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Serum elaidic acid concentration and risk of dementia

The Hisayama Study

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Abstract

Objective

The associations between trans fatty acids and dementia have been unclear. We investigated the prospective association between serum elaidic acid (trans 18:1 n-9) levels, as an objective biomarker for industrial trans fat, and incident dementia and its subtypes.

Methods

In total, 1,628 Japanese community residents aged 60 and older without dementia were followed prospectively from when they underwent a screening examination in 2002–2003 to November 2012 (median 10.3 years, interquartile range 7.2–10.4 years). Serum elaidic acid levels were measured using gas chromatography/mass spectrometry and divided into quartiles. The Cox proportional hazards model was used to estimate the hazard ratios for all-cause dementia, Alzheimer disease (AD), and vascular dementia by serum elaidic acid levels.

Results

During the follow-up, 377 participants developed some type of dementia (247 AD, 102 vascular dementia). Higher serum elaidic acid levels were significantly associated with greater risk of developing all-cause dementia (p for trend = 0.003) and AD (p for trend = 0.02) after adjustment for traditional risk factors. These associations remained significant after adjustment for dietary factors, including total energy intake and intakes of saturated and polyunsaturated fatty acids (both p for trend <0.05). No significant associations were found between serum elaidic acid levels and vascular dementia.

Conclusions

The findings suggest that higher serum elaidic acid is a possible risk factor for the development of all-cause dementia and AD in later life. Public health policy to reduce industrially produced trans fatty acids may assist in the primary prevention of dementia.

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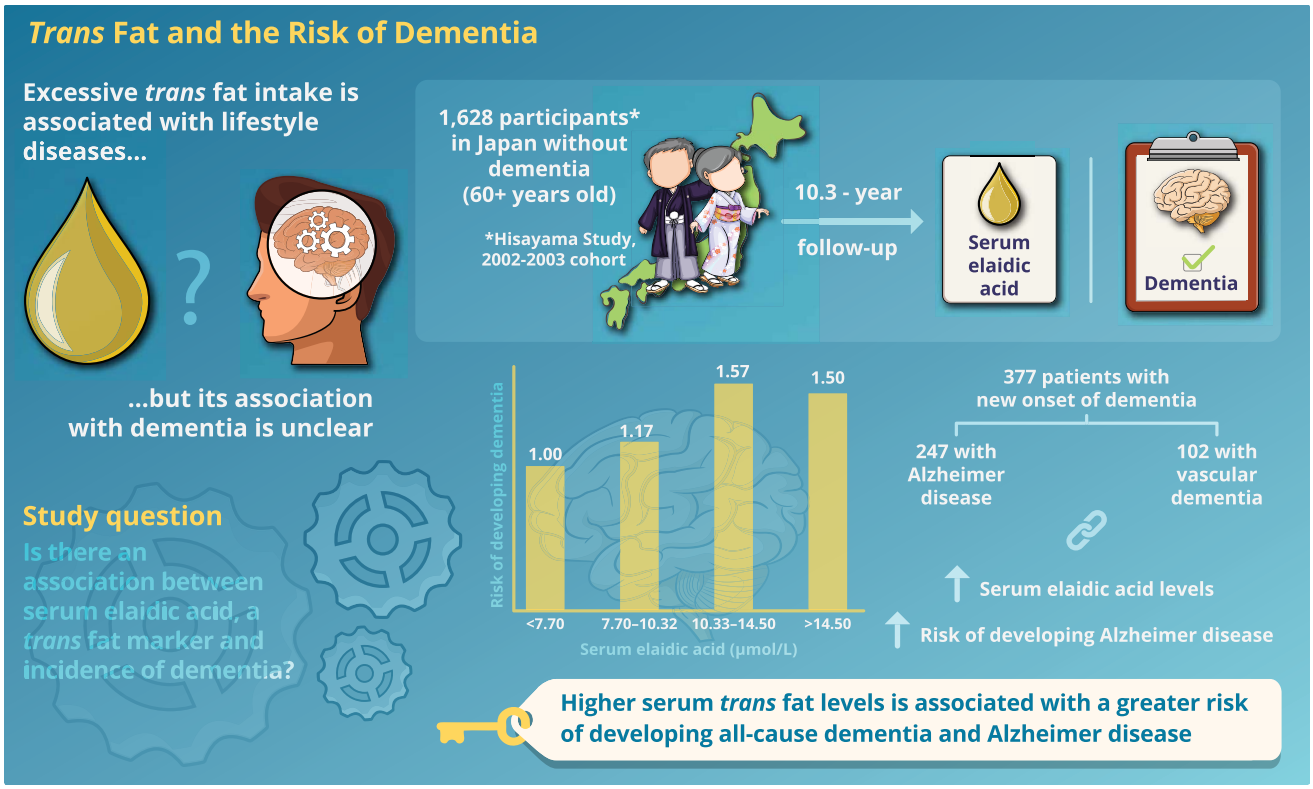
Glossary

AD = Alzheimer disease; **CI** = confidence interval; **DHQ** = diet history questionnaire; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition, revised; **HR** = hazard ratio; **hs-CRP** = high-sensitivity C-reactive protein; **IQR** = interquartile range; **VaD** = vascular dementia.



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Trans fatty acids, unsaturated fatty acids that contain at least one double bond in the trans configuration, are found in food products from ruminant animals and from partially hydrogenated vegetable oils. Intake of excessive industrial trans fat has been shown to be associated with development of lifestyle-related diseases such as coronary heart diseases and diabetes.[1–3] Elaidic acid (trans 18:1 n-9), an isomer of oleic acid formed by partial hydrogenation of vegetable oils, is the major industrially produced trans fatty acid.

Certain types of fats, such as n-3 polyunsaturated and saturated, have been examined in relation to risk of dementia and cognitive decline in epidemiologic studies.[4–7] In contrast, few studies have investigated the association between trans fat and dementia, and they have shown inconsistent results,[5,8,9] probably due to the inaccuracy of the methods for estimating dietary industrial trans fat intakes.[10,11] Serum elaidic acid levels are thought to be an indicator of industrial trans fat intake.[12] Moreover, recent epidemiologic studies have demonstrated that individuals with coronary artery disease or insulin resistance have an elevated serum elaidic acid level compared to those without these conditions.[13–15] To our knowledge, however, no prospective study has investigated the association between serum elaidic acid and dementia. Therefore, we aimed to investigate the association between serum elaidic acid levels and incident dementia and its subtypes.

Methods

Population

The Hisayama Study is an ongoing prospective cohort study of cerebrovascular and cardiovascular diseases, which was established in 1961, being conducted in the town of Hisayama, a suburban community adjacent to the metropolitan area of Fukuoka on Kyushu Island, Japan. The population of the town in 2016 was 8,500. Health examinations for the town residents aged ≥40 years have been repeated annually since 1961. To establish a cohort baseline, our study team attempted to examine >80% of the residents in that age group in health examinations every 2–5 years. In the present study, blood samples as well as information on other covariates were obtained from the data of the cohort established in 2002–2003.

In addition to the health examination described above, a screening survey of the prevalence of dementia for elderly residents including neuropsychological tests was conducted in 1985, 1992, 1998, 2005, and 2012.[16] In addition, we followed up all elderly residents in our community for dementia since 1985. For the present baseline survey, we identified residents with dementia diagnosed in the surveys in 1985, 1992, and 1998, and those with dementia newly developed between 1985 and 2003.

In 2002 and 2003, a total of 1,760 residents aged 60 and older (participation rate 83.4%) consented to participate in a health examination for the present study. After excluding 122 participants who had already developed dementia at baseline and 10 for whom no blood sample for serum elaidic acid measurement was obtained, the remaining 1,628 participants (703 men, 925 women) were enrolled in this study.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was given by the participants.

Follow-up

The participants were followed prospectively from the time of their screening examination to November 2012. We have reported details of the procedures for screening potential dementia events elsewhere.[17] To collect information about new events, including dementia as well as stroke and cognitive impairment, we established a daily monitoring system among our study team and local physicians in the town or the town's Health and Welfare Office members. In the daily monitoring system, the physicians in the study team collect information on the occurrence of stroke and dementia, including suspected cases, by regularly visiting neighborhood clinics and hospitals, and the town's Health and Welfare office. For the cases missed by the daily monitoring, we also acquired this information at regular annual health examinations. In addition, our study team conducted follow-up screening surveys of dementia, which included neuropsychological assessments, in 2005 and 2012 in order to precisely identify dementia cases, as mentioned above. For participants who did not take part in health examinations or who had moved out of town, we collected the health information by communication by telephone or postal service. When a study participant was suspected to have experienced new neurologic symptoms, the study team, including the psychiatrists and stroke physicians, evaluated the individual through comprehensive investigations including physical and neurologic examinations, a review of the clinical records, and interviews of the family or attending physician. When a participant died, we collected and reviewed all available clinical information, and interviewed the family members and the attending physician of the deceased participant. We also tried, to the extent possible, to contact the participant's family to obtain consent to perform an autopsy. During the follow-up period, 369 participants died. Of those, a brain examination at autopsy was performed in 237 participants. Aside from the decedents, only 3 participants were lost to follow-up (follow-up rate 99.8%).

Ascertainment of endpoints

We used the DSM-III-R guidelines to define participants with dementia.[18] The criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association were used to define the diagnosis of Alzheimer disease (AD),[19] and the National Institute of Neurologic Disorders and Stroke–Association International pour la Recherche et l'Enseignement en Neurosciences criteria were used for a diagnosis of vascular dementia (VaD).[20] We used all available clinical information including neuroimaging in order to make a diagnosis of possible and probable dementia subtypes. For participants with dementia who underwent autopsy, definitive diagnosis of subtypes was also made by combining the clinical and neuropathologic information. The procedure used to diagnose dementia subtypes in autopsy cases was reported previously.[21] We used neuropathologic information only for determining definitive subtypes of dementia, and modified the clinical diagnosis of subtypes to a definitive one for the cases undergoing autopsy. The concordance rate between the clinical diagnosis and the definitive diagnosis based on autopsy findings was 78.7%. Expert stroke physicians and psychiatrists adjudicated the diagnosis of dementia and its subtypes for every case of dementia.

Measurement of serum elaidic acid levels

Blood samples were collected from an antecubital vein. Portions of the serum were stored at −80°C. Frozen samples were thawed in 2017 to measure the elaidic acid levels. Serum elaidic acid levels were measured by gas chromatography/mass spectrometry (GC/MS QP2010; Shimadzu, Kyoto, Japan). The details of the determination procedure were published elsewhere.[13] A quality control sample (10 μmol/L of elaidic acid standard) was measured in each analytical batch to calibrate the serum elaidic acid concentrations. The reproducibility (% coefficient of variation) of elaidic acid measurement was ≤2%. Serum elaidic acid concentrations were categorized into quartiles. The median values (ranges) for each quartile were as follows: Q1, 6.24 (2.64–7.69) μmol/L; Q2, 9.02 (7.70–10.32) μmol/L; Q3, 12.11 (10.33–14.50) μmol/L; and Q4, 18.83 (14.51–64.37) μmol/L.

Other covariates

Blood pressure was measured 3 times using an automated sphygmomanometer with participants in the sitting position after at least 5 minutes of rest. The average of the 3 measurements was used for the present analysis. We defined hypertension as blood pressure ≥140/90 mm Hg or current use of antihypertensive medication. Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. A fasting blood sample was obtained from 1,584 participants, and the remaining 44 had already had breakfast before blood collection. Plasma glucose levels were determined by a hexokinase method. Diabetes

mellitus was defined as a plasma fasting glucose level of ≥7.0 mmol/L, 2-hour postloaded or casual glucose levels of ≥11.1 mmol/L, or current use of oral glucose-lowering agents or insulin. Serum total cholesterol and triglycerides were measured enzymatically. Serum high-sensitivity C-reactive protein (hs-CRP) was assayed using the serum portion thawed in 2004, which was measured using a modification of the Behring Latex-Enhanced CRP assay on a BN-100 Nephelometer (Behring Diagnostics, Westwood, MA).

Each study participant completed a self-administered questionnaire that covered information on educational status, smoking habits, intake of alcoholic beverages, regular exercise, and antihypertensive and antidiabetic treatments; trained interviewers checked the answers. Educational level was categorized as ≤9 or >9 years of formal education. Smoking habits and alcohol intake were categorized as either current habitual use or not. We defined regular exercise as engaging in recreational sports or any other forms of exercise at least 3 times in a week during leisure time. History of stroke was defined as a preexisting sudden onset of nonconvulsive and focal neurologic deficit that persisted for at least 24 hours based on all available clinical data. A dietary survey was conducted using a comprehensive self-administered semiquantitative diet history questionnaire (DHQ) regarding the frequency of 150 food items from 23 food groups.[22] The amounts of dietary intake for each of the 150 food items, total energy intake (kcal/d), and saturated, monounsaturated, and polyunsaturated fatty acid intakes (g/d) were calculated.

Statistical analysis

All statistical analyses were performed with the SAS statistical software program, version 9.4 (SAS Institute Inc., Cary, NC). A 2-sided value of $p < 0.05$ was considered to be statistically significant in all analyses. We computed descriptive statistics according to the quartiles of serum elaidic acid levels. The trends in mean values or frequencies of risk factors for the quartiles were tested with linear or logistic regression analysis, as appropriate. Triglycerides and hs-CRP were log-transformed prior to analysis to correct for skewness. The incidence rates of dementia and its subtypes were calculated by a person-year method. The hazard ratios (HRs) with their 95% confidence intervals (CIs) of serum elaidic acid levels for the development of dementia were estimated with the Cox proportional hazards model. For multivariable analysis, covariates included age, sex, educational status, hypertension, diabetes, total cholesterol, triglycerides, hs-CRP, smoking habits, alcohol intake, and regular exercise. We further adjusted for dietary energy intake and dietary intake of saturated and polyunsaturated fatty acids to clarify the potential effects of dietary fat intake on the associations. The trends in risk of dementia and its subtypes across serum elaidic acid levels were tested with the Cox proportional hazards model by assigning ordered natural numbers (i.e., 1, 2, 3, and 4) to the quartiles. In addition, we ran the same analysis using elaidic acid concentrations as a continuous variable (1 log increment). To examine the influence of competing risk of death, we repeated the analysis using the Fine and Gray[23] model. We conducted sensitivity analyses excluding participants who developed dementia during the initial 3 years of follow-up (n = 75) and those without fasting blood samples. The heterogeneity in the association between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model.

To examine the potential food sources influencing the levels of serum elaidic acid in this cohort, we utilized a linear regression model with backward elimination. In this analysis, serum elaidic acid levels were log-transformed due to the skewed distribution, and all dietary variables were energy-adjusted by using the residual method. The DHQ included 150 food items comprising 23 food groups. Out of the total 23 food groups, we first selected 7 food groups reported to contain C18:1 trans fatty acids[24–26]; namely, cereals, confectioneries, animal and plant fat, sugar and sweeteners, seasonings, meat, and dairy products. These 7 food groups comprised 62 food items. Among the 62 food items, 3 items related to milk were combined into a single item because they were mutually exclusive. Similarly, 3 food items related to yogurt and 3 items related to ice cream were each combined into a single item for the same reason. The remaining 56 food items were used to fit the multivariable linear regression model. To form a parsimonious model, any variables with a p value greater than 0.01 were removed.

Data availability

The datasets used in the current study are not publicly available, because they contain confidential clinical data on the study participants. However, the data are available on reasonable request and with the permission of the Principal Investigator of the Hisayama Study, Toshiharu Ninomiya (Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan).

Results

The median serum elaidic acid level was 9.40 μmol/L (interquartile range [IQR] 6.97–13.71 μmol/L) for men and 10.90 μmol/L (IQR 8.23–15.14 μmol/L) for women. Baseline characteristics of the study participants are shown in table 1. Participants with higher serum elaidic acid levels were on average younger and less likely to be men, current drinkers, or physically active. Systolic and diastolic blood pressure, serum total cholesterol, serum triglycerides, body mass index, and dietary intake of saturated fat increased with higher serum elaidic acid levels. In contrast, total energy intake decreased with higher quartiles of serum elaidic acid.

During the median follow-up of 10.2 years (IQR 7.2–10.3 years), 377 participants developed all-cause dementia, 247 developed AD, and 102 developed VaD. Table 2 shows the incidence rates and the HRs for dementia and its subtypes according to the quartiles of elaidic acid levels. The age- and sex-adjusted HRs for all-cause dementia and its subtypes

Table 1 Baseline characteristics of study participants according to serum elaidic acid levels, 2002

Variables	Quartiles of serum elaidic acid level (μmol/L)				*p* for trend
	Q1 (2.64–7.69)	Q2 (7.70–10.32)	Q3 (10.33–14.50)	Q4 (14.51–64.37)	
Age, y, mean (SD)	71.4 (7.6)	70.8 (7.8)	70.3 (7.2)	70.6 (8.1)	0.02
Men, %	55	43	38	37	<0.001
Education, ≤9 years, %	53	52	56	50	0.64
Systolic blood pressure, mm Hg, mean (SD)	136.0 (21.2)	135.6 (19.1)	136.6 (20.6)	141.4 (22.0)	<0.001
Diastolic blood pressure, mm Hg, mean (SD)	78.3 (11.2)	79.2 (10.4)	78.6 (11.6)	81.0 (12.4)	0.004
Antihypertensive drug, %	37	34	38	34	0.66
Hypertension, %	58	57	58	62	0.23
Diabetes, %	21	21	25	22	0.42
Total cholesterol, mmol/L, mean (SD)	4.90 (0.81)	5.19 (0.83)	5.30 (0.84)	5.58 (0.99)	<0.001
Triglycerides, mmol/L[a]	0.91 (0.88–0.95)	1.07 (1.03–1.11)	1.18 (1.13–1.24)	1.53 (1.46–1.61)	<0.001
hs-CRP, mg/L[a]	0.57 (0.50–0.64)	0.59 (0.53–0.67)	0.69 (0.61–0.78)	0.65 (0.58–0.73)	0.10
Body mass index, kg/m^2	22.7 (2.9)	23.1 (3.3)	23.4 (3.4)	23.1 (3.4)	0.04
History of stroke, %	6	3	5	7	0.44
Current smoker, %	19	13	13	15	0.13
Current drinker, %	49	36	33	26	<0.001
Regular exercise, %	16	13	11	11	0.02
Dietary factors, mean (SD)					
Energy intake, kcal/d	2,055 (586)	1,965 (569)	1,894 (501)	1,912 (535)	<0.001
Saturated fat, g/d[b]	13.7 (4.6)	14.3 (4.3)	14.8 (4.4)	15.1 (4.3)	<0.001
Polyunsaturated fat, g/d[b]	13.7 (4.1)	13.5 (3.8)	13.3 (3.3)	13.5 (3.5)	0.54

Abbreviation: hs-CRP = high-sensitivity C reactive protein.
[a] Geometric means (95% confidence intervals).
[b] Values were adjusted for total energy intake by the residual method.

increased significantly with higher serum elaidic acid levels. In the multivariable model adjusted for traditional risk factors, there were positive associations between serum elaidic acid levels and the risk of all-cause dementia and AD. These significant associations remained unchanged even after adjusting for dietary factors including saturated and polyunsaturated fatty acids. In contrast, although the HRs for VaD were higher in the upper quartile groups, the trend across the quartiles was not statistically significant. The association was attenuated after adjusting for dietary factors.

The numbers of participants who died during the follow-up were 101, 81, 76, and 111 in Q1–Q4, respectively. The analysis using the Fine and Gray model showed that the association between serum elaidic acid levels and dementia was similar even when competing risk of death was accounted for (table 3). The sensitivity analyses excluding participants who developed dementia in the initial 3 years of follow-up did not materially change the association (table 4). The findings were also not altered substantially when the participants without fasting blood samples (n = 1,584) were excluded from the analyses (data not shown).

Table 5 shows the association between serum elaidic acid levels and the risk of all-cause dementia by subgroups of demographic and lifestyle factors. The HRs indicate the risk of developing dementia in those with a serum elaidic acid concentration of ≥10.33 μmol/L (median value) compared to those with a serum elaidic acid concentration of <10.33 μmol/L. There was a significant interaction between the serum elaidic acid levels and age groups. The association between serum elaidic acid levels and the risk of incident all-cause dementia was more pronounced in the older age group. With regard to dementia subtypes, there was a significant heterogeneity in the association of the serum elaidic acid level with the risk of AD between age groups, whereas no significant heterogeneity was observed in the association with the risk of VaD between age groups. No heterogeneity of the association between subgroups of other demographic or lifestyle factors with all-cause dementia was found.

Table 2 Association between serum elaidic acid levels and risk of dementia, 2002–2012

Serum elaidic acid level	No. of events/ participants	Incidence(per 10^3 person-years)	Age- and sex-adjusted HR (95% CI)	*p* Value	Multivariable-adjusted model 1,[a] HR (95% CI)	*p* Value	Multivariable-adjusted model 2,[b] HR (95% CI)	*p* Value
Total dementia								
Q1	82/407	21.3	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	88/407	23.0	1.24 (0.92–1.68)	0.16	1.32 (0.97–1.80)	0.08	1.17 (0.84–1.64)	0.37
Q3	103/407	27.6	1.63 (1.21–2.18)	0.001	1.74 (1.28–2.37)	<0.001	1.57 (1.13–2.19)	0.008
Q4	104/407	29.8	1.53 (1.14–2.04)	0.004	1.52 (1.10–2.12)	0.01	1.50 (1.04–2.15)	0.03
***p* for trend**				0.001		0.003		0.008
1-log increment			1.40 (1.14–1.73)	0.002	1.16 (1.07–1.72)	0.01	1.28 (0.98–1.68)	0.07
Alzheimer disease								
Q1	53/407	13.1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	56/407	14.9	1.22 (0.83–1.77)	0.31	1.22 (0.83–1.80)	0.31	1.08 (0.72–1.62)	0.72
Q3	73/407	19.8	1.79 (1.25–2.56)	0.002	1.88 (1.29–2.73)	0.001	1.60 (1.08–2.39)	0.02
Q4	65/407	18.2	1.43 (0.99–2.06)	0.05	1.44 (0.96–2.16)	0.08	1.39 (0.90–2.16)	0.14
***p* for trend**				0.01		0.02		0.04
1-log increment			1.35 (1.04–1.75)	0.02	1.37 (1.02–1.84)	0.04	1.20 (0.86–1.67)	0.29
Vascular dementia								
Q1	19/407	5.4	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	28/407	7.2	1.73 (0.96–3.10)	0.07	2.11 (1.15–3.87)	0.02	1.95 (0.98–3.86)	0.06
Q3	25/407	6.6	1.71 (0.94–3.12)	0.08	1.93 (1.03–3.64)	0.04	1.79 (0.87–3.66)	0.11
Q4	30/407	8.9	1.98 (1.11–3.53)	0.02	1.97 (1.02–3.81)	0.04	1.97 (0.92–4.20)	0.08
***p* for trend**				0.03		0.04		0.11
1-log increment			1.61 (1.09–2.39)	0.02	1.44 (0.92–2.25)	0.11	1.51 (0.89–2.56)	0.13

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariable model 1 was adjusted for age, sex, education, hypertension, diabetes, total cholesterol, log triglycerides, log high-sensitivity C-reactive protein, body mass index, history of stroke, current smoking, current drinking, and regular exercise.
[b] Multivariable model 2 was adjusted for the variables in model 1 plus dietary factors including saturated and polyunsaturated fatty acid and total energy intake.

Table 3 Association between serum elaidic acid level and the risk of dementia with adjustment for competing risk due to death, 2002–2012

Serum elaidic acid level, quartiles	Age- and sex-adjusted, HR (95% CI)	*p*	Multivariable-adjusted model 1,[a] HR (95% CI)	*p*	Multivariable-adjusted model 2,[b] HR (95% CI)	*p*
Total dementia						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	1.15 (0.84–1.58)	0.39	1.19 (0.85–1.65)	0.32	1.14 (0.79–1.63)	0.49
Q3	1.53 (1.12–2.09)	0.01	1.63 (1.19–2.24)	0.003	1.56 (1.10–2.20)	0.01
Q4	1.45 (1.06–1.99)	0.02	1.39 (0.97–1.99)	0.07	1.45 (0.98–2.14)	0.06
***p* for trend**		0.01		0.02		0.02
1-log increment	1.36 (1.08–1.71)	0.01	1.30 (1.00–1.69)	0.05	1.29 (0.97–1.71)	0.08
Alzheimer disease						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	1.11 (0.75–1.65)	0.59	1.14 (0.76–1.71)	0.54	1.06 (0.68–1.64)	0.80
Q3	1.63 (1.12–2.39)	0.01	1.77 (1.20–2.61)	0.004	1.57 (1.03–2.39)	0.04
Q4	1.32 (0.89–1.94)	0.16	1.34 (0.87–2.07)	0.18	1.28 (0.80–2.06)	0.30
***p* for trend**		0.05		0.04		0.10
1-log increment	1.28 (0.98–1.67)	0.08	1.34 (0.98–1.83)	0.06	1.18 (0.84–1.64)	0.34
Vascular dementia						
Q1	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	1.60 (0.89–2.87)	0.12	1.88 (1.01–3.50)	0.047	1.88 (0.93–3.79)	0.08
Q3	1.61 (0.88–2.95)	0.12	1.72 (0.90–3.28)	0.10	1.75 (0.85–3.58)	0.13
Q4	1.78 (0.99–3.20)	0.054	1.71 (0.87–3.38)	0.12	1.82 (0.87–3.81)	0.11
***p* for trend**		0.07		0.17		0.14
1-log increment	1.49 (0.99–2.25)	0.06	1.35 (0.85–2.13)	0.20	1.47 (0.90–2.41)	0.13

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariable model 1 was adjusted for age, sex, education, hypertension, diabetes, total cholesterol, log triglycerides, log high-sensitivity C-reactive protein, body mass index, history of stroke, current smoking, current drinking, and regular exercise.
[b] Multivariable model 2 was adjusted for the variables in model 1 plus dietary factors including saturated and polyunsaturated fatty acid and total energy intake.

Table 6 demonstrates the variables associated with serum elaidic acid levels that were selected by means of backward elimination. Seven variables were selected from 56 food items, and the standardized coefficients and their 95% CIs for the included variables in the final model are shown. Sweet pastries were the strongest contributor, followed by margarine, sugar confectioneries (candies, caramels, and chewing gum), and croissants. Nondairy creamers, ice cream, and rice crackers also remained in the final model.

Discussion

The present study revealed that higher serum elaidic acid levels were linked to a greater risk of the development of dementia. The associations were independent of a number of covariates, including dietary saturated and polyunsaturated fatty acid intake, suggesting that these fats had little effect on the observed association. Since elaidic acid is an exogenous fatty acid, circulating levels of elaidic acid may largely depend on the amounts of dietary intake of processed foods containing partially hydrogenated vegetable oils. Our findings raise the possibility that intake of elaidic acid would be a potential risk factor for future dementia onset. Public health efforts to reduce dietary trans fatty acids may be necessary to decrease the burden of dementia.

A recent report from the US National Health and Nutrition Survey showed that the median elaidic acid levels derived from plasma free fatty acid in a representative sample of the US population was 33.4 μmol/L in 1999–2000, and decreased to 13.5 μmol/L in 2009–2000.[27] Although there was a difference in measurement methods, the elaidic acid levels in the present population were markedly lower than these values. Moreover, the elaidic acid levels in the present study were even lower than the levels among a sample of Japanese patients with and without coronary artery disease in a hospital.[13]

Table 4 Association between serum elaidic acid levels and the risk of dementia with exclusion of participants who developed dementia in the initial 3 years, 2002–2012

Serum elaidic acid level, quartiles	No. of events/ participants	Age- and sex-adjusted, HR (95% CI)	*p* Value	Multivariable-adjusted model 1,[a] HR (95% CI)	*p* Value	Multivariable-adjusted model 2,[b] HR (95% CI)	*p* Value
Total dementia							
Q1	67/392	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	70/389	1.21 (0.86–1.69)	0.28	1.29 (0.91–1.81)	0.15	1.12 (0.78–1.60)	0.54
Q3	87/391	1.67 (1.21–2.31)	0.002	1.79 (1.28–2.50)	0.001	1.56 (1.10–2.22)	0.01
Q4	78/381	1.42 (1.02–1.97)	0.04	1.45 (1.00–2.09)	0.05	1.46 (0.98–2.16)	0.06
***p* for trend**			0.009		0.01		0.02
Alzheimer disease							
Q1	45/392	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	43/389	1.10 (0.72–1.67)	0.66	1.11 (0.72–1.71)	0.63	1.01 (0.65–1.58)	0.96
Q3	64/391	1.85 (1.25–2.72)	0.002	1.91 (1.28–2.86)	0.002	1.70 (1.11–2.60)	0.02
Q4	49/381	1.28 (0.85–1.92)	0.24	1.34 (0.85–2.11)	0.21	1.43 (0.88–2.32)	0.15
***p* for trend**			0.05		0.04		0.03
Vascular dementia							
Q1	15/392	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	25/389	1.93 (1.01–3.66)	0.046	2.44 (1.26–4.73)	0.008	1.92 (0.97–3.82)	0.06
Q3	18/391	1.52 (0.76–3.03)	0.24	1.80 (0.88–3.69)	0.11	1.41 (0.66–3.00)	0.37
Q4	21/381	1.77 (0.91–3.46)	0.09	1.84 (0.86–3.94)	0.12	1.58 (0.70–3.57)	0.27
***p* for trend**			0.18		0.23		0.40

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariable model 1 was adjusted for age, sex, education, hypertension, diabetes, total cholesterol, log triglycerides, log high-sensitivity C-reactive protein, body mass index, history of stroke, current smoking, current drinking, and regular exercise.
[b] Multivariable model 2 was adjusted for the variables in model 1 plus dietary factors including saturated and polyunsaturated fatty acid and total energy intake.

There have been 2 observational studies investigating the associations of dietary intake of trans fatty acids with dementia.[5,9] The Chicago Health and Aging Project reported that individuals with a high dietary intake of trans fatty acids have an elevated risk of developing AD.[5] In contrast, the Rotterdam Study failed to reveal a significant relationship between dietary intake of trans fatty acids and risk of dementia and its subtypes.[9] This discrepancy may be due to the inaccuracy of self-reported dietary questionnaires for trans fatty acids or the difficulty in discriminating industrial from ruminant trans fat. On the other hand, the serum level of trans fatty acids may be a good indicator of dietary intake of processed foods, as shown in a previous ecological survey[12] and our present analysis. Our finding of positive associations between serum elaidic acid levels and the risk of all-cause dementia and AD supports the above-mentioned findings from the Chicago Health and Aging Project.[5] Although significant linear trends were observed, the risk of developing dementia and AD appeared to increase at the level of the third quartile. In addition, the associations between a continuous variable of serum elaidic acid (1 log increment) and the risk of total dementia and AD did not reach the statistically significant level after additional adjustment for dietary factors, possibly suggesting a nonlinear association between elaidic acid levels and dementia. However, because of the relatively low number of dementia cases in the present study, we could not confirm the shape of the association or elucidate whether there were specific cutoffs of elaidic acid levels to predict dementia. Since studies on the associations between trans fatty acid and dementia are scarce, further investigations are clearly needed.

In the present study, participants aged 75 years and older were more likely to be affected by higher serum elaidic acid levels in relation to all-cause dementia and AD, which was probably attributable to their longer exposure to trans fatty acid–containing foods. The circulatory elaidic acid concentration is likely to reflect the accumulation of industry-processed foods during a certain period.[12] The health hazards of industrial trans fatty acids have been affirmed since the 1970s, and public efforts have been made to reduce trans fatty acids in the food supply.[28] Therefore, it is possible that older people were exposed to greater amounts of trans fatty acids in the foods

Table 5 Effects of high elaidic acid levels on the risk of all-cause dementia by subgroups of lifestyle factors

Subgroups	Hazard ratio (95% CI)[a]	*p* Value	*p* For heterogeneity
Age, y			
<75	0.91 (0.63–1.31)	0.60	<0.001
≥75	1.86 (1.35–2.58)	<0.001	
Sex			
Men	1.53 (1.02–2.29)	0.04	0.21
Women	1.41 (1.03–1.93)	0.03	
Education, y			
<9	1.59 (1.18–2.14)	0.003	0.36
≥9	1.10 (0.72–1.68)	0.66	
Hypertension			
No	1.52 (1.01–2.29)	0.04	0.53
Yes	1.39 (1.02–1.89)	0.04	
Diabetes			
No	1.43 (1.09–1.89)	0.01	0.69
Yes	1.20 (0.70–2.04)	0.51	
Total cholesterol, mmol/L			
<5.7	1.42 (1.07–1.87)	0.01	0.17
≥5.7	1.46 (0.89–2.39)	0.13	
Triglycerides, mmol/L			
<1.7	1.44 (1.11–1.86)	0.005	0.30
≥1.7	1.67 (0.77–3.60)	0.19	
hs-CRP, mg/L			
<1.0	1.31 (0.98–1.75)	0.07	0.12
≥1.0	1.71 (1.07–2.72)	0.02	
Body mass index, kg/m^2			
<25	1.45 (1.10–1.92)	0.01	0.88
≥25	1.27 (0.76–2.12)	0.37	
History of stroke			
No	1.35 (1.05–1.73)	0.02	0.26
Yes	1.83 (0.50–6.69)	0.36	
Current smoking			
No	1.47 (1.13–1.91)	0.004	0.28
Yes	1.38 (0.69–2.77)	0.36	
Current drinking			
No	1.33 (0.99–1.78)	0.06	0.66
Yes	1.66 (1.07–2.59)	0.02	
Regular exercise			
No	1.44 (1.11–1.87)	0.01	0.77
Yes	1.03 (0.48–2.21)	0.95	
Total energy intake, kcal/d (median)			
<1,901.5	1.60 (1.14–2.25)	0.01	0.72
≥1,901.5	1.25 (0.87–1.79)	0.23	
Saturated fat intake, g/d (median)			
<14.4	1.23 (0.87–1.76)	0.24	0.45
≥14.4	1.64 (1.16–2.31)	0.01	
Polyunsaturated fat intake, g/d (median)			
<13.3	1.33 (0.94–1.89)	0.11	0.78
≥13.3	1.50 (1.06–2.12)	0.02	

Abbreviations: CI = confidence interval; hs-CRP = high-sensitivity C-reactive protein.
[a] The hazard ratio (95% CI) represents the risk of dementia among those with ≥ the median serum elaidic acid level (vs < median). Values were adjusted for age, sex, education, hypertension, diabetes, total cholesterol, log triglycerides, log hs-CRP, body mass index, history of stroke, current smoking, current drinking, regular exercise, and dietary factors (total energy intake, saturated fatty acids, and polyunsaturated fatty acids): the variables for stratification were removed from the model for each analysis.

Table 6 Major dietary variables predicting serum elaidic acid levels

Selected variables	Individuals with intake of each food, %	Amount of intake, g/d[a]	Standardized coefficients (95% CI)[b]	*p* Value
Sweet pastries/stuffed bread	40.6	33.8 (18.1–46.9)	0.14 (0.09–0.19)	<0.001
Margarine	32.5	2.9 (1.1–7.1)	0.11 (0.07–0.16)	<0.001
Candies, caramels, and chewing gum	59.8	1.7 (1.0–4.8)	0.09 (0.04–0.14)	<0.001
Croissants	14.9	13.7 (5.9–20.6)	0.08 (0.03–0.13)	0.001
Nondairy creamer	30.0	2.4 (1.1–4.5)	0.07 (0.02–0.12)	0.004
Ice cream	65.0	21.4 (12.5–53.6)	0.07 (0.02–0.12)	0.005
Rice crackers	55.4	4.3 (2.5–10.7)	0.07 (0.02–0.12)	0.005

The overall R^2 for the model was 0.08.
[a] Values are median (interquartile range) calculated among individuals with intake of each food.
[b] Dietary variables were adjusted for total energy intake using the residual method prior to analysis.

they consumed when they were young, compared to the amounts currently consumed by younger people.

The possible pathway underlying the association between serum elaidic acid and dementia has not been clarified, therefore we performed the analysis adjusted for the dietary intakes of saturated fat and polyunsaturated fat in order to elucidate whether these fat intakes could mediate the association between elaidic acid and dementia. As a consequence, the point estimates of HRs for total dementia and AD were not substantially changed after adjusting for saturated fat or polyunsaturated fat, suggesting that there was no mediation by these fats. On the other hand, we found that the risk of VaD was significantly elevated with higher elaidic acid levels, but was attenuated after adjusting for dietary factors, and there was no linear trend for this association. The Rotterdam Study also failed to reveal a significant association between the dietary intake of trans fat and the risk of VaD.[9] In addition, no population-based prospective studies have investigated the association between industrial trans fat intake or serum elaidic acid concentrations and the risk of stroke, as mentioned in a previous systematic review.[29] Although our findings suggested the association between trans fatty acids and the risk of VaD was possibly mediated by dietary fat intakes, the limited number of VaD cases in the present study and in the Rotterdam Study[9] precluded the conclusion, since the statistical power may be insufficient. This association should be further investigated in a large sample size before drawing any definitive conclusions.

The possible mechanisms underlying the link between serum elaidic acid levels and dementia are unknown. One possible explanation is that elaidic acid increases cardiovascular risk, including atherosclerosis, chronic inflammation, and impairments in insulin secretion and glucose metabolism.[30–35] These effects are thought to be linked to an increased risk of dementia,[36–39] and therefore we adjusted for the factors related to atherogenesis, glucose metabolism, and inflammation in our analysis. There have been experimental studies suggesting that trans fatty acids may be related to oxidative stress in endothelial cells,[40] neuronal cell apoptosis,[41] and the production and aggregation of β-amyloid peptide.[42] However, further investigation is needed to clarify the potential role of elaidic acid in the development of dementia.

Finally, our findings showing the foods related to higher serum elaidic acid concentrations were in line with those of an earlier study on 225 Japanese middle-aged adults, which showed that bakery products, confectionaries, and industrially produced fats/oils were the major contributors to trans fatty acid intake.[43] Nondairy creamer is also known to frequently contain hydrogenated vegetable oils. In addition, ice cream and snacks have been reported to contain elaidic acid.[44] Our findings suggested that serum elaidic acid concentrations reflected, to some extent, the dietary intake of processed foods containing partially hydrogenated vegetable oils.

The strengths of the current study included the measurement of elaidic acid levels as an objective marker of trans fatty acid instead of relying on a food frequency questionnaire, the high participation rate in the baseline examination, the almost complete follow-up rate (99.8%), and the consideration of various covariates, including dietary factors. In addition, the sensitivity analysis in fasting samples suggested that short-term variations in elaidic acid measurements had little effect on the present findings. Several limitations of the current study should also be noted. First, serum elaidic acid was only measured at baseline. The variability of serum elaidic acid concentrations during the follow-up period was not taken into consideration. This limitation could weaken the association observed in the present study, biasing the results toward the null hypothesis. In addition, dietary fat intake tends to have different effects on the fatty acid composition of lipids from different components of blood.[45] In contrast, we measured elaidic acid from total lipids in serum, which could increase the stability of measurement against exogenous factors. Second, although we accounted for a wide range of confounders, residual confounding cannot be excluded. Specifically, other major trans fatty acid compounds such as vaccenic and linoelaidic acids[27] were not measured in

this population due to technical difficulties in the isolation and measurement of these trans fats. Furthermore, information on some covariates such as lifestyle factors and medications was based on self-report, which may lead to insufficient adjustment of the models. Third, we were unable to eliminate the possibility that prodromal dementia cases were included in the participants with elevated serum elaidic acid levels at baseline. However, the sensitivity analyses excluding participants who developed dementia during the initial 3 years of follow-up did not materially alter the observed association. Fourth, although we investigated the food sources of elaidic acid, we did not have data on dietary elaidic acid intake itself. Because the contents of trans fat have not been labeled on food products in Japan, we could not evaluate them retrospectively. Finally, the generalizability of these findings is limited, because the participants of the present study were recruited from one town. The population levels of dietary intake of trans fatty acids strongly depend on a study's historical period or countries/regions.[46] Therefore, our findings should be validated in other populations.

The serum elaidic acid level, a marker of industrial trans fatty acids, was a risk factor for development of dementia and AD in our study population. Given the health concerns in relation to cardiovascular events, the US government set bans on industrial trans fat in June 2018. At the same time, the WHO released the REPLACE action package to accelerate the elimination of industrially produced trans fat from the food supply globally by 2023.[47] Public health policy to augment food industry efforts to reduce trans fatty acids in the food supply and to educate the public about healthy food choices may additively contribute to the primary prevention of dementia.

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Continued

Appendix *(continued)*

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Shigenobu Kanba, MD, PhD	Kyushu University, Fukuoka, Japan	Author	Data interpretation and critical revision of the manuscript
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