11 (2.5)	174.5	429 (97.5)	10,791.0	0.50 (0.26–0.96)
		Cerebral infarction		No cerebral infarction		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Fresh fish (*sashimi*,	–	15 (6.1)	251.4	231 (93.9)	5,716.4	1.00
boiled fish, fried fish)	+	32 (2.9)	525.3	1,069 (97.1)	26,558.1	0.50 (0.27–0.92)
		Hemorrhagic stroke		No hemorrhagic stroke		
Food	Intake	n (%)	Person-years	n (%)	Person-years	HR (95% confidence interval)
Yogurt[♭]	–	26 (2.9)	412.7	881 (97.1)	21,673.0	1.00
	+	3 (0.7)	51.9	437 (99.3)	10,913.6	0.29 (0.09–0.96)

[#]Cerebrovascular events included cerebral infarctions and hemorrhagic strokes. [*]Adjusted by age, BMI (according to "underweight", "normal weight", and "overweight"), abnormal blood pressure, serum lipid abnormality, serum glucose abnormality, alcohol consumption, and smoking at baseline. [♭]A significant food item in Model 1. –: no intake; +: intake; BMI: Body mass index; HR: hazard ratio.

antioxidant activity, (2) anti-inflammatory properties, (3) lipid metabolism modulation, (4) platelet function modulation, and (5) antihypertensive effects. Gao *et al.*[20] reported that higher consumption of flavonoid-rich fruits by Japanese women, particularly citrus fruits, strawberries, and grapes, was associated with a lower risk of stroke development. Furthermore, fish intake has been reported to prevent diabetes mellitus[21] and lipidosis[22], leading to a reduction in the risk of ischemic stroke[17]. The potential mechanisms of action of omega-3 polyunsaturated fatty acids, or the n-3PUFAs found in fish in reducing the incidence of stroke by decreasing blood pressure[23], improving endothelial function[22], and inhibiting platelet aggregation[24].

In our survey questions regarding fish intake, the types of fish consumed were classified into five groups: (1) fresh fish (*sashimi*, boiled fish, fried fish), (2) dried fish and dried salted salmon, (3) minced fish products, (4) canned and pickled fish, and (5) small fish (whitebait, *zyako*, *mezashi*, *tukudani*). The four fish Groups (2) to (5) contained more sodium chloride (NaCl) per 100 g edible portion than the fresh fish in group (1)[25]. Accordingly, as this NaCl disparity could be associated with the risk of hypertension in groups (2) to (5), it could also confound any protective effects that these dietary fish groups may offer in relation to CI prevention.

Calcium ions in dairy products play a role in reducing blood pressure[26] and insulin receptor expression through 1,25-dihydroxyvitamin D_3 (activated vitamin D)[27]. Whey proteins found in dairy products potentially have an antihypertensive effect because they inhibit the activity of angiotensin-converting enzyme (ACE)[28] and promote pancreatic insulin secretion[29]. It is conceivable that calcium ion intake, in addition to the whey proteins present in dairy products, could prevent hypertension[30, 31] and diabetes mellitus[32, 33] and reduce the risk of stroke.

Our survey questions regarding dairy product intake included two categories of dairy products: (1) cheese and (2) yogurt. Japanese people who eat cheese tend to choose natural cheeses[34]. As cheese products have more saturated fatty acid equivalents per 100 g of edible portion compared with yogurt[25], the intake of cheese product intake may increase serum cholesterol. Accordingly, because the low amount of saturated fatty acids in yogurt compared to cheese products is associated with a decrease in the risk of dyslipidemia, yogurt intake may prevent HS.

For women, a low intake of either fresh fish or yogurt was correlated with the occurrence of a CVE and found to be statistically significant, HR=0.46 (95% confidence interval: 0.29–0.75) and HR=0.43 (95% confidence interval: 0.23–0.82), respectively. Conversely, for men, neither the intake of fresh fish nor yogurt was significantly related to the occurrence of CVE (HR=0.83 (95% confidence interval: 0.39–1.78) and HR=0.67 (95% confidence interval: 0.24–1.90), respectively); however, these results tended to play a role in stroke prevention.

The small number of male participants potentially reduced the power of the survey results to detect the relationship between an individual food item and the occurrence of CVE. Nevertheless, in men, a low orange intake showed a significant inverse correlation with the occurrence of CI. In 1997, the results of the National Health and Nutrition Survey indicated a 52.7% smoking rate among men[35]; however, in our survey, 69.1% of male participants reported smoking. Takachi *et al.*[36] have reported a clearer inverse association between fruit intake and the risk of cardiovascular disease among women and nonsmokers than among men and smokers. Generally, smoking causes oxidative stress. Due to the higher rate of smoking among male survey participants, the intake of oranges with antioxidant activity likely had a preventative effect on the occurrence of CI.

In our survey, we investigated whether participants experienced their first stroke during a 26-year follow-up period. Using information from medical records or death certificates related to stroke, many epidemiological studies[37–40] report risk factors related to fatal stroke. However, surveys using death resulting from stroke as an endpoint may not accurately identify factors associated with stroke occurrence.

In our cohort study, which used the onset of stroke as an endpoint, our stroke registry was able to determine whether the survey participants had a stroke and could classify the stroke subtypes. To identify risk factors for stroke, it is necessary to obtain information with certainty regarding whether the survey participants had a stroke. To identify stroke onset based on certain criteria, a stroke registry that works in collaboration with a core hospital should be established. A reliable stroke registry would ideally be located in an area where emergency patients are not required to be transported to hospitals outside the study area, particularly for cases in the acute phase of stroke. Because there are a limited regions where it is possible to conduct a survey using occurrence of stroke as an endpoint rather than death caused by stroke, O City was a fitting location for this cohort survey.

By using the occurrence of stroke as an endpoint, we found that fresh fish intake was significantly associated with CI prevention of a CI. In Japan, few cohort surveys have used stroke occurrence as an endpoint to determine the relationship between food consumption and stroke occurrence. To our knowledge, this is the first Japanese cohort survey to suggest that fresh fish intake is associated with the prevention of CI among women.

In Japan, the JPHC is a cohort study involving 11 health centers, including the National Cancer Center, the National Cardiovascular Center, and medical institutions across Japan. The JPHC study involved ~140,000 residents who regularly underwent health examinations, completed questionnaires, and participated in follow-up surveys. Using stroke occurrence as an endpoint, the JPHC study has been used in several reports describing risk factors for stroke onset.

In a JPHC study, Umesawa *et al.*[41] reported an association between calcium intake from dairy products and stroke prevention. Gao *et al.*[20] reported an association between flavonoid intake from fruits and stroke prevention. These two reports emanated from one of the few cohort studies in the Japanese population that selected the occurrence of stroke as the endpoint. These reports have elucidated the association between dairy products and citrus fruits and stroke prevention. The most recent findings support the results of these studies.

Clarifying the relationship between the 33-items of food and the occurrence of stroke may provide important knowledge for the prevention of stroke.

Study limitations

To ensure a fair balance, we addressed several perceived limitations related to our study. As the portion sizes of the 33-items in the FFQ were not specified, we were unable to calculate the amount of nutrients in each food item. Also, because we organized the responses into five categories—a1 (almost never), a2 (seldom), a3 (1–2 days /week), a4 (3–4 days/week) and a5 (almost every day)—for the 33 items in the FFQ and used two groups—“do not consume” groups (a1, a2) and “do consume” groups (a3, a4, a5)—it was difficult to accurately evaluate the weekly nutrient intake from individual foods. As the objective of our survey was to elucidate factors associated with the occurrence of stroke related to the frequency of consuming 33 foods rather than to nutrient intake per meal, we opted to have classifications of “do not consume” (a1, a2) and “consume” (a3, a4, and a5).

We concede that we had a small number of participants in our survey and did not assess the dose-response relationship between individual foods and the occurrence of CVEs. For men, because of the small number of survey participants, the power to detect a relationship between individual food and the occurrence of CVE using a survey was potentially reduced. Based on our survey, there were a small number of CVEs; therefore, we were unable to analyze the relationship between the subtypes of CI, including cardiogenic infarction, lacunar infarction, atherothrombotic infarction, and individual foods. In addition, we combined SAH and ICH to calculate the HS.

We likely overlooked the potential residual confounding relationship between daily dietary habits and the occurrence of CVE. The daily eating habits of our survey participants likely changed during the 26-year follow-up period from the baseline period (1996–1998).

Conclusion

The results of our survey suggest that in men, a low intake of oranges was associated with the occurrence of CI. In women, low intakes of fresh fish or yogurt were associated with the occurrence of CI or HS, respectively. Conversely, the intake of fresh fish by women in a Japanese cohort survey was associated with the prevention of CI. Furthermore, low yogurt intake was associated with the occurrence of HS in women.

Conflict of interest: All authors declare no conflicts of interest.

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Ethics approval and consent to participate: The Research Ethics Committee of the Faculty of Education at Ehime University approved the study protocol. Written informed consent was obtained from individuals prior to the use of confidential information from medical examinations, health-related questionnaires, and registration data for cerebro-cardiovascular events. Furthermore, each hospital that cooperated with the disease registry of cerebrovascular events notified participants of their opt-out rights.

Consent for publication: Consent was obtained from all co-authors to publish this manuscript.

Data availability statement: The dataset for this survey is not publicly available because of privacy and ethical restrictions.

Author contributions: MT conducted data analysis and wrote the manuscript. KM participated in the data analysis and manuscript review. IS collected the data and participated in data analysis. ST reviewed and wrote the manuscript. YT participated in data collection and analysis. HO reviewed and wrote the manuscript TK designed the study and managed the entire process. All the authors have read and approved the final version of the manuscript.

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