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Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study[1–3]

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ABSTRACT

Background: Prospective epidemiologic studies have generated mixed results regarding the association between saturated fatty acid (SFA) intake and risk of ischemic heart disease (IHD) and stroke. These associations have not been extensively studied in Asians.

Objective: The aim of this study was to test the hypothesis that SFA intake is associated with the risk of cardiovascular disease mortality in Japanese whose average SFA intake is low.

Design: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) comprised 58,453 Japanese men and women who completed a food-frequency questionnaire. Participants were aged 40–79 y at baseline (1988–1990) and were followed up for 14.1 y. Associations of energy-adjusted SFA intake with mortality from stroke (intraparenchymal and subarachnoid hemorrhages and ischemic stroke) and heart diseases (IHD, cardiac arrest, and heart failure) were examined after adjustment for age, sex, and cardiovascular disease risk and dietary factors.

Results: We observed inverse associations of SFA intake with mortality from total stroke [n = 976; multivariable hazard ratio (95% CI) for highest compared with lowest quintiles: 0.69 (0.53, 0.89); P for trend = 0.004], intraparenchymal hemorrhage [n = 224; 0.48 (0.27, 0.85); P for trend = 0.03], and ischemic stroke [n = 321; 0.58 (0.37, 0.90); P for trend = 0.01]. No multivariable-adjusted associations were observed between SFA and mortality from subarachnoid hemorrhage [n = 153; 0.91 (0.46, 1.80); P for trend = 0.47] and heart disease [n = 836; 0.89 (0.68, 1.15); P for trend = 0.59].

Conclusion: SFA intake was inversely associated with mortality from total stroke, including intraparenchymal hemorrhage and ischemic stroke subtypes, in this Japanese cohort. *Am J Clin Nutr* 2010;92:759–65.

INTRODUCTION

A few, but not all, studies have documented an increased risk of ischemic heart disease (IHD) with intake of saturated fatty acids (SFAs) since the Seven Countries Study showed an ecologic association several decades ago (1). SFA intake is strongly correlated with blood cholesterol concentrations (2), and high blood cholesterol is a strong risk factor for IHD (3). Nonetheless, the association between SFA intake and IHD has been controversial. SFA intake has been shown to be positively associated with the risk of IHD (4, 5), and replacing SFA intake with polyunsaturated fatty acid (PUFA) intake was associated with a lower risk of IHD (6). SFA intake, however, was inversely associated with the progression of coronary atherosclerosis (7). A recent meta-analyses of cohort studies did not support an adverse effect of SFA intake on risk of IHD (8, 9).

An association of SFA intake with ischemic stroke has been less clear (10–14), even though ischemic stroke is considered an atherosclerotic disease in Western societies. This is probably because nonatherosclerotic pathophysiologic pathways, such as arteriolosclerosis, are also involved in the etiology of ischemic stroke, especially lacunar stroke in perforator areas (15). Moreover, SFA intakes (11, 16) and blood total and LDL-cholesterol concentrations (3, 17–19) have been inversely associated with the incidence of intraparenchymal hemorrhage because of its nonatherosclerotic etiology (15).

SFA intake increases blood concentrations of HDL cholesterol as well as of total and LDL cholesterols; thus, the net effect on cardiovascular outcomes could be different with that of total or

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LDL cholesterol alone. In this context, we sought to examine the association between SFA intake and mortality from stroke in a Japanese cohort. Our a priori hypothesis was that a low intake of SFAs is associated with an increased risk of mortality from stroke, primarily intraparenchymal hemorrhage, in this Japanese sample. We also hypothesized that the association of SFA intake with mortality from heart diseases (IHD, cardiac arrest, and heart failure) would be null, because the distribution of SFA intake among the Japanese is far lower than that among Americans (11, 16).

SUBJECTS AND METHODS

Study cohort

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Ministry of Education, Culture, Sports, Science and Technology of Japan (JACC Study) is an ongoing cohort study that comprised a nationwide community-based sample of 110,792 persons (46,465 men and 64,327 women) aged 40–79 y during the baseline period (1988–1990), from 45 communities of Japan, as described elsewhere in detail (20). Participants completed self-administered questionnaires about their lifestyles and medical histories of previous cardiovascular disease or cancer. The subjects, measurements, and statistical analyses were basically the same as in a recent JACC publication (21). Briefly, we excluded persons who reported a history of heart disease, stroke, or cancer at baseline and those with incomplete answers for the foods making a major contribution to SFA intake in the dietary questionnaire. Participants from 11 communities were also excluded because the complete version of the food-frequency questionnaire (FFQ) was not distributed in these communities. As a result, we included 23,024 men and 35,429 women from 34 communities. Informed consent was obtained before participants completed the questionnaire or sometimes from community leaders instead of individuals, because this had been a common practice for informed consent in Japan at that time. The JACC Study protocol was approved by the institutional review board of the University of Tsukuba and the Osaka University School of Medicine.

Mortality surveillance

In each community, investigators conducted a systematic review of death certificates through the end of 2003, except for 3 communities where the follow-up had ended in 1999. In Japan, registration of death is legally required and is believed to be followed across Japan. Thus, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was censored. We used the underlying cause of death coded with the *International Statistical Classification of Diseases and Related Health Problems–10th Revision* (ICD-10) (22) to identify mortality endpoints: I60-I69 for total stroke, I60 for subarachnoid hemorrhage, I61 for intraparenchymal hemorrhage, I63 for ischemic stroke, I20-I25 for IHD, I21 for myocardial infarction, I46-49 for cardiac arrest, I50 for heart failure, and I00-I99 for total cardiovascular disease. The date of moving from the community was verified by population-register sheets. Four percent of participants (n = 2472) moved from their original communities during follow-up.

Baseline questionnaire

The FFQ included 33 food items and 5 choices for frequency of intake offered for each item (23). The amount of SFA that each food item contained was estimated based on the *Japan Food Table, fourth version.* The intake of SFA was then calculated by multiplying the frequency scores by the estimated SFA intake from each food and summing across all 33 items as validated previously (23). Intakes of SFA and of vegetables, fruit, ω-3 (n−3) and ω-6 (n−6) PUFAs, and cholesterol were adjusted for energy intake by using the nutrient residual model (24). The quintiles of energy-adjusted SFA intake were 1.6 to <6.9, 6.9 to <8.5, 8.5 to <9.8, 9.8 to <11.3, and 11.3–25.3 g/d and were underestimated by 36.7% according to the validation study that compared them with dietary records in a subsample (n = 85, mostly female; median: 9.5 compared with 15.0 g/d) (23). Spearman's correlation coefficient between SFAs derived from the FFQ and dietary records was 0.50 (23).

Statistical analyses

The mortality rates of each outcome were calculated according to quintiles of energy-adjusted SFA intake. Hazard ratios (HRs) with 95% CIs were calculated after adjustment for age, sex, and other potential risk factors with Cox proportional hazards models. The risk factors included baseline body mass index, history of hypertension or diabetes, smoking status, alcohol intake, perceived mental stress, walking, sports, educational level, total energy intake, and energy-adjusted intakes of cholesterol, ω-3 and ω-6 PUFAs, vegetables, and fruit as in a previous publication (23). Because animal protein intake was highly correlated with SFA intake (Spearman's r = 0.73), we also present HRs with further adjustment for energy-adjusted animal protein intake. The linear trend of HRs across the quintiles was tested by an ordinal variable for successive quintiles. Multiplicative interactions with sex were tested by using a cross-product term.

As supplemental analyses, we ran substitution models to examine whether replacing SFA with PUFA, monounsaturated fatty acid (MUFA), or carbohydrate would still be associated with an increased risk of mortalities from IHD and stroke. The model simultaneously included total energy (kcal/d), protein (% of energy), PUFA (% of energy), MUFA (% of energy), carbohydrate (% of energy), alcohol (% of energy), and other cardiovascular disease risk factors.

We used SAS version 9.1.3 Service Pack 4 (SAS Institute Inc, Cary, NC) for the analyses. All probability values for statistical tests were 2-tailed, and P values < 0.05 were considered statistically significant.

RESULTS

As shown in **Table 1**, most risk factors at baseline correlated with energy-adjusted SFA intake. During a median follow-up of 58,453 persons for 14.1 y, we documented 976 deaths due to stroke—including 224 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 321 ischemic strokes—and 420 IHDs, 330 myocardial infarctions, 107 cardiac arrests, and 309 heart failures. Because no interactions with sex were observed for the association of SFA intake with any mortality endpoint, we combined men and women for further analyses.

TABLE 1
Baseline cardiovascular disease risk factors and select dietary variables in a cohort of 23,024 men and 35,429 women according to quintile of saturated fatty acid (SFA) intake[1]

	Quintile of SFA intake (g/d)[2]					
	2.5 to <11.0	11.0 to <13.4	13.4 to <15.4	15.4 to <17.9	17.9–40.0	*P* value[3]
Men						
Median SFA intake (g/d)[2]	9.2	12.2	14.4	16.5	20.3	
Number at risk	5076	4573	4194	4157	5024	
Age at baseline (y)[4]	55.2 ± 9.7	55.7 ± 9.8	55.7 ± 9.6	56.5 ± 10.1	56.5 ± 10.3	<0.001
Mean BMI (kg/m^2)	22.7	22.8	22.8	22.6	22.5	<0.001
History of hypertension (%)	22.1	21.3	18.6	17.4	15.3	<0.001
History of diabetes (%)	5.6	5.6	6.3	5.7	7.4	<0.001
Current smoker (%)	60.0	53.8	52.4	51.2	51.6	<0.001
Current drinker (%)	83.1	80.5	76.5	72.8	62.6	<0.001
Sports ≥1 h/wk (%)	26.3	28.7	29.6	34.6	36.9	<0.001
Walking ≥1 h/d (%)	51.1	51.6	50.8	48.2	47.1	<0.001
College or higher education (%)	14.0	16.1	16.9	20.2	24.9	<0.001
High perceived mental stress (%)	22.5	21.9	24.3	25.3	28.2	<0.001
Mean energy intake (kcal/d)	1607	1698	1699	1657	1592	<0.001
Dietary cholesterol (mg/d)	164	226	250	271	302	<0.001
MUFAs (g/d)	6.2	8.5	9.7	10.7	12.4	<0.001
PUFAs (g/d)	6.4	7.9	8.4	8.8	9.2	<0.001
ω-3 PUFAs (g/d)	1.2	1.6	1.7	1.8	1.9	<0.001
ω-6 PUFAs (g/d)	5.1	6.3	6.7	7.0	7.2	<0.001
Animal protein intake (g/d)	17	23	26	29	34	<0.001
Plant protein intake (g/d)	27	30	30	29	28	<0.001
Vegetable intake (g/d)	70	87	95	102	108	<0.001
Fruit intake (g/d)	90	108	125	131	143	<0.001
Women						
Median SFA intake (g/d)[2]	9.4	12.3	14.4	16.5	19.8	
Number at risk	6614	7118	7497	7534	6666	
Age at baseline (y)[4]	58.0 ± 9.9	56.8 ± 9.9	56.2 ± 9.7	55.8 ± 9.6	54.5 ± 9.8	<0.001
Mean BMI (kg/m^2)	23.2	23.1	23.0	22.9	22.6	<0.001
History of hypertension (%)	22.2	20.5	22.0	19.5	18.2	<0.001
History of diabetes (%)	2.9	3.0	3.5	3.6	4.1	<0.001
Current smoker (%)	6.7	4.6	3.7	3.7	5.6	<0.001
Current drinker (%)	23.2	23.7	23.2	23.0	24.4	0.28
Sports ≥1 h/wk (%)	17.5	20.6	23.8	25.2	28.4	<0.001
Walking ≥1 h/d (%)	54.5	53.8	51.3	50.1	48.2	<0.001
College or higher education (%)	7.2	8.6	10.1	11.8	15.7	<0.001
High perceived mental stress (%)	20.1	19.9	20.6	21.8	22.0	0.005
Mean energy intake (kcal/d)	1309	1352	1347	1348	1283	<0.001
Dietary cholesterol (mg/d)	165	223	248	273	287	<0.001
MUFAs (g/d)	6.5	8.7	9.7	10.8	11.9	<0.001
PUFAs (g/d)	6.5	7.8	8.1	8.4	8.2	<0.001
ω-3 PUFAs (g/d)	1.3	1.6	1.7	1.8	1.8	<0.001
ω-6 PUFAs (g/d)	5.2	6.2	6.3	6.6	6.4	<0.001
Animal protein intake (g/d)	17	24	27	30	33	<0.001
Plant protein intake (g/d)	27	27	27	26	24	<0.001
Vegetable intake (g/d)	87	101	109	113	114	<0.001
Fruit intake (g/d)	124	144	152	155	157	<0.001

[1] All values are age-adjusted means or percentages unless otherwise indicated. MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
[2] Energy-adjusted values were derived by using a nutrient residual model. Ranges and median values for SFA were divided by an underestimation rate of 63.3%.
[3] *P* values for overall differences between quintiles based on ANCOVA.
[4] Values are unadjusted means ± SDs.

The HRs of death from cardiovascular diseases, according to dietary SFA intake, are shown in **Table 2**. SFA was inversely associated with age- and sex-adjusted risks of total stroke, intraparenchymal hemorrhage, and ischemic stroke. These associations remained statistically significant after further adjustment for potential cardiovascular disease risk factors and nutrients: HR (95% CI) for the highest compared with the lowest quintile = 0.69 (0.53, 0.89) for total stroke, 0.48 (0.27, 0.85) for intraparenchymal hemorrhage, and 0.58 (0.37, 0.90) for ischemic stroke. Mortality from intraparenchymal hemorrhage had the lowest HR for the highest compared with the lowest SFA intake quintile. No associations were observed for subarachnoid hemorrhage [HR (95%

TABLE 2
Multivariate hazard ratios (HRs) (and 95% CIs) for mortality from stroke, ischemic heart disease, cardiac arrest, heart failure, and total cardiovascular disease according to quintiles of saturated fatty acid (SFA) intake in 23,024 men and 35,429 women combined[1]

	Quintile of SFA intake (g/d)[2]					
Mortality endpoint	2.5 to <11.0	11.0 to <13.4	13.4 to <15.4	15.4 to <17.9	17.9–40.0	*P* for trend
Person-years	147,057	148,710	149,314	148,995	145,920	
Total stroke (*n*)	245	213	193	177	148	
Absolute rate	1.67	1.43	1.29	1.19	1.01	
HR (95% CI)						
Model 1	1.0	0.90 (0.75, 1.08)	0.86 (0.71, 1.03)	0.76 (0.63, 0.93)	0.66 (0.53, 0.80)	<0.001
Model 2	1.0	0.90 (0.74, 1.09)	0.89 (0.72, 1.10)	0.80 (0.64, 1.00)	0.69 (0.53, 0.89)	0.004
Intraparenchymal hemorrhage (*n*)	63	48	45	45	23	
Absolute rate	0.43	0.32	0.30	0.30	0.16	
HR (95% CI)						
Model 1	1.0	0.78 (0.54, 1.14)	0.77 (0.52, 1.12)	0.75 (0.51, 1.10)	0.39 (0.24, 0.63)	<0.001
Model 2	1.0	0.87 (0.58, 1.29)	0.89 (0.58, 1.36)	0.90 (0.57, 1.42)	0.48 (0.27, 0.85)	0.03
Subarachnoid hemorrhage (*n*)	29	46	28	30	20	
Absolute rate	0.20	0.31	0.19	0.20	0.14	
HR (95% CI)						
Model 1	1.0	1.59 (1.00, 2.53)	0.98 (0.58, 1.64)	1.05 (0.63, 1.75)	0.77 (0.44, 1.36)	0.14
Model 2	1.0	1.77 (1.08, 2.89)	1.12 (0.64, 1.98)	1.22 (0.68, 2.20)	0.91 (0.46, 1.80)	0.47
Ischemic stroke (*n*)	86	66	64	54	51	
Absolute rate	0.58	0.44	0.43	0.36	0.35	
HR (95% CI)						
Model 1	1.0	0.79 (0.58, 1.09)	0.81 (0.59, 1.13)	0.65 (0.47, 0.92)	0.62 (0.44, 0.88)	0.004
Model 2	1.0	0.74 (0.53, 1.04)	0.79 (0.55, 1.14)	0.63 (0.42, 0.93)	0.58 (0.37, 0.90)	0.01
Ischemic heart disease (*n*)	108	80	79	76	77	
Absolute rate	0.73	0.54	0.53	0.51	0.53	
HR (95% CI)						
Model 1	1.0	0.76 (0.57, 1.02)	0.79 (0.59, 1.06)	0.73 (0.55, 0.99)	0.76 (0.56, 1.01)	0.08
Model 2	1.0	0.83 (0.61, 1.13)	0.93 (0.68, 1.28)	0.89 (0.63, 1.24)	0.93 (0.65, 1.35)	0.86
Myocardial infarction (*n*)	88	65	64	53	60	
Absolute rate	0.60	0.44	0.43	0.36	0.41	
HR (95% CI)						
Model 1	1.0	0.76 (0.55, 1.05)	0.79 (0.57, 1.08)	0.63 (0.45, 0.88)	0.72 (0.52, 1.00)	0.03
Model 2	1.0	0.82 (0.58, 1.14)	0.92 (0.65, 1.31)	0.74 (0.50, 1.10)	0.85 (0.56, 1.29)	0.40
Cardiac arrest (*n*)	29	22	19	21	16	
Absolute rate	0.20	0.15	0.13	0.14	0.11	
HR (95% CI)						
Model 1	1.0	0.77 (0.44, 1.34)	0.71 (0.40, 1.26)	0.74 (0.42, 1.31)	0.59 (0.32, 1.09)	0.12
Model 2	1.0	0.73 (0.41, 1.31)	0.64 (0.34, 1.21)	0.69 (0.36, 1.34)	0.50 (0.23, 1.10)	0.11
Heart failure (*n*)	77	61	46	65	60	
Absolute rate	0.52	0.41	0.31	0.44	0.41	
HR (95% CI)						
Model 1	1.0	0.83 (0.59, 1.16)	0.66 (0.46, 0.95)	0.91 (0.65, 1.26)	0.87 (0.62, 1.22)	0.62
Model 2	1.0	0.88 (0.62, 1.25)	0.75 (0.50, 1.11)	1.01 (0.69, 1.48)	0.99 (0.64, 1.52)	0.83
Total cardiovascular disease (*n*)	507	424	383	392	346	
Absolute rate	3.45	2.85	2.57	2.63	2.37	
HR (95% CI)						
Model 1	1.0	0.86 (0.76, 0.98)	0.82 (0.72, 0.94)	0.82 (0.72, 0.93)	0.74 (0.65, 0.85)	<0.001
Model 2	1.0	0.89 (0.78, 1.02)	0.89 (0.77, 1.03)	0.89 (0.77, 1.04)	0.82 (0.69, 0.97)	0.05

[1] Absolute rate is presented per 1000 person-years. HRs for each outcome were calculated by using a Cox proportional hazards model. Model 1 was adjusted for age and sex. Model 2 was adjusted as for model 1 and for a history of hypertension and diabetes, smoking status, alcohol consumption, BMI, mental stress, walking, sports, educational level, and dietary intakes of total energy, cholesterol, ω-3 and ω-6 polyunsaturated fatty acids, vegetables, and fruit.
[2] Energy-adjusted values were derived by using a nutrient residual model. Ranges and median values for SFA were divided by an underestimation rate of 63.3%.

CI) for the highest compared with the lowest quintile = 0.91 (0.46, 1.80), *P* for trend = 0.47] and heart diseases [IHD, cardiac arrest and heart failure pooled, HR = 0.89 (0.68, 1.15), *P* for trend = 0.59].

Further adjustment for animal protein did not change the stroke results materially: HRs for the highest compared with the lowest quintile = 0.67 (0.49, 0.92), *P* for trend = 0.01 for total stroke; 0.45 (0.22, 0.89), *P* for trend = 0.048 for intraparenchymal

hemorrhage; and 0.56 (0.32, 0.97), P for trend = 0.046 for ischemic stroke (data not shown in the tables).

SFA intake was consistently inversely associated with stroke mortality in substitution models; replacement of SFA by increasing MUFA, PUFA, or carbohydrate intakes was significantly or nonsignificantly positively associated with stroke mortality. The HRs of each nutrient (MUFA, PUFA, or carbohydrate) for which 1% of energy was substituted for SFA were as follows: 1.06 (0.89, 1.27), 1.19 (1.09, 1.30), and 1.05 (0.98, 1.13), respectively. We found no protective effects on IHD when SFA was replaced with MUFA, PUFA, or carbohydrates; the respective HRs were 0.95 (0.74, 1.23), 1.02 (0.89, 1.16), and 1.00 (0.91, 1.11) (data not shown in the tables).

DISCUSSION

In this large community-based prospective cohort study, SFA intake was inversely associated with mortality from stroke. This inverse association was similarly observed for intraparenchymal hemorrhage and ischemic stroke, but not for subarachnoid hemorrhage. Indeed, decreasing SFA intake by increasing PUFA was significantly positively associated with stroke mortality in the JACC Study. It is consistent with the previous JACC finding that dietary intake of PUFA was not associated with stroke mortality (21).

It is well known that a greater intake of SFA increases the blood total cholesterol concentration (2), and blood total and LDL-cholesterol concentrations are inversely associated with risk of intraparenchymal hemorrhage (3, 17–19, 25–27). Inverse associations of dietary SFA intake with intraparenchymal hemorrhage have been consistently observed in previous studies of Japanese (16) and Americans (11). Therefore, an inverse association between SFA intake and mortality from intraparenchymal hemorrhage in this study was not surprising.

In contrast, reports on the association of SFA intake or blood cholesterol with risk of ischemic stroke have been less consistent. Whereas several (3, 18, 19, 28, 29), but not all (25, 27, 30–32), studies have found positive associations between serum total or LDL cholesterol and ischemic stroke, dietary studies have shown significantly (10) or nonsignificantly (13) inverse or null (11, 12, 14) associations between SFA and ischemic stroke. Notably, a recent Japanese study reported a significant positive association of serum LDL cholesterol with large-artery occlusive infarction, but none with lacunar infarction and even an inverse association with cardioembolic infarction (33). A pathologic study of Japanese showed that serum blood cholesterol concentrations were high among fatal cases of large-artery occlusive stroke decedents, intermediate among lacunar stroke decedents, and low among intraparenchymal hemorrhage decedents (15). Ischemic stroke is considered to be an atherosclerotic disease because a large proportion of cases are large-artery occlusive infarctions in Western countries; however, in Asia, most ischemic strokes are lacular infarctions in perforator areas. We speculated that SFA may play different roles in intracranial large arteries as opposed to intracranial small vessels, and hemorrhage and ischemia in perforator areas may have a common pathophysiologic etiology, that is, very low blood cholesterol concentrations lead to angionecrosis in intracerebral arterioles through disappearance of medial smooth muscle cells and increased fragility of the vascular wall (15). Low intakes of SFAs may lower blood HDL cholesterol (34) and total and LDL cholesterols, which could partly explain the inverse association between SFA intake and stroke. This also explains in part the null association between SFA intake and IHD because the net effect of these lipids on risk of IHD could be cancelled. Adverse effects of SFAs other than on LDL cholesterol (eg, lipoproteins, blood pressure, insulin sensitivity, thrombosis, inflammation, or vascular function) have not yet been conclusive (35).

The strengths of this study include its prospective cohort design, a reasonable number of events for statistical power, multiple adjustments for multiple relevant confounders, and evaluation of an important but understudied population (ie, Japanese). The limitations of this study warrant discussion. First, we used an FFQ with only 33 food items to identify SFA intake and death certificates to define events. Diet misclassification will attenuate findings toward the null in this prospective study; outcome misclassification would also attenuate findings toward the null, because this misclassification was unlikely to be related to baseline SFA intake. Second, the exclusion of missing dietary information may affect generalizability, although it may not greatly affect the present results as discussed previously (21). Third, the possibility of residual confounding by unmeasured or incompletely adjusted stroke risk factors also applies to this study. Fourth, we did not include MUFA intake in the multivariate models because it was highly correlated with both SFA and animal protein intakes (Spearman's r = 0.82 and 0.85, respectively). Nevertheless, when we included energy-adjusted MUFA intakes in model 2, the association between SFA and total stroke was attenuated to some extent, probably because of multicolinearity [HR for the highest compared with the lowest SFA quintiles: 0.75 (95% CI: 0.53, 1.05), P for trend = 0.10]. Because MUFAs did not show a strong association in this model (P for trend =0.37), we believe that our findings were mainly explained by SFA rather than by MUFA intakes. Last, this study was conducted among Japanese, so extrapolation to other populations should be made with caution.

Assuming that the inverse association between SFA and stroke mortality is causal, it would nevertheless be inappropriate to recommend an increased consumption of SFA-containing products to the general Japanese population, because it might increase population levels of total cholesterol and the risk of IHD. Replacing SFA with PUFA had no benefit on the prevention of IHD, which contrasts with a recent pooling project of Americans and Europeans (6). Application of discrepant results to public health practice must be cautious. We believe that this discrepancy could be explained in part by a low distribution of SFA intake among Japanese. The median SFA intake, albeit underestimated by ≈37%, was very low (9.4 g/d). It is well known that the SFA intake is far lower in Japan than in Western countries; for example, the median intake of SFAs for the highest quartile of a Japanese rural population (1970–1980s) was 17 g/d (16) lower than that for the lowest quartile of intake in the Nurses' Health Study in 1980 (20 g/d) (11). These findings indicated almost no overlap of SFA intakes between the 2 populations.

In conclusion, we found an inverse association of dietary SFA intake with stroke mortality, for both ischemic stroke and intraparenchymal hemorrhage, in this Japanese population with low SFA intakes.

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The authors' responsibilities were as follows—KY and HI: developed the study hypothesis; KY: conducted the analysis and drafted the manuscript; and HI, HY, NT, CD, SK, AY, YI, and AT: critically revised the manuscript. None of the authors had a personal or financial conflict of interest.

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Dietary Folate and Vitamin B6 and B12 Intake in Relation to Mortality From Cardiovascular Diseases: Japan Collaborative Cohort Study

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Dietary Folate and Vitamin B_6 and B_{12} Intake in Relation to Mortality From Cardiovascular Diseases

Japan Collaborative Cohort Study

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Background and Purpose—The association of dietary folate and B vitamin intakes with risk of cardiovascular disease is controversial, and the evidence in Asian populations is limited.

Methods—A total of 23 119 men and 35 611 women, age 40 to 79 years, completed a food frequency questionnaire in the Japan Collaborative Cohort Study. During the median 14-year follow-up, there were 986 deaths from stroke, 424 from coronary heart disease, and 2087 from cardiovascular disease.

Results—Dietary folate and vitamin B_6 intakes were inversely associated with mortality from heart failure for men and with mortality from stroke, coronary heart disease, and total cardiovascular disease for women. These inverse associations did not change materially after adjustment for cardiovascular risk factors. No association was found between vitamin B_{12} intake and mortality risk.

Conclusions—High dietary intakes of folate and vitamin B_6 were associated with reduced risk of mortality from stroke, coronary heart disease, and heart failure among Japanese. (***Stroke*. 2010;41:1285-1289.**)

Key Words: folate ■ vitamin B ■ coronary heart disease ■ stroke ■ follow-up study

Folate, vitamin B_6, and vitamin B_{12} are cofactors in homocysteine metabolism, and low intakes of these nutrients are associated with higher blood homocysteine concentrations, a potential risk factor for coronary heart disease (CHD) and stroke.[1] However, the effect of supplementation with these nutrients on secondary prevention of CHD or stroke has been controversial.[2,3] Furthermore, the evidence for an association between dietary intakes of folate and B vitamins and risk of cardiovascular disease (CVD) in Asian populations remains limited. No investigators have prospectively examined the associations of these vitamin intakes with heart failure, although blood homocysteine concentrations higher than the median (≥11.8 mmol/L for men and ≥11.1 mmol/L for women) were associated with a 2-fold increased risk.[4] There is thus an urgent need for a prospective study to replicate previous results in different populations and validate the associations.

Subjects and Methods

Study Population

The Japan Collaborative Cohort Study began in 1988 to 1990.[5] The data from food frequency questionnaires were available for 24 386 men and 37 493 women age 40 to 79 years at baseline. We excluded persons who self-reported a history of CVD (n=2294) and cancer (n=855) at baseline because they were likely to change their dietary habits. The remaining 23 119 men and 35 611 women were enrolled in our study. The ethics committees of the Nagoya University School of Medicine and Osaka University Graduate School of Medicine approved the present study.

Exposure Assessment and Mortality Surveillance

The method for mortality surveillance has been described in detail elsewhere.[5] The underlying causes of death were determined according to the International Classification of Diseases, 10th revision, as follows: death from stroke (ICD I60-I69), CHD (ICD I20-I25), heart failure (ICD I50), and CVD (ICD I01-I99). Follow-up was conducted until the end of 2003, except for 4 communities, in which follow-up ended in 1999.

The daily intake of nutrients for individuals was calculated by consulting the *Standardized Tables of Food Composition*, 5th ed.[6] Intakes of folate and vitamin B_6 were adjusted for total energy intake by means of a sex-specific residual model to reduce the influence of energy intake.

Statistical Analysis

The hazard ratios and their 95% CIs of mortality outcomes according to quintiles of dietary intakes of folate (<272, 272–351, 352–430, 431–535, and ≥536 μg/d), vitamin B_6 (<0.79, 0.79–0.96, 0.97–1.11, 1.12–1.32, and ≥1.33 mg/d), and B_{12} (<4.5, 4.5–5.9, 6.0–7.6, 7.7–9.8, and ≥9.9 μg/d) were calculated by using the Cox proportional-hazards model.

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Table 1. Age-Adjusted Mean Values and Prevalence of CVD Risk Factors According to Quintiles of Dietary Folate, Vitamin B_6, and B_{12} Intakes

	Folate, μg/d				Vitamin B_6, mg/d				Vitamin B_{12}, μg/d			
Quintile	1 (Low)	3	5 (High)	*P* for Trend	1 (Low)	3	5 (High)	*P* for Trend	1 (Low)	3	5 (High)	*P* for Trend
Men, median values	217	389	631		0.6	1.0	1.5		3.6	7.0	12.2	
No. at risk	4623	4624	4624		4623	4624	4624		4623	4624	4624	
Age, y	54.3	55.8	57.9	<0.001	54.6	55.8	57.3	<0.001	55.1	55.8	56.9	<0.001
Ethanol intake, g/d	33.5	33.9	34.9	0.04	33.9	33.7	35.3	<0.001	30.7	33.4	37.8	<0.001
Current smoker, %	55	53	54	0.54	58	53	51	<0.001	55	52	55	0.99
Body mass index, kg/m^2	22.7	22.7	22.7	0.53	22.6	22.7	22.8	<0.001	22.6	22.8	22.7	0.002
History of hypertension, %	21	20	16	0.01	21	18	17	<0.001	21	19	16	<0.001
History of diabetes, %	7	6	5	<0.001	7	7	5	<0.001	7	6	5	<0.001
Frequency of fish intake, times/wk	3	4	5	<0.001	3	4	5	<0.001	3	4	4	<0.001
Saturated fatty acid, g/d	7	10	12	<0.001	7	9	13	<0.001	7	10	12	<0.001
n-3 unsaturated acid, g/d	1.1	1.6	2.2	<0.001	0.9	1.6	2.6	<0.001	0.9	1.6	2.5	<0.001
n-6 unsaturated acid, g/d	4.6	6.4	8.3	<0.001	4.1	6.3	9.2	<0.001	4.2	6.5	8.7	<0.001
Intake of calories, kcal/d	1430	1751	2043	<0.001	1299	1731	2211	<0.001	1394	1739	2104	<0.001
Women, median values	225	391	619		0.7	1.1	1.5		3.5	6.6	11.5	
No. at risk	7122	7122	7122		7122	7122	7122		7122	7122	7122	
Age, y	55.6	56.0	57.5	<0.001	56.4	56.1	56.8	<0.001	56.6	55.9	56.5	0.26
Ethanol intake, g/d	11.7	9.7	9.5	0.38	12.0	10.0	8.6	<0.001	11.0	9.7	10.1	0.48
Current smoker, %	7	4	4	0.04	8	4	3	<0.001	8	4	4	<0.001
Body mass index, kg/m^2	23.0	22.9	23.0	0.09	22.9	22.9	23.0	0.20	22.9	22.9	23.0	0.07
History of hypertension, %	23	20	17	<0.001	23	21	17	<0.001	24	21	17	<0.001
History of diabetes, %	4	4	3	0.41	5	3	2	<0.001	4	3	3	0.002
Frequency of fish intake, times/wk	3	4	4	<0.001	3	4	5	<0.001	3	4	4	<0.001
Saturated fatty acid, g/d	8	10	12	<0.001	7	10	13	<0.001	7	10	13	<0.001
n-3 unsaturated acid, g/d	1.2	1.7	2.1	<0.001	0.9	1.6	2.5	<0.001	0.9	1.6	2.4	<0.001
n-6 unsaturated acid, g/d	4.6	6.2	7.7	<0.001	4.0	6.0	8.6	<0.001	4.2	6.3	8.1	<0.001
Intake of calories, kcal/d	1206	1445	1659	<0.001	1095	1426	1799	<0.001	1166	1442	1710	<0.001

The confounding variables comprised age (year), body mass index (sex-specific quintiles), smoking status (never, ex-smoker, and current smoker of 1–19 and ≥20 cigarettes/d), alcohol intake category (never, ex-drinker, and current drinker of 1–22, 23–45, 46–68, and ≥69 g of ethanol per day), history of hypertension and diabetes (yes), as well as saturated fatty acids and n-3and n-6 polyunsaturated fatty acids (sex-specific quintiles). SAS version 9.1 (SAS Institute Inc, Cary, NC) was used to perform all statistical analyses (2 tailed).

Results

Table 1 shows baseline characteristics according to quintiles (lowest, middle, and highest) of dietary folate and vitamin B_6 and B_{12} intakes. During the median 14-year follow-up, we documented 986 (500 in men and 486 in women) deaths from stroke, 424 (233 in men and 191 in women) from CHD, 318 (151 in men and 167 in women) from heart failure, and 2,087 (1066 in men and 1021 in women) from CVD.

Dietary folate and vitamin B_6 intakes were inversely associated with mortality from heart failure for men and with mortality from stroke, CHD, and total CVD for women (Table 2). These inverse associations did not change materially after adjustment for CVD risk factors.

When we excluded the subjects who were using multivitamin supplements (n=7334), the results did not change materially. For example, the multivariable hazard ratios (and 95% CIs) of CHD for the highest versus lowest quintiles were 0.62 (0.42–0.89) for folate, 0.51 (0.29–0.91) for vitamin B_6, and 1.35 (0.80–2.27) for vitamin B_{12} intakes and those for heart failure were 0.76 (0.51–1.13) for folate, 0.60 (0.32–1.13) for vitamin B_6, and 1.57 (0.90–2.73) for vitamin B_{12} (data not shown).

Discussion

We found inverse associations between folate and vitamin B_6 intakes and risk of mortality from stroke and CHD for Japanese, which are consistent with previous reports of these associations for Americans[7] and Europeans.[8]

Furthermore, this study is the first to show that high dietary intakes of folate and vitamin B_6 were associated with a reduced risk of heart failure mortality for men. Mechanisms for these observed associations may involve the effects of these vitamin intakes on reductions of blood homocysteine concentrations. A meta-analysis of observational studies provided evidence that a 3-μmol/L reduction in homocysteine level was associated with an 11% reduction in CHD risk and a 19% reduction in stroke risk.[1] A single, large, clinical trial of women, however, did not show any beneficial effect of

Table 2. Sex-Specific Hazard Ratio (HRs) and 95% CIs of CVD According to Quintiles of Folate, Vitamin B_6, and B_{12} Intake

	Men					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Total No.	4623	4624	4624	4624	4624	
Folate						
Person-years	56 921	57 485	57 895	58 443	58 401	
Stroke	81	91	93	115	120	
Age-adjusted HR	1.00	1.04 (0.77–1.41)	0.96 (0.71–1.29)	1.15 (0.86–1.52)	1.05 (0.79–1.39)	0.74
Multivariable HR	1.00	1.06 (0.78–1.44)	1.01 (0.73–1.38)	1.19 (0.87–1.63)	1.12 (0.81–1.55)	0.50
CHD	54	43	39	52	45	
Age-adjusted HR	1.00	0.74 (0.49–1.01)	0.61 (0.40–0.92)	0.78 (0.53–1.14)	0.60 (0.41–0.90)	0.01
Multivariable HR	1.00	0.79 (0.52–1.19)	0.69 (0.45–1.07)	0.92 (0.60–1.40)	0.72 (0.45–1.14)	0.16
Heart failure	31	34	34	29	23	
Age-adjusted HR	1.00	1.02 (0.63–1.67)	0.93 (0.57–1.51)	0.77 (0.46–1.28)	0.54 (0.31–0.92)	0.02
Multivariable HR	1.00	1.08 (0.65–1.78)	1.03 (0.61–1.73)	0.80 (0.45–1.41)	0.50 (0.27–0.94)	0.03
CVD	190	197	197	244	238	
Age-adjusted HR	1.00	0.96 (0.79–1.17)	0.87 (0.71–1.06)	1.04 (0.86–1.25)	0.89 (0.74–1.08)	0.24
Multivariable HR	1.00	1.00 (0.82–1.23)	0.94 (0.76–1.17)	1.12 (0.91–1.38)	0.97 (0.77–1.21)	0.75
Vitamin B_6						
Person-years	55 793	56 872	58 008	59 072	59 404	
Stroke	87	91	104	107	111	
Age-adjusted HR	1.00	0.96 (0.71–1.28)	1.01 (0.76–1.34)	0.99 (0.75–1.31)	0.95 (0.72–1.26)	0.74
Multivariable HR	1.00	0.95 (0.68–1.32)	1.14 (0.78–1.66)	1.19 (0.77–1.82)	1.08 (0.65–1.78)	0.77
CHD	58	46	41	42	46	
Age-adjusted HR	1.00	0.72 (0.49–1.06)	0.60 (0.40–0.89)	0.58 (0.39–0.86)	0.59 (0.40–0.87)	<0.001
Multivariable HR	1.00	0.65 (0.41–1.01)	0.52 (0.30–0.88)	0.54 (0.29–0.98)	0.64 (0.32–1.30)	0.22
Heart failure	36	24	35	32	24	
Age-adjusted HR	1.00	0.62 (0.37–1.04)	0.87 (0.55–1.38)	0.75 (0.46–1.20)	0.53 (0.31–0.89)	0.02
Multivariable HR	1.00	0.71 (0.39–1.29)	0.96 (0.49–1.89)	0.73 (0.34–1.60)	0.39 (0.15–1.00)	0.05
CVD	210	192	211	222	231	
Age-adjusted HR	1.00	0.83 (0.69–1.01)	0.85 (0.70–1.03)	0.85 (0.70–1.03)	0.82 (0.68–0.99)	0.04
Multivariable HR	1.00	0.85 (0.68–1.07)	0.92 (0.71–1.20)	0.96 (0.72–1.29)	0.93 (0.66–1.30)	0.66
Vitamin B_{12}						
Person-years	55 945	57 141	58 601	58 930	58 533	
Stroke	80	104	104	82	130	
Age-adjusted HR	1.00	1.26 (0.94–1.68)	1.15 (0.86–1.54)	0.86 (0.63–1.17)	1.38 (1.05–1.83)	0.02
Multivariable HR	1.00	1.21 (0.85–1.71)	1.36 (0.91–2.02)	1.03 (0.66–1.62)	1.59 (1.01–2.52)	0.05
CHD	50	50	44	47	42	
Age-adjusted HR	1.00	0.95 (0.64–1.41)	0.77 (0.52–1.16)	0.78 (0.52–1.16)	0.71 (0.47–1.06)	0.10
Multivariable HR	1.00	0.93 (0.58–1.49)	0.81 (0.46–1.43)	0.90 (0.49–1.67)	0.93 (0.48–1.80)	0.83
Heart failure	28	34	31	28	30	
Age-adjusted HR	1.00	1.19 (0.72–1.97)	1.02 (0.61–1.70)	0.88 (0.52–1.48)	0.95 (0.57–1.60)	0.86
Multivariable HR	1.00	1.72 (0.95–3.14)	1.61 (0.79–3.29)	1.53 (0.69–3.36)	1.53 (0.65–3.46)	0.34
CVD	191	215	209	208	243	
Age-adjusted HR	1.00	1.08 (0.89–1.32)	0.97 (0.79–1.18)	0.91 (0.75–1.11)	1.08 (0.89–1.30)	0.43
Multivariable HR	1.00	1.16 (0.92–1.47)	1.20 (0.91–1.58)	1.20 (0.89–1.62)	1.43 (0.89–1.95)	0.03

Multivariable adjustment on age, body mass index, history of hypertension and diabetes, smoking status, ethanol and energy intakes, as well as intakes of saturated fatty acids and n-3 and n-6 polyunsaturated fatty acids.

Table 2. Continued

Women					
1 (Low)	2	3	4	5 (High)	*P* for Trend
7122	7122	7122	7122	7122	
89 723	90 439	91 288	91 784	92 778	
110	95	90	87	104	
1.00	0.92 (0.70–1.21)	0.81 (0.61–1.07)	0.74 (0.56–0.98)	0.82 (0.63–1.07)	0.14
1.00	0.93 (0.70–1.23)	0.81 (0.60–1.09)	0.74 (0.55–1.01)	0.83 (0.61–1.12)	0.22
54	44	21	44	28	
1.00	0.89 (0.60–1.32)	0.40 (0.24–0.64)	0.77 (0.52–1.15)	0.46 (0.29–0.72)	<0.001
1.00	0.97 (0.64–1.46)	0.43 (0.26–0.73)	0.89 (0.58–1.37)	0.57 (0.34–0.96)	0.03
37	32	31	29	38	
1.00	0.95 (0.59–1.53)	0.85 (0.53–1.37)	0.76 (0.47–1.23)	0.92 (0.59–1.45)	0.72
1.00	1.00 (0.61–1.62)	0.92 (0.56–1.53)	0.83 (0.49–1.41)	1.03 (0.61–1.75)	0.91
245	189	179	200	208	
1.00	0.80 (0.69–1.00)	0.73 (0.60–0.88)	0.77 (0.64–0.93)	0.74 (0.61–0.89)	0.001
1.00	0.86 (0.71–1.05)	0.77 (0.63–0.94)	0.83 (0.67–1.01)	0.83 (0.67–1.03)	0.08
87 482	89 596	91 447	92 705	94 781	
115	108	79	93	91	
1.00	1.01 (0.78–1.32)	0.71 (0.54–0.95)	0.83 (0.63–1.09)	0.79 (0.60–1.04)	0.09
1.00	0.88 (0.64–1.20)	0.56 (0.39–0.81)	0.62 (0.41–0.93)	0.63 (0.39–1.03)	0.06
66	32	37	26	30	
1.00	0.53 (0.35–0.81)	0.59 (0.39–0.88)	0.41 (0.26–0.64)	0.46 (0.30–0.71)	<0.001
1.00	0.48 (0.29–0.77)	0.55 (0.32–0.94)	0.40 (0.20–0.77)	0.47 (0.21–1.04)	0.06
42	33	29	35	28	
1.00	0.87 (0.55–1.38)	0.74 (0.46–1.19)	0.89 (0.57–1.40)	0.71 (0.44–1.15)	0.16
1.00	0.97 (0.57–1.65)	0.86 (0.46–1.63)	1.01 (0.50–2.05)	0.86 (0.37–2.02)	0.73
259	208	191	188	175	
1.00	0.87 (0.73–1.05)	0.77 (0.64–0.93)	0.75 (0.62–0.90)	0.68 (0.56–0.82)	<0.001
1.00	0.84 (0.68–1.04)	0.73 (0.57–0.94)	0.73 (0.55–0.97)	0.73 (0.52–1.02)	0.06
87 605	90 087	92 094	92 768	93 458	
106	99	91	105	85	
1.00	1.01 (0.77–1.33)	0.94 (0.71–1.33)	1.06 (0.81–1.38)	0.86 (0.65–1.15)	0.32
1.00	1.03 (0.73–1.44)	0.99 (0.66–1.48)	1.25 (0.82–1.92)	1.13 (0.71–1.79)	0.61
52	38	42	28	31	
1.00	0.80 (0.53–1.22)	0.90 (0.60–1.35)	0.59 (0.37–0.93)	0.66 (0.42–1.04)	0.07
1.00	0.97 (0.59–1.61)	1.71 (0.94–3.11)	1.18 (0.60–2.35)	1.39 (0.67–2.89)	0.37
43	31	31	30	32	
1.00	0.80 (0.50–1.27)	0.82 (0.51–1.30)	0.78 (0.49–1.24)	0.85 (0.54–1.34)	0.48
1.00	1.02 (0.59–1.77)	1.31 (0.67–2.57)	1.38 (0.68–2.81)	1.79 (0.85–3.76)	0.13
244	210	195	189	183	
1.00	0.94 (0.78–1.13)	0.88 (0.73–1.06)	0.83 (0.69–1.01)	0.82 (0.67–0.99)	0.04
1.00	1.01 (0.81–1.26)	1.11 (0.85–1.45)	1.21 (0.91–1.62)	1.33 (0.97–1.81)	0.07

folic acid supplementation on risk of CVD.[2] A more recent clinical trial of men and women has demonstrated that the lowering of homocysteine by supplementation with folic acid, vitamin B_6, and vitamin B_{12} reduced the risk of stroke.[3] Taken together, our results suggest that dietary intakes of folate and vitamin B_6 may be useful to prevent CVD.

The supplementation with folate and vitamin B_6 was not taken into account in the present study, but the observed associations did not change after exclusion of persons who were taking multivitamin supplements. Also, we used the mortality data as end points, which may have led to misclassification in the diagnosis of stroke, CHD, and heart failure. However, previous validation studies indicated the validity of death certificate diagnoses for these outcomes because of the widespread use of computed tomography or magnetic resonance imaging for stroke diagnosis[9] and of ECG and cardiac enzyme examinations for CHD and heart failure.[10]

In summary, high dietary folate and vitamin B_6 intakes were associated with a reduced risk of mortality from stroke, CHD, and heart failure among Japanese.

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Disclosures

None.

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Parental longevity and offspring's home blood pressure: the Ohasama study

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Objective **Longevity is clustered in particular families. Some studies using conventional blood pressure (BP) reported an association between parental longevity and offspring's BP. No study has used self-measurement of BP at home (home BP). We examined the association between parental longevity and home BP values of adult Japanese offspring.**

Method **Home and conventional BPs were measured in 1961 residents aged 40 years and over in the general population of Ohasama, Japan. Information about the ages of offspring's parents (age at death or current age) was obtained from a standardized questionnaire.**

Results **The mean ± SD values of systolic/diastolic home BP in offspring whose mothers died at less than 69 years of age, at 69–84 years of age, and in offspring whose mothers were alive at age 84 years were 127.4 ± 13.2/76.2 ± 9.1, 124.8 ± 15.0/74.4 ± 10.0, and 123.4 ± 15.2/74.4 ± 10.3 mmHg ($P = 0.0002/0.009$), respectively. Corresponding values in offspring whose fathers died at less than 66 years of age, at 66–80 years of age, and in offspring whose fathers were alive at age 80 years were 125.7 ± 15.2/75.6 ± 10.6, 124.7 ± 14.1/75.0 ± 9.2 and 122.4 ± 14.6/73.6 ± 9.5 mmHg ($P = 0.001/0.003$), respectively. Multivariate analysis demonstrated associations that were only weakly observed for conventional BP values (conventional BP: $P = 0.3/0.4$ for maternal and $P = 0.3/0.3$ for paternal longevity; home BP: $P = 0.05/0.2$ for maternal and $P = 0.0004/0.007$ for paternal longevity).**

Conclusion **Parental premature death was significantly associated with higher home BP levels in adult offspring, suggesting that parental longevity might be a useful additional marker for screening adult offspring at higher risk of hypertension. *J Hypertens* 28:272–277 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: general population, home blood pressure, hypertension, offspring, parental longevity

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure

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Introduction

Longevity is clustered in particular families [1]. This phenomenon may be caused by genetic and environmental factors, but these factors are not well known. Hypertension, which is also caused by genetic and environmental factors [2,3], is a major risk factor for cardiovascular events such as stroke and myocardial infarction [4,5]. Some studies have focused on associations between hypertension and noncardiovascular mortality [6].

Although some studies in Western countries have reported an association between parental longevity and offspring's conventional blood pressure (BP) [7], no study has investigated the association using self-measurement of BP (home BP). Conventional BP measurements are known to have biases, such as observer biases, regression dilution biases, and the so-called white-coat effect. In contrast, home BP allows multiple BP measurements outside the hospital, is free of these biases, provides more reproducible information, and has more predictive power than conventional BP measurements [8–12]. The Japanese population is known to have the longest longevity in the world, but no studies have investigated this association [13].

In this Japanese study, the association between parental longevity and home BP values of adult offspring was examined.

Methods

Design

The present study is based on a longitudinal observation of individuals who had been participating in a BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. Ohasama, a rural community, had a total population

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of 7496 in 1992. The socioeconomic and demographic characteristics of this region and the details of this project have been previously described [5]. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of Ohasama Town Government.

Participants

In Japan, annual health check-ups were available for farmers, the self-employed, pensioners, and dependents aged at least 40 years. Among the residents of Ohasama, 3076 were eligible for annual health check-ups in 1992 [14]. Home and conventional BPs were measured in 1961 residents aged 40 years and over, representing 64% of the total eligible population.

Classification of longevity status

Information on the ages of offspring's parents (at death or current age) was obtained from a standardized questionnaire. The cut-off points of parental longevity status were determined such that the number of offspring in each tertile was the same (Table 1). Paternal and maternal longevity classes were analyzed separately. Offspring whose mothers died at less than 69 years of age were classified into the premature death group, whose mothers were alive at age 69 but died by 84 years of age were classified into the intermediate group, and whose mothers were alive at age 84 were classified into the longevity group. Similarly, offspring whose fathers died at less than 66 years of age were classified into the premature death group, whose fathers were alive at age 66 but died by 80 years of age were classified into the intermediate group, and whose fathers were alive at age 80 were classified into the longevity group. Offspring whose mothers were still alive and were less than 84 years old (618 mothers) or offspring whose fathers were still alive and were less than 80 years old (478 fathers) were excluded from corresponding analyses because these offspring could be classified into both intermediate and longevity groups.

Conventional blood pressure measurement

Two consecutive measurements of BP were taken by a nurse or technician at local medical centers, using a semiautomatic device (USM-700F; UEDA Electronic Works Co. Ltd, Tokyo, Japan) with the participants seated and at rest for at least 2 min. The conventional BP was defined as the average of the two readings.

Table 1 Classification of parental longevity status

	Premature death	Intermediate	Longevity	Other	Total
Mother's age (years)	<69	69 to 84	≥84		
Number of offspring	438	466	439	618	1961
Father's age (years)	<66	66 to 80	≥80		
Number of offspring	514	484	485	478	1961

We classified the offspring into three groups according to the ages of their parents (at death or current age). Maternal and paternal longevity classes were analyzed separately. Offspring whose mothers were still alive and were less than 84 years old (618 mothers) or whose fathers were still alive and were less than 80 years old (478 fathers) were excluded from corresponding analyses.

Home blood pressure measurement

Home BP was measured with the HEM401C, a semiautomatic device based on the cuff-oscillometric method that generates a digital display of both systolic and diastolic BP (Omron Healthcare, Kyoto, Japan). The devices used met the criteria of the Association for the Advancement of Medical Instrumentation [15].

Public health nurses calibrated the devices and instructed the participants on how to measure BP. All participants were asked to measure BP at home once in the morning within 1 h after waking, after micturition, sitting after 1–2 min of rest, before drug ingestion, and before breakfast. This protocol was the same as the guidelines of the Japanese Society of Hypertension [11]. Participants were asked to record the results over a 4-week period.

Home BP measurements were collected from participants who measured their own BP data on at least 3 days during the 4-week study period. The home BP was defined as the mean of all measurements obtained in each individual.

Definition of hypertension

On the basis of several guidelines [11,12,16–18], participants with home systolic BP at least 135 mmHg and/or home diastolic BP at least 85 mmHg or taking antihypertensive medication were classified as having home hypertension, whereas those with conventional systolic BP at least 140 mmHg and/or conventional diastolic BP at least 90 mmHg or taking antihypertensive medication were classified as having conventional hypertension.

Data collection and analysis

Information on smoking status, parental hypertension, history of diabetes mellitus, hypercholesterolemia, and/or cardiovascular disease, as well as use of antihypertensive medication, was obtained from questionnaires and from the medical charts of the Ohasama Hospital, which included the results of laboratory investigations performed during annual health check-ups. Participants using lipid-lowering drugs or those with serum cholesterol levels of 5.68 mmol/l were considered to have hypercholesterolemia. Participants with a fasting glucose level of 7.0 mmol/l or a nonfasting glucose level of 11.1 mmol/l, or those using insulin or oral hypoglycemic drugs, were defined as having diabetes mellitus. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Variables were compared using the chi-squared test, analysis of variance (ANOVA), and analysis of covariance (ANCOVA) adjusted for sex, age, BMI, smoking status, parental hypertension, and history of diabetes mellitus, hypercholesterolemia and/or cardiovascular disease, as

appropriate. Statistical analysis was performed using SAS software, Version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Parametric data are shown as means ± SD SD or means [95% confidence interval (CI)]. Values of $P < 0.05$ were considered statistically significant.

Results

Characteristics of offspring by parental longevity status

The offspring's characteristics by parental longevity status are shown in Table 2. The percentages of offspring classified into the maternal premature death, intermediate, and longevity groups were 32.6% ($n = 438$), 34.7% ($n = 466$), and 32.7% ($n = 439$), respectively (Table 2). The corresponding percentages for fathers were 34.7% ($n = 514$), 32.6% ($n = 484$), and 32.7% ($n = 485$), respectively (Table 2).

Maternal longevity was significantly associated with offspring's younger age, a lower percentage receiving antihypertensive medication, and lower prevalence of home and conventional hypertension (Table 2).

Height and weight were slightly but significantly associated with paternal longevity. Although the prevalence of home hypertension was higher in the paternal premature death group, it did not reach statistical significance ($P = 0.1$) (Table 2).

Parental longevity and offspring's blood pressure

The mean ± SD values of systolic/diastolic BP according to parental longevity status are shown in Table 3. Parental longevity was significantly associated with offspring's home BP ($P = 0.0002/0.009$ for maternal and $P = 0.001/0.003$ for paternal longevity, respectively). Such associations were only weakly observed for conventional BP values ($P = 0.01/0.1$ for maternal and $P = 0.3/0.1$ for paternal longevity, respectively). We found similar significant relationships using home BP values defined as the average of the first two readings ($P = 0.002/0.01$ for maternal and $P = 0.002/0.008$ for paternal longevity, respectively). Multivariate analyses adjusted for possible confounding factors did not modify most of these significant associations (Table 3). The adjusted mean values and their 95% CIs in each group were 126.4/75.6 (125.2–127.5/74.8–76.4), 124.5/74.5 (123.4–125.6/73.7–75.3) and 124.7/74.9 (123.6–125.9/74.1–75.7) for maternal ($P = 0.05/0.2$); and 125.8/75.5 (124.7–126.8/74.8–76.2), 124.4/74.9 (123.3–125.5/74.1–75.6), 122.7/73.8 (121.6–123.8/73.0–74.6) for paternal ($P = 0.0004/0.007$), respectively.

Similar relationships were observed for those not on antihypertensive medications (Table 3). Separate analyses according to sex of offspring showed consistent results (data not shown).

Combination of paternal and maternal longevity and offspring's blood pressure

The combination of maternal longevity and paternal longevity was strongly associated with offspring's home BP levels. Offspring whose mothers died at less than 69 years of age and whose fathers died at less than 66 years of age had a significantly higher level of home systolic BP

Table 2 Characteristics of offspring according to maternal and paternal longevity status

	Maternal longevity status				Paternal longevity status			
	Premature death	Intermediate	Longevity	*P*	Premature death	Intermediate	Longevity	*P*
Number of offspring (*n*)	438	466	439		514	484	485	
Age (years)	61.6 ± 9.0	61.8 ± 8.9	60.0 ± 7.9	0.003	59.5 ± 9.5	60.0 ± 9.5	59.9 ± 8.9	0.6
Men (%)	36.8	33.7	32.8	0.4	36.6	33.5	33.6	0.5
Height (cm)	152.4 ± 6.3	151.9 ± 6.2	152.6 ± 6.3	0.5	153.5 ± 6.7	152.6 ± 6.1	152.1 ± 6.2	0.02
Weight (kg)	54.7 ± 8.8	54.9 ± 8.7	54.8 ± 8.8	0.9	56.0 ± 9.1	55.0 ± 8.6	54.4 ± 8.7	0.01
BMI (kg/m^2)	23.5 ± 3.2	23.7 ± 2.9	23.5 ± 3.1	0.5	23.7 ± 3.2	23.6 ± 3.0	23.5 ± 3.0	0.4
Ever smoker (%)	16.4	17.4	15.0	0.6	16.5	15.7	16.7	0.9
Ever drinker (%)	24.9	23.2	24.8	0.8	27.0	24.2	24.1	0.5
Antihypertensive medication (%)	43.4	35.2	27.8	<0.0001	32.7	35.5	30.9	0.3
History of parental hypertension (%)	23.7	23.4	20.3	0.4	21.6	24.0	22.1	0.6
Previous history of hypercholesterolemia (%)	32.7	33.5	30.8	0.7	31.5	32.0	30.5	0.9
Diabetes mellitus (%)	11.4	10.5	10.7	0.9	11.3	10.5	9.9	0.8
Cardiovascular disease (%)	8.0	5.8	4.8	0.1	7.2	5.0	5.8	0.3
Antihypertensive medication (%)	43.4	35.2	27.8	<0.0001	32.7	35.5	30.9	0.3
Hypertension								
Conventional BP (%)	55.0	48.1	39.0	<0.0001	47.3	45.5	41.2	0.1
Home BP (%)	52.5	45.3	37.1	<0.0001	45.5	42.2	39.2	0.1
Number of offspring with antihypertensive medication (*n*)	190	164	122		168	172	150	
Uncontrolled hypertension								
Conventional BP (%)	42.6	38.4	44.3	0.6	39.9	43.0	42.7	0.8
Home BP (%)	45.3	49.4	55.7	0.2	51.2	52.3	42.0	0.1

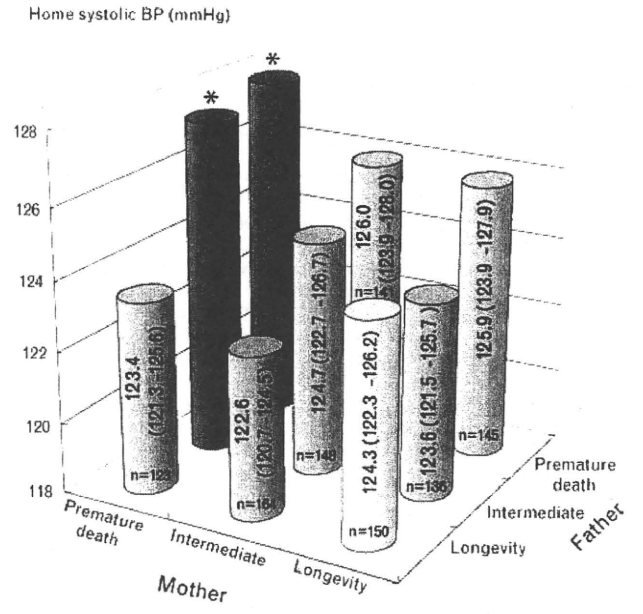
Data are given as mean ± SD or percentage of offspring. Statistical significance among three groups was compared using the ANOVA for continuous variables and the chi-squared test for categorical variables. Definitions of hypertension: home BP, systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg or taking antihypertensive medication; conventional BP, systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg or taking antihypertensive medication. Definitions of uncontrolled hypertension: home BP, systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg; conventional BP, systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg. BMI, body mass index; BP, blood pressure.

Table 3 Parental longevity and offspring's BP

	All offspring						Untreated offspring					
	Maternal longevity status						Maternal longevity status					
	Premature death	Intermediate	Longevity	*P*	*P**	*P***	Premature death	Intermediate	Longevity	*P*†	*P*††	*P*†††
Number of offspring	438	466	439				248	302	317			
Conventional												
Systolic BP (mmHg)	132.8 ± 16.0	131.4 ± 15.8	129.6 ± 15.9	0.01	0.3	0.3	129.2 ± 14.4	128.5 ± 15.0	126.5 ± 15.0	0.07	0.2	0.2
Diastolic BP (mmHg)	74.7 ± 11.4	73.9 ± 10.6	73.2 ± 10.7	0.1	0.4	0.4	73.4 ± 9.7	72.6 ± 10.4	72.0 ± 10.2	0.2	0.4	0.4
Home												
Systolic BP (mmHg)	127.4 ± 13.2	124.8 ± 15.0	123.4 ± 15.2	0.0002	0.05	0.05	122.7 ± 11.5	120.4 ± 13.9	119.0 ± 13.2	0.004	0.02	0.02
Diastolic BP (mmHg)	76.2 ± 9.1	74.4 ± 10.0	74.4 ± 10.3	0.009	0.2	0.2	73.7 ± 7.9	72.2 ± 9.1	72.1 ± 9.4	0.06	0.2	0.2
Pulse pressure (mmHg)	51.3 ± 9.1	50.3 ± 9.7	49.0 ± 9.2	0.002	0.2	0.2	49.0 ± 8.1	48.2 ± 8.8	46.9 ± 7.7	0.01	0.04	0.04
Heart rate (b.p.m.)	66.4 ± 8.2	67.6 ± 7.8	66.8 ± 7.3	0.08	0.07	0.07	66.8 ± 7.7	68.2 ± 7.0	67.4 ± 7.0	0.09	0.1	0.1
	Paternal longevity status						Paternal longevity status					
	Premature death	Intermediate	Longevity	*P*	*P**	*P***	Premature death	Intermediate	Longevity	*P*†	*P*††	*P*†††
Number of offspring	514	484	485				346	312	335			
Conventional												
Systolic BP (mmHg)	131.3 ± 15.9	130.7 ± 15.9	129.7 ± 16.1	0.3	0.3	0.3	128.4 ± 15.0	126.9 ± 14.6	126.4 ± 15.1	0.2	0.1	0.1
Diastolic BP (mmHg)	74.3 ± 11.4	74.0 ± 10.4	73.0 ± 10.9	0.1	0.3	0.3	73.2 ± 11.2	72.8 ± 9.4	71.4 ± 10.3	0.06	0.08	0.07
Home												
Systolic BP (mmHg)	125.7 ± 15.2	124.7 ± 14.1	122.4 ± 14.6	0.001	0.0004	0.0003	121.5 ± 13.8	119.5 ± 12.0	118.3 ± 12.6	0.005	0.002	0.001
Diastolic BP (mmHg)	75.6 ± 10.6	75.0 ± 9.2	73.6 ± 9.5	0.003	0.007	0.007	73.4 ± 10.0	72.5 ± 8.3	71.6 ± 8.6	0.03	0.04	0.03
Pulse pressure (mmHg)	50.1 ± 9.4	49.7 ± 9.1	48.9 ± 9.7	0.1	0.03	0.03	48.0 ± 8.3	47.1 ± 7.5	46.7 ± 8.4	0.08	0.01	0.01
Heart rate (b.p.m.)	67.2 ± 8.3	66.8 ± 7.7	67.4 ± 7.2	0.5	0.6	0.7	67.8 ± 7.6	67.4 ± 7.2	67.8 ± 7.0	0.7	0.5	0.5

Data are given as means ± SD. *P* shows *P* values of ANOVA among three groups. *P** shows *P* values adjusted for sex, age, BMI, smoking status, a history of diabetes mellitus, hypercholesterolemia, or cardiovascular disease. *P*** shows *P* value adjusted for sex, age, BMI, smoking status, a history of diabetes mellitus, hypercholesterolemia, or cardiovascular disease, and parental hypertension. *P*†, *P*†† and *P*††† shows *P* values of ANOVA/ANCOVA among three groups in untreated offspring. BP, blood pressure.

Fig. 1



Combination of maternal and paternal longevity and offspring's home BP. Home systolic BP among nine groups defined according to maternal and paternal longevity. Gray bars and * show significant associations compared with both parental longevity group adjusted for sex, age, BMI, smoking status, a history of diabetes mellitus, hypercholesterolemia, and/or cardiovascular disease. Data are given as adjusted mean values and their 95% confidence intervals. BP, blood pressure.

than offspring whose mothers were alive by age 84 and whose fathers were alive by age 80 ($128.9 \pm 12.7/77.2 \pm 9.6$ mmHg vs. $122.5 \pm 14.1/74.3 \pm 9.5$ mmHg, $P = 0.0001/0.009$); no significant associations were observed for conventional BP ($133.1 \pm 14.5/75.6 \pm 11.9$ mmHg vs. $129.5 \pm 15.8/73.8 \pm 10.8$ mmHg, $P = 0.05/0.2$). Similar relationships were observed using home BP values defined as the average of the first two readings ($P = 0.0007/0.04$). These associations were significant after adjustment for possible confounding factors (Fig. 1).

Parental longevity and history of parental hypertension

When maternal longevity and history of maternal hypertension were entered into the same model simultaneously, only maternal longevity was significantly associated with offspring's systolic BP ($P = 0.04$ for maternal longevity, $P = 0.1$ for history of maternal hypertension). Paternal longevity and paternal hypertension were independently and significantly related with offspring's systolic BP ($P = 0.0004$ for paternal longevity, $P = 0.01$ for history of paternal hypertension) when paternal longevity and history of paternal hypertension were entered into the same model.

Discussion

We found significant associations between parental longevity and offspring's BP using home BP measurement. Hypertension was more frequent, and home systolic and diastolic BPs were higher in the parental premature death group than in the parental longevity group. Parental longevity was more strongly associated with offspring's home BP than with offspring's conventional BP.

To our knowledge, no previous studies have examined the association between parental longevity and offspring's BP using home BP. Home BP makes it possible to obtain multiple measurements of BP over a long observation period under well controlled conditions [8], and it has stronger predictive power for mortality and morbidity than conventional BP [9–11], indicating that these BP values provide a better phenotype for BP. In the present study, the effects of parental longevity on offspring's BP were analyzed on the basis of both home BP and conventional BP measurements, and we found that associations between parental longevity and offspring's BP were more marked for home BP than for conventional BP. Furthermore, home BP values were significantly associated with parental longevity, even with home BP values defined as the average of the first two readings. We previously reported that the predictive value of home BP increased progressively with the number of measurements, but that home BP had a stronger predictive power than conventional BP, even for a lower number of measurements [19]. Measurement conditions might be important, as well as the number of measurements.

Previous studies reported the relationships of BP with age at death of parents and longevity. Hammond *et al.* [20] reported that a history of high BP was more frequent in offspring with the shortest-lived parents (a group defined by both parents having died at <70 years of age) than in other groups. Another study showed that the prevalence of hypertension was lower in the offspring of centenarians [21]. In the PRIME study, systolic and diastolic BPs were lower in offspring whose fathers and mothers were alive at 80 years of age [22]. A recent study reported that paternal longevity but not maternal longevity was associated with offspring's BP [7]. These studies used the same cut-off points for the age at death of fathers and mothers. Our results using home BP further demonstrated that both paternal and maternal longevities contribute equally to offspring's BP.

In this study, parental longevity was associated with offspring's home BP equal to or greater than the association with parental hypertension. Previous studies showed the association between parental hypertension and offspring's BP [23,24]. A self-reported family history of hypertension is sometimes known to be inaccurate. In the Framingham Offspring study, a negative offspring report of parental high BP had a negative predictive value of only 53%, whereas a positive offspring report of parental high BP had a positive predictive value of 83% [25]. In our study, parental longevity was also more

closely associated with offspring's BP than with parental hypertension. Since parental age is easy to remember, it is possible that the ages of parents (at death or current age) appear to be a more accurate predictor than a family history of hypertension.

Our study should be interpreted within the context of its potential limitations. Our analyses were based on all-cause mortality of parents because the questionnaire did not require that the primary causes of parental deaths be specified. Unlike the previous study, associations between parental longevity and offspring's conventional BP were not significant in this study. Some differences in the characteristics of offspring may have influenced the findings. Offspring in our present study were about 10 years older, and standard deviations were also larger than those in the previous study. Regardless of potential limitations, home BP detected significant differences in a dispersed population.

In conclusion, parental premature death was significantly associated with higher home BP levels in adult offspring, suggesting that parental longevity might be useful additional information in screening adult offspring who may be at higher risk for hypertension.

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There are no conflicts of interest.

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