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Relationship between saturated fatty acid intake and hypertension and oxidative stress

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ABSTRACT

Objectives: This study investigated the relationship between saturated fatty acid (SFA) intake and hypertension and oxidative stress.
Methods: The present cross-sectional study was conducted among the residents of Shika town, a rural area in Japan, using health examination data received between March 2014 and January 2016. Dietary intake was measured using a brief-type self-administered diet history questionnaire. Urinary 8-hydroxy-2'-deoxyguanosine levels were used to assess oxidative stress and were measured with an enzyme linked immunosorbent assay. We defined hypertension as the use of antihypertensive medication and/or blood pressure of 140/90 mmHg or higher, and elderly as subjects aged 65 years or older.
Results: Subjects comprised 585 Japanese individuals aged 40 years and older. The prevalence of hypertension was 54.2%. SFA intake was lower in hypertensive subjects and this relationship was significantly stronger for elderly subjects. A multiple logistic regression analysis after adjustments for various confounding factors revealed that SFA intake, such as total SFA, C8:0, C12:0, C14:0, C16:0, C17:0, C18:0, C20:0, and C22:0, was inversely related to hypertension in elderly subjects. It also showed that lower urinary 8-hydroxy-2'-deoxyguanosine levels correlated with a high intake of SFA, C4:0, C6:0, C8:0, C10:0, and C12:0.
Conclusions: Our results support a relationship existing between SFA intake and hypertension and oxidative stress, and suggest that the regular consumption of SFA contributes to the prevention and treatment of hypertension in elderly patients.

Introduction

Hypertension is a major risk factor for cardiovascular morbidity and mortality worldwide [1]. Blood pressure (BP) is known to increase with age. The Framingham Heart Study reported that the residual lifetime risk for hypertension is 90%, whereas the probability of the new onset of hypertension is 60% for middle-aged and elderly individuals [2]. Therefore, the primary prevention of hypertension among middle-aged and elderly individuals an important public health issue.

Previous studies demonstrated a relationship between lifestyle choices and reductions in BP [3]. Among lifestyle choices, dietary factors such as a reduced sodium intake [4], the consumption of potassium [5], and moderation in drinking [6], are considered to play an important role in the prevention of hypertension and treatment of hypertensive individuals. The relationship between the consumption of fat and BP has been investigated and recent studies indicated that the intake of polyunsaturated fatty acids (PUFAs) reduced the risk for hypertension [7]. Furthermore, previous meta-analyses showed that a high-dose intake of ω-3 PUFAs reduced BP in hypertensive patients [8,9].

Saturated fatty acids (SFAs) are considered to be unhealthy in the cardiovascular field because of their negative effects on cholesterol metabolism, with several health authorities recommending a limited intake of SFA in the diet [10]. Conversely, few studies have examined the effects of SFA on BP. A previous study showed that C8:0 and C12:0 decreased BP in spontaneously hypertensive rats [11]. The ARIC (Atherosclerosis Risk in Communities) study, which is a longitudinal study designed to investigate the relationship between the fatty acid (FA) composition of plasma cholesterol esters and the incidence of hypertension, demonstrated that after adjustments for various confounding factors, SFA, C:16:0, and the PUFA-to-SFA ratio were positively associated with the incidence of

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hypertension. However, this relationship differed depending on statistical corrections for confounding factors, and total SFA did not correlate with the incidence of hypertension after adjustments for all confounding factors in that study [12].

A relationship has been reported between oxidative stress and hypertension [13,14]. Endothelial dysfunction owing to oxidative damage to membrane lipids is considered to contribute to chronic hypertension, and the sensitivity of biological membrane lipids to oxidative stress varies depending on their compositions, such as the presence of a double carbon–carbon bond in the FA tail, with more PUFAs than SFA or monounsaturated fatty acids (MUFAs) in membranes increasing susceptibility to oxidation [13,15]. Furthermore, the dietary intake of FAs has been shown to influence the composition of membrane lipids to some extent [16,17]. Regarding the relationship between dietary SFA intake and oxidative stress, although previous studies demonstrated the antioxidant effects of SFA, limited information is currently available [18,19].

Therefore, the present cross-sectional study was performed in an attempt to elucidate the relationship between dietary SFA intake and hypertension and oxidative stress.

Methods

Study design and participants

The present study was a cross-sectional analysis of baseline data from the SHIKA study, a longitudinal community-based observational study that was conducted with the residents of Shika, Ishikawa Prefecture, a rural area in Japan, using health examination data received between March 2014 and January 2016. This study was supported by the Shika Municipal Government, which provided a list of all residents.

The population of Shika town was 21 666 in 2016. Among all residents, 15 220 were ≥40 y of age [20]. The target population of the SHIKA study was all middle-aged individuals residing in a specific elementary school district (N = 2500). The population demographic characteristics of this model district were similar to those of Shika.

All participants (N = 2500) were asked to complete a self-administered questionnaire. Among 2500 participants, applicants for medical examinations were included in the present study. In all, 837 participants were voluntary collaborators and underwent a comprehensive medical examination; 1663 participants did not undergo a medical examination. Ninety-five participants did not complete the questionnaire or data from medical examinations were missing. Nine participants were excluded owing to extremely high or low energy intakes. Furthermore, 148 participants who were undergoing treatments for diabetes (n = 52), dyslipidemia (n = 66), coronary artery disease (n = 19), and cerebrovascular disease (n = 11) were excluded based on the treatment effect bias of lifestyle guidance by their doctors. Data from 585 participants were ultimately analyzed (Fig. 1).

Measurements

Age, sex, height, weight, waist circumference, and systolic and diastolic BP (SBP and DBP) were measured at health checkups for all participants. We defined those ≥65 y of age as being elderly. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. BP was assessed by well-trained nurses and clinical technologists who have completed training courses in specialized medical check-up centers (Ishikawa Health Service Association, Ishikawa, Japan) and was measured using a suitably sized cuff attached to UM-15 P (Parama-tech Co., Ltd., Fukuoka, Japan) and HEM-907 (OMRON Co., Ltd., Kyoto, Japan), automated digital sphygmomanometers based on the oscillometric method, with participants at rest in a sitting position. BP was measured twice (right arm where possible) in succession in the morning and its average was adopted. Hypertension was defined as the use of antihypertensive medication or BP of ≥140/90 mm Hg.

Nutrition status

We used a brief-type self-administered diet history questionnaire (BDHQ) to estimate habitual food consumption and nutrient intake. BDHQ was a short version of a self-administered diet history questionnaire and was developed in Japan [21–23]. BDHQ asked participants about the consumption frequency of selected food and beverage items commonly consumed in Japan, mainly from the food list used in the National Health and Nutrition Survey of Japan. In the validation study, the estimated energy and nutrient intakes derived from BDHQ among healthy Japanese adults were compared with 16-d dietary records. Pearson's correlation coefficients with dietary records for the energy-adjusted intakes of 42 nutrients ranged between 0.41 and 0.63 (median 0.56) in men and between 0.45 and 0.61 (median 0.54) in women [23]. These data demonstrated that BDHQ has a satisfactory ranking ability for many nutrients in the Japanese population.

Oxidative stress

Urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels were used to assess oxidative stress and were measured using an enzyme-linked immunosorbent assay (new 8-OHdG Check ELISA; Japan Institute for the Control of Aging, Nikken Seil Co., Ltd., Shizuoka, Japan). The results obtained were expressed as ratios to creatinine contents. Because the measurement of urinary 8-OHdG levels was noninvasive and technically easier, it has been frequently performed to estimate the extent of oxidative stress [24]. In addition, urinary 8-OHdG is regarded as a reliable oxidative stress marker in hypertension. A previous study reported that urinary 8-OHdG levels were elevated in patients with hypertension, and also that an antihypertensive treatment significantly reduced urinary 8-OHdG levels with decreases in BP in these patients [25].

Other variables

Self-administered questionnaires were used to assess other variables. Smoking habits were classified into two groups: Non-smokers and ex-smokers or current smokers. Regarding the frequency of exercise, participants were categorized according to their answer to the following questions: “Have you exercised for more than 30 min at least two times a week for 1 y?” or “Do you perform tasks such as walking, cleaning, and carrying baggage for more than 1 h a day daily?” Those who replied in the affirmative to either of these questions, were considered to have an exercise habit.

Statistical analysis

We used *t* tests to compare the average of continuous variables and the χ^2 test to compare the proportions of categorical variables. All participants were stratified into two groups: BP groups (hypertension group and normal BP group) and age groups (elderly and middle-aged). We examined differences in SFA intake between these groups using a two-way analysis of variance. To assess the relationship between BP and related nutrient intake, we used a multiple logistic regression analysis after adjustments for the following independent factors: sex, age, BMI, estimated glomerular filtration rate (eGFR), smoking status, frequency of exercise, use of antihypertensive medication, energy intake, sodium intake, and alcohol intake. A multiple linear regression analysis, controlling for sex, age, BMI, eGFR, BP groups, smoking status, frequency of exercise, use of antihypertensive medication, energy intake, and alcohol consumption, was used to evaluate the relationship between urinary 8-OHdG levels and SFA intake. In all analyses, the threshold for significance was $P < 0.05$. All statistical analyses were performed using SPSS version 24 (IBM, Armonk, NY, USA).

Ethics statement

This study was conducted with the approval of the Ethics Committee of Kanazawa University. Informed consent was obtained from all participants.

Results

Table 1 shows the basic characteristics of participants. The mean (standard deviation [SD]) age, BMI, SBP, and DBP of all participants (N = 585) were 60.9 y (11.6), 23.1 kg/m^2 (3.26), 139 mm Hg (20.4), and 80.8 mm Hg (11.9), respectively. Of the participants, 286 were men, accounting for 49% of all participants. Men had significantly higher BP, higher BMI, lower eGFR, and lower urinary 8-OHdG levels and consumed more energy, protein, carbohydrates, sodium, and alcohol than women. No significant differences were observed in fat intake between men and women.

When participants were classified into two groups according to the definition of hypertension, the hypertension group was significantly older, had a higher BMI and a lower eGFR, and consumed more sodium and alcohol than the normal BP group (Table 2). The consumption of SFA ($P = 0.022$), particularly C12:0 ($P = 0.001$), was significantly higher in the normal BP group than in the hypertension group. The consumption of other SFA, such as C4:0 ($P = 0.004$), C6:0 ($P = 0.003$), C8:0 ($P < 0.001$), C10:0 ($P = 0.001$), C14:0 ($P = 0.022$), and C18:0 ($P = 0.037$), was also significantly higher in the normal BP group than in the hypertension group. No significant differences were observed in urinary 8-OHdG levels, total energy

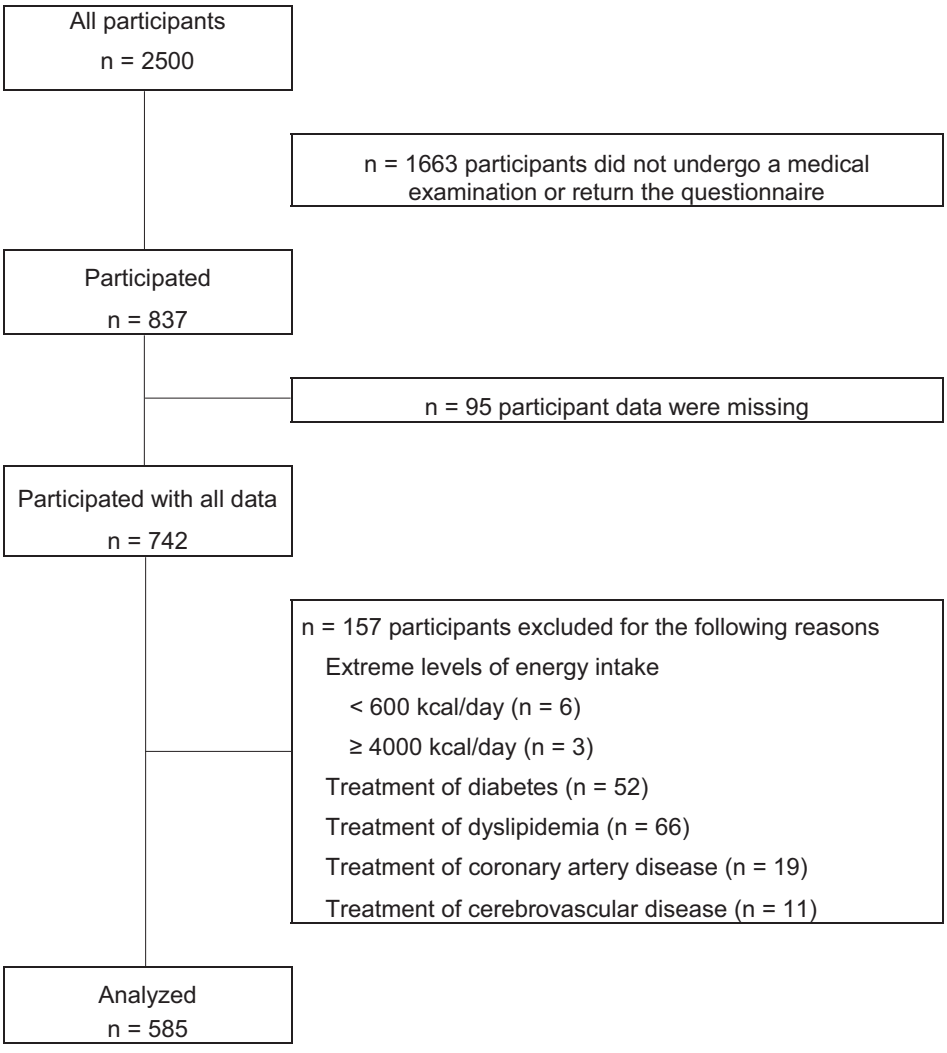

Fig. 1. Flowchart.

intake, or the consumption of protein, fat, carbohydrate, potassium, MUFAs, PUFAs, or total dietary fiber between the BP groups. The consumption of nutrients by hypertensive participants using antihypertensive drugs was similar to that by those who did not use antihypertensive drugs (Supplementary Table 1).

We also assessed differences in the intake of SFA between the BP and age groups using a two-way ANOVA (Table 3). The results obtained revealed a significant interaction effect between BP groups and age groups on total SFA, C8:0, C12:0, C14:0, and C18:0 ($P = 0.018$, 0.026, 0.008, 0.010, and 0.044 respectively). In addition, we analyzed differences in the intake of SFA between BP and sex groups. No significant interaction effects were observed (Supplementary Table 2).

When hypertensive participants were classified into two groups according to the definition of elderly, elderly individuals in the hypertension group had a significantly lower DBP, higher pulse pressure, higher urinary 8-OHdG levels, and consumed more alcohol than middle-aged participants in the normal BP group (Supplementary Table 3). Among hypertensive participants, no significant differences were observed in SBP or SFA intake (except for C12:0) between those who were elderly and those who were middle-aged.

Table 4 showed the relationship between BP and the consumption of SFA using a multiple logistic regression analysis after adjustments for the following independent factors: sex, age, BMI, eGFR, smoking status, frequency of exercise, use of antihypertensive medication, energy intake, sodium intake, and alcohol intake. Based on the interaction effect between the BP and age groups (Table 3), we performed a separate analysis on elderly and middle-aged participants. The results obtained demonstrated that a high consumption of SFA, C12:0, C13:0, C14:0, C16:0, C20:0, and C22:0, was inversely related to hypertension in elderly participants. In all participants, the relationship between SFA and hypertension was similar to that in the elderly group; the high consumption of specific SFA, such as total SFA, C14:0, C15:0, C16:0, C17:0, C18:0, and C20:0, was inversely related to hypertension. The relationship between SFA intake and BP was not significant in middle-aged participants. We also conducted a logistic regression analysis with nutrient data adjusted for energy using the density method as a percentage of the daily energy intake (Supplementary Table 4). Relationships remained significant (SFA, C12:0, C14:0, C16:0, C17:0, C18:0, C20:0, and C22:0) in elderly participants. Furthermore, by taking the possibility of the confounding effect of ω-3 FA intake into consideration, we performed an additional analysis to investigate the relationship between SFA intake and hypertension (Supplementary Table 4). An additional multiple logistic regression analysis was performed after adjustments for the following independent factors: sex, age, BMI, eGFR, smoking status, frequency of exercise, use of antihypertensive medication, energy intake, sodium intake, ω-3 FA intake, and alcohol intake. These relationships were attenuated but remained significant (C8:0, C12:0, C22:0) in

Table 1
Baseline characteristics of 585 participants according to sex

Characteristics	All participants	Men	Women	*P*-value
Participants, n (%)	585	286 (49)	299 (51)	
Age, mean (SD)	60.9 (11.6)	60.6 (11.2)	61.2 (11.9)	0.531
Smoking status, n (%)				<0.001
Non- or ex-smoker	462 (79)	187 (65)	275 (92)	
Current	123 (21)	99 (35)	24 (8)	
Exercise habit, n (%)				0.561
Yes	323 (55)	154 (54)	169 (57)	
No	262 (45)	132 (46)	130 (43)	
BMI (kg/m^2), mean (SD)	23.1 (3.26)	23.9 (2.97)	22.4 (3.36)	<0.001
SBP (mm Hg), mean (SD)	139 (20.4)	143 (20.4)	135 (19.6)	<0.001
DBP (mm Hg), mean (SD)	80.8 (11.9)	83.7 (12)	78.0 (11)	<0.001
eGFR (mL/min/1.73 m^2), Mean (SD)	63.9 (113)	53.4 (10.3)	73.9 (13.7)	<0.001
Urinary 8-OHdG (ng/mL*Cr), mean (SD)	12.8 (4.53)	11.9 (3.84)	13.6 (4.97)	<0.001
Energy and nutrients, mean (SD)				
Total energy (kcal/d)	1885 (624)	2100 (631)	1680 (544)	<0.001
Protein (g/d)	71.5 (28.3)	75.7 (29.3)	67.4 (26.8)	0.001
Fat (g/d)	51.4 (20)	52.9 (21.1)	49.9 (18.7)	0.076
Carbohydrate (g/d)	252 (89.6)	276 (89.7)	229 (83.4)	<0.001
Sodium (mg/d)	4504 (1542)	4920 (1536)	4107 (1442)	<0.001
Alcohol (g/d)	14.7 (23.2)	25.9 (27.4)	3.93 (10)	<0.001

8-OHdG, 8-hydroxy-2′-deoxyguanosine; BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation.
P-values by the *t* test for continuous variables and by the χ^2 test for categorical variables.

Table 2
Characteristics of the study population in different BP groups

Characteristics	Hypertension	Normal BP	*P*-value*
Participants, n	317	268	
Age, mean (SD)	64.3 (10.8)	56.9 (11.1)	<0.001
Smoking status, n (%)			0.196
Non- or ex-smoker	244 (77)	218 (81)	
Current	73 (23)	50 (19)	
Exercise habit, n (%)			0.620
Yes	178 (56)	145 (54)	
No	139 (44)	123 (46)	
BMI (kg/m^2), mean (SD)	23.8 (3.22)	22.3 (3.13)	<0.001
SBP (mm Hg), mean (SD)	151 (18.5)	124 (9.17)	<0.001
DBP (mm Hg), mean (SD)	86.1 (12.3)	74.5 (7.40)	<0.001
Pulse pressure (mm Hg), mean (SD)	65.3 (16.9)	49.1 (8.64)	<0.001
eGFR (mL/min/1.73 m^2), mean (SD)	60.7 (15.4)	67.7 (15.7)	<0.001
Urinary 8-OHdG (ng/mL*Cr), mean (SD)	13.0 (4.26)	12.5 (4.82)	0.192
Energy and nutrients, mean (SD)			
Total energy (kcal/d)	1929 (632)	1834 (611)	0.067
Protein (g/d)	72.5 (28.7)	70.3 (27.9)	0.361
Fat (g/d)	50.4 (20.1)	52.5 (19.7)	0.189
Carbohydrate (g/d)	258 (93.4)	245 (84.6)	0.077
Sodium (mg/d)	4678 (1556)	4299 (1503)	0.003
Potassium (mg/d)	2593 (1026)	2523 (1053)	0.415
Calcium (mg/d)	547 (249)	537 (259)	0.627
Cholesterol (g/d)	382 (189)	382 (181)	0.987
Total dietary fiber (g/d)	12.4 (5.22)	11.7 (5.37)	0.130
Alcohol (g/d)	18.0 (23.9)	10.8 (21.8)	<0.001
Saturated fatty acids (g/d)	13.0 (5.53)	14.1 (5.66)	0.022
Monounsaturated fatty acids (g/d)	17.8 (7.44)	18.7 (7.38)	0.153
Polyunsaturated fatty acids (g/d)	12.6 (5.02)	12.8 (4.96)	0.767
C4:0 (mg/d)	138 (112)	167 (127)	0.004
C6:0 (mg/d)	85 (70.2)	104 (82.7)	0.003
C7:0 (mg/d)	0.676 (0.772)	0.799 (0.843)	0.066
C8:0 (mg/d)	85.8 (82.7)	111 (104)	<0.001
C10:0 (mg/d)	143 (113)	178 (141)	0.001
C12:0 (mg/d)	348 (330)	455 (446)	0.001
C13:0 (mg/d)	1.91 (2.28)	2.27 (2.51)	0.072
C14:0 (mg/d)	1010 (531)	1119 (610)	0.022
C15:0 (mg/d)	95.1 (48.8)	103.0 (52.0)	0.058
C16:0 (mg/d)	7837 (3206)	8339 (3171)	0.058
C17:0 (mg/d)	130.6 (59.7)	136.7 (58.9)	0.215
C18:0 (mg/d)	2838 (1204)	3046 (1189)	0.037
C20:0 (mg/d)	144 (57.8)	151 (57.9)	0.155
C22:0 (mg/d)	74.9 (30.6)	77.4 (30.6)	0.332
C24:0 (mg/d)	31.3 (13.4)	32.4 (13.2)	0.289

8-OHdG, 8-hydroxy-2′-deoxyguanosine; BMI, body mass index; BP, blood pressure; Cr, creatinine; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.
**P*-values by the *t* test for continuous variables and by the χ^2 test for categorical variables.

elderly participants. An inverse association was observed between total SFA intake and hypertension ($P = 0.058$). In all participants and in those who were middle-aged, the relationship between SFA intake and BP was not significant.

We also investigated the relationship between urinary 8-OHdG levels and SFA intake. A multiple linear regression analysis was used to evaluate this relationship. The results obtained are shown in Table 5. This analysis revealed a correlation between a high consumption of SFA, C4:0, C6:0, C8:0, C10:0, and C12:0, and a decrease in urinary 8-OHdG levels. No correlation was observed between urinary 8-OHdG levels and the consumption of long-chain fatty acids (LCFAs). We also performed a linear regression analysis with nutrient data adjusted for energy using the density method as a percentage of daily energy intake (Supplementary Table 5). Relationships between a high consumption of SFA, C4:0, C6:0, C8:0, C10:0, and C12:0, and a decrease in urinary 8-OHdG levels also were significant. In an additional multiple linear regression analysis adjusting for the sex, age, BMI, eGFR, BP, smoking, frequency of exercise, antihypertensive drug use, energy intake, ω-3 FA intake, and alcohol consumption, more various types of FAs showed a significant negative correlation with the urinary 8-OHdg level compared with those in the analytical model shown in Table 5. This analysis revealed a correlation between a high consumption of SFA, C4:0, C6:0, C8:0, C10:0, C12:0, C14:0, C15:0, C16:0, C18:0, and C24:0, and a decrease in urinary 8-OHdG levels (Supplementary Table 5). Although we also assessed the effects of differences in the intake of SFA between the BP and age or sex groups on urinary 8-OHdG levels using a two-way ANOVA, there were no significant interaction effects (Supplementary Table 6).

Discussion

The present cross-sectional study was performed in an attempt to elucidate the relationship between dietary SFA intake and hypertension and oxidative stress. The results obtained suggest that a high intake of specific SFA, such as total SFA, C12:0, C13:0, C14:0, C16:0, C20:0, and C22:0, is inversely associated with hypertension in individuals ≥65 y of age. In addition, we found a correlation between the intake of specific SFA, such as total SFA, C4:0, C6:0, C8:0, C10:0, and C12:0, and a decrease in urinary 8-OHdG levels.

The effects of FAs vary depending on chain lengths; short-chain fatty acids (SCFAs) are considered to have ≤6 carbon atoms, medium-chain fatty acids (MCFAs) have between 8 and 12 carbons, and LCFAs generally have ≥14 carbon chains. Differences in chain lengths are considered to contribute to differences in their effects on the risk for coronary artery disease (CAD). A previous prospective cohort study on women reported that SCFAs and MCFAs, such as C4:0, C6:0, C8:0 and C10:0, were not associated with the risk for CAD. On the other hand, mainly LCFAs, including C12:0, C14:0, C16:0, and C18:0, were associated with a risk of CAD [26].

Depending on the degree of unsaturation, FAs are divided into three groups: SFA, MUFAs, and PUFAs. Regarding MUFAs, previous

Table 3
Interaction effect between BP groups and age groups on SFA intake

		Hypertension*	Normal BP	*P*-value†		
SFA	Age	Mean (SD)	Mean (SD)	P1 for age group	P2 for BP group	P3 for interaction
SFA (g/d)	Elderly‡	12.9 (5.59)	15.5 (6.13)	0.099	0.002	0.018
	Middle-aged	13.2 (5.46)	13.5 (5.39)			
C4:0 (mg/d)	Elderly‡	143 (121)	184 (140)	0.224	0.116	0.547
	Middle-aged	132 (101)	160 (121)			
C6:0 (mg/d)	Elderly‡	86.3 (74.5)	113 (93.7)	0.361	0.140	0.466
	Middle-aged	83.5 (65.4)	101 (78.2)			
C7:0 (mg/d)	Elderly‡	0.732 (0.858)	0.750 (0.798)	0.827	0.444	0.194
	Middle-aged	0.614 (0.660)	0.817 (0.860)			
C8:0 (mg/d)	Elderly‡	78.4 (66.7)	126 (139)	0.926	0.345	0.026
	Middle-aged	94.1 (87.7)	106 (87.5)			
C10:0 (mg/d)	Elderly‡	140 (111)	200 (176)	0.649	0.266	0.100
	Middle-aged	147 (116)	170 (125)			
C12:0 (mg/d)	Elderly‡	308 (262)	526 (608)	0.951	0.396	0.008
	Middle-aged	392 (387)	428 (366)			
C13:0 (mg/d)	Elderly‡	2.05 (2.53)	2.08 (2.38)	0.945	0.467	0.188
	Middle-aged	1.75 (1.97)	2.34 (2.56)			
C14:0 (mg/d)	Elderly‡	1023 (534)	1326 (760)	0.439	0.405	0.010
	Middle-aged	996 (529)	1041 (525)			
C15:0 (mg/d)	Elderly‡	98.1 (51.2)	121 (61.3)	0.338	0.371	0.043
	Middle-aged	91.8 (46.0)	96.4 (46.6)			
C16:0 (mg/d)	Elderly‡	7752 (3275)	9143 (3338)	0.604	0.452	0.023
	Middle-aged	7933 (3135)	8038 (3061)			
C17:0 (mg/d)	Elderly‡	131 (60.3)	156 (68.7)	0.464	0.507	0.018
	Middle-aged	130 (59.2)	130 (53.2)			
C18:0 (mg/d)	Elderly‡	2787 (1215)	3279 (1217)	0.707	0.418	0.044
	Middle-aged	2895 (1194)	2959 (1169)			
C20:0 (mg/d)	Elderly‡	140 (57.7)	165 (59.3)	0.780	0.578	0.006
	Middle-aged	149 (57.9)	146 (56.7)			
C22:0 (mg/d)	Elderly‡	73.3 (30.9)	84.1 (31.8)	0.721	0.607	0.019
	Middle-aged	76.7 (30.2)	74.8 (29.8)			
C24:0 (mg/d)	Elderly‡	30.3 (13.3)	34.4 (12.9)	0.907	0.593	0.049
	Middle-aged	32.3 (13.5)	31.7 (13.3)			

BP, blood pressure; SD, standard deviation; SFA, saturated fatty acid.
*Hypertension defined as use of antihypertensive medication and/or BP of ≥140/90 mm Hg (n = 317). Among hypertensive participants, 167 were elderly.
†*P*-values by a two-way analysis of variance, P1 between age groups, P2 between BP groups, and P3 between age groups × BP groups (interaction effect).
‡Elderly defined as being ≥65 y of age (n = 240). Among elderly participants, 73 had hypertension.

studies reported an inverse relationship between MUFAs and cardiovascular mortality [27,28]. Although they demonstrated that MUFA intake contributes to reductions in the risk for cardiovascular disease, information on BP was not provided and the influence of the consumption of MUFAs on BP remained unclear. Regarding PUFAs, decreases in BP owing to the consumption of ω-6 FAs, mainly linoleic acid from vegetable oils, have been reported [13,29]. The consumption of ω-3 FAs from marine oils is known to be beneficial for preventing cardiovascular disease [30,31]. Furthermore, the hypotensive effects of an intake of ω-3 FAs have been demonstrated. Previous meta-analyses showed that a high-dose intake of ω-3 PUFAs reduced BP in hypertensive individuals [8,9].

Various types of FAs correlated more strongly with hypertension in the elderly than in all other groups; the high consumption of specific SFA, such as total SFA, C12:0, C13:0, C14:0, C16:0, C20:0, and C22:0, was inversely related to hypertension. The relationship between SFA intake and BP was not significant in middle-aged individuals. In consideration of the interaction effect between BP and age groups on SFA intake, the effect of elderly was considered to have a strong influence on the overall results. Limited information is currently available on the specific effects of SFA on BP. The ARIC study, which is a longitudinal study designed to investigate the relationship between the FA compositions of plasma cholesterol esters and the 6-y incidence of hypertension, demonstrated that after adjustments for various confounding factors, SFA, C:16:0, and the PUFA-to-SFA ratio were positively associated with the incidence of hypertension. Regarding the relationship between hypertension and SFA intake, it was found to differ depending on statistical corrections for confounding factors, and SFA did not correlate with the incidence of hypertension after adjustments for all confounding factors assumed in the study; the odds ratio estimate of the incidence of hypertension for SFA was 1.15 (95% confidence interval [CI], 0.97–1.36) [13]. One of the reasons for differences in the results obtained may be the different distribution of age. Participants in the present study were older than those in the ARIC study. In the ARIC study, the mean (SD) ages of non-hypertensive and hypertensive participants were 54.2 y (5.8) and 52.8 y (5.3), respectively. On the other hand, animal experimental investigation showing decreases in BP by C12:0 in spontaneously hypertensive rats supported the results of the present study [11,12]. The present results are of value because few studies have reported a relationship between the dietary intake of SFA and hypertension in humans.

We also found a correlation between a high intake of SFA, such as total SFA, C4:0, C6:0, C8:0, C10:0, and C12:0, and decrease in urinary 8-OHdG levels. Urinary 8-OHdG is an oxidative stress marker. Regarding the relationship between MCFA intake and oxidative stress, previous studies demonstrated that MCFAs exerted antioxidant effects [18,19]. In addition, rice bran oils containing rich MCFAs (C8:0, C10:0, and C12:0) increased antioxidant enzyme activities in rats [19]. These enzymes included superoxide dismutase, catalase, and glutathione peroxidase and are regarded as some of the most important enzymes forming the first line of defense against reactive

Table 4
Relationship between hypertension and SFA intake according to age

		OR	95% CI		*P*-value*
			Lower	Upper	
All participants (N = 585)	SFA	0.925	0.867	0.986	0.017
	C4:0	0.998	0.996	1.000	0.121
	C6:0	0.998	0.994	1.001	0.138
	C7:0	0.945	0.706	1.265	0.705
	C8:0	0.998	0.996	1.001	0.185
	C10:0	0.998	0.996	1.000	0.110
	C12:0	1.000	0.999	1.000	0.199
	C13:0	0.984	0.893	1.084	0.742
	C14:0	0.999	0.999	1.000	0.029
	C15:0	0.993	0.987	0.999	0.017
	C16:0	1.000	1.000	1.000	0.013
	C17:0	0.994	0.988	1.000	0.040
	C18:0	1.000	0.999	1.000	0.043
	C20:0	0.993	0.987	1.000	0.036
	C22:0	0.990	0.979	1.001	0.071
	C24:0	0.984	0.958	1.010	0.219
Elderly† participants (n = 240)	SFA	0.872	0.779	0.977	0.018
	C4:0	0.999	0.996	1.002	0.651
	C6:0	0.999	0.994	1.004	0.669
	C7:0	1.627	0.989	2.678	0.055
	C8:0	0.995	0.990	1.000	0.068
	C10:0	0.998	0.995	1.001	0.167
	C12:0	0.998	0.997	1.000	0.023
	C13:0	1.184	1.002	1.398	0.048
	C14:0	0.999	0.998	1.000	0.047
	C15:0	0.993	0.983	1.002	0.127
	C16:0	1.000	1.000	1.000	0.012
	C17:0	0.991	0.981	1.000	0.059
	C18:0	1.000	0.999	1.000	0.064
	C20:0	0.982	0.969	0.994	0.005
	C22:0	0.979	0.959	0.999	0.043
	C24:0	0.960	0.912	1.010	0.118
Middle-aged participants (n = 345)	SFA	0.944	0.866	1.029	0.190
	C4:0	0.998	0.995	1.001	0.200
	C6:0	0.997	0.993	1.002	0.204
	C7:0	0.752	0.498	1.134	0.174
	C8:0	1.000	0.996	1.003	0.900
	C10:0	0.999	0.996	1.002	0.428
	C12:0	1.000	0.999	1.001	0.824
	C13:0	0.909	0.792	1.042	0.172
	C14:0	1.000	0.999	1.000	0.376
	C15:0	0.994	0.986	1.002	0.146
	C16:0	1.000	1.000	1.000	0.145
	C17:0	0.995	0.987	1.004	0.250
	C18:0	1.000	0.999	1.000	0.135
	C20:0	0.997	0.989	1.005	0.396
	C22:0	0.993	0.979	1.007	0.315
	C24:0	0.988	0.957	1.021	0.466

BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SFA, saturated fatty acid.
*_P_-values by a multiple logistic regression analysis after adjustments for sex, age, BMI, eGFR, use of antihypertensive medication, smoking status, frequency of exercise, energy intake, sodium intake, and alcohol intake.
†Elderly defined as being ≥65 y of age.

Table 5
Relationship between urinary 8-OHdG levels and SFA intake

	β*	95% CI		*P*-value†
		Lower	Upper	
SFA	−0.109	−0.212	−0.006	0.038
C4:0	−0.004	−0.008	−0.001	0.014
C6:0	−0.007	−0.012	−0.001	0.013
C7:0	−0.418	−0.889	0.053	0.082
C8:0	−0.005	−0.009	−0.001	0.020
C10:0	−0.004	−0.007	−0.001	0.010
C12:0	−0.001	−0.002	0.000	0.034
C13:0	−0.138	−0.295	0.019	0.086
C14:0	−0.001	−0.002	0.000	0.058
C15:0	−0.008	−0.018	0.002	0.098
C16:0	0.000	0.000	0.000	0.080
C17:0	−0.004	−0.013	0.005	0.421
C18:0	0.000	−0.001	0.000	0.094
C20:0	−0.005	−0.015	0.005	0.348
C22:0	−0.010	−0.028	0.008	0.269
C24:0	−0.040	−0.083	0.002	0.062

8-OHdG, 8-hydroxy-2′-deoxyguanosine; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; SFA, saturated fatty acid.
*β means an unstandardized regression coefficient.
†*P*-values by a multiple linear regression analysis after adjustments for sex, age, BMI, use of antihypertensive medication, eGFR, BP groups, smoking status, frequency of exercise, energy intake, and alcohol consumption.

oxygen species [32]. Furthermore, the present study showed that a high consumption of SFA, such as total SFA, C12:0, C13:0, C14:0, C16:0, C20:0, and C22:0, was inversely related to hypertension, particularly in elderly participants. This is biologically plausible for C12:0 because endothelial functions, such as baroreflex sensitivity, are impaired with age owing to oxidative stress. Vascular aging is closely related to baroreflex sensitivity. Moreover, a previous study demonstrated that impaired baroreflex sensitivity was associated with the onset of hypertension [33]. The generation of reactive oxygen species is considered to contribute to reductions in baroreflex sensitivity [34, 35]. Therefore, the inverse relationship observed between the intake of MCFAs and hypertension in the elderly may be attributed to their antioxidant activities.

The effects of the interaction between BP and age groups on SFA intake also may be explained because the hypotensive effects of antioxidants have been demonstrated in hypertensive individuals, particularly in those was a high pulse pressure value. Pulse pressure is considered to increase with age and has been identified as an independent predictor of mortality among elderly individuals [36]. One of the characteristics of hypertension in elderly patients is considered to be a high pulse pressure value. A previous cross-sectional study showed that pulse pressure and age correlated with oxidative stress in Japanese individuals [37]. Moreover, ascorbic acid, which is considered to exert antioxidant effects, significantly reduced SBP and pulse pressure in elderly patients with refractory hypertension [38]. These findings suggest that oxidative stress plays an important role in isolated systolic hypertension in the elderly. In the present study, elderly individuals in the hypertension group had significantly higher pulse pressure values and higher urinary 8-OHdG levels than middle-aged participants in the same group (Supplementary Table 3). We also found a correlation between a high intake of SFA and a decrease in urinary 8-OHdG levels. We consider these results to support the relationship between oxidative stress and hypertension in the elderly. However, in the present study, an interaction effect between the BP and age groups on urinary 8-OHdG levels was not demonstrated. One of the reasons for this may be the characteristic of BP in all participants. Mean (SD) SBP and DBP were 138.7 (20.4) and 80.8 mm Hg (11.9), respectively. In SBP, the mean minus the SD appeared to involve some subjects with normal BP; on the other hand, the mean of DBP was within the normal range. Taking into consideration the correlation between pulse pressure and oxidative stress, this distribution of BP among the study participants attenuated the statistical power of the interaction. In addition, we defined hypertension as the use of antihypertensive medication or BP of ≥ 140/90 mm Hg. A previous study showed that antihypertensive treatments significantly reduced urinary 8-OHdG levels in patients with hypertension [25]. In the present study, no significant

differences were observed in urinary 8-OHdG levels between the hypertension and normal BP groups (Table 2). The use of antihypertensive drugs decreased urinary 8-OHdG levels in the hypertension group and its effect also attenuated the statistical power of the interaction effect between SFA intake and age groups on urinary 8-OHdG levels. The absence of a significant interaction between age and oxidative stress in the present study does not necessary deny the contribution of the antioxidant activities of SFA to the prevention of hypertension in elderly individuals.

In terms of SCFAs, a relationship was not observed between the intake of SCFAs and the risk for hypertension in a multiple logistic regression analysis; however, a *t* test revealed that the intake of C4:0 and C6:0 was significantly lower in the hypertension group than in the normal BP group. Previous findings indicated that changes in the gut microbiota, including decreases in C4:0-producing bacteria and increases in the lactate-producing bacterial population, were associated with hypertension in rats [39]. Previous study also showed an abundance of C4:0-producing bacteria, and butyrate production was negatively associated with SBP and DBP in obese pregnant women [40]. Furthermore, we found a correlation between a high intake of SCFAs and decrease in urinary 8-OHdG levels. Previous findings showing a relationship between SCFA and the suppression of nuclear factor-κB activation, which is an inflammatory mediator that is activated by reactive oxygen species, support the present results [41]. Therefore, a dietary intake of SCFAs has potential as a nutritional therapeutic strategy for hypertension. One of the reasons for the absence of a relationship between SCFA intake and hypertension in the multiple logistic regression analysis performed in the present study may be the lack of statistical power.

We reported that a high intake of the LCFAs, C14:0, C16:0, C20:0, and C20:0, was inversely correlated with hypertension in the elderly. The main LCFAs in human food are considered to be C16:0 and C18:0. Because of their negative effects on cholesterol metabolism, increases in low-density lipoprotein cholesterol levels, and decreases in high-density cholesterol levels, SFA, particularly LCFAs, have a negative image in the cardiovascular field [10]. However, a limited number of studies have reported the effects of a dietary intake of LCFAs on BP. A previous cross-sectional study on 156 middle-aged healthy men free of CAD and stroke and not receiving medication for hypertension reported an inverse relationship between serum C18:0 and BP, and C16:0 did not correlate with BP [42]. In the ARIC study, C:16:0 was positively associated with the incidence of hypertension; C18:0 was inversely related to the incidence of hypertension after adjustments for age, sex, BMI, the waist-to-hip ratio, smoking status, ethanol intake, education level, and sort index (95% CI, 0.69–0.98) and did not correlate with hypertension after adjustments for previous confounding factors plus baseline SBP (95% CI, 0.71–1.01) [12]. Because the inverse relationship between C18:0 intake and hypertension was also close to significance ($P = 0.064$), the results obtained for C18:0 are consistent with previous findings. On the other hand, discordant findings for C16:0 may be attributed to study designs and differences in the distribution of the age of participants as well as the confounding factors adjusted for in the multiple regression model.

Sex differences in hypertension and CAD are well known in the cardiovascular field. The onset of essential hypertension occurs earlier in men than in women and a previous population-based cohort study of 90 000 patients followed for 1 to 9 y reported that women with hypertension had a better prognosis than men regardless of ethnicity [43,44]. Regarding SFA and hypertension, a previous review indicated that a high level of serum SFA was related to hypertension in men but not in women through several experimental investigations [45]. The present study analyzed sex interactions and differences in the intake of SFA between the BP groups and sex groups and found no significant interaction effects (Supplementary Table 2). Although premenopausal women have lower BP than men, the prevalence of hypertension is higher in elderly women partly because of reductions in ovarian estrogen production owing to menopause-associated increases in BP [46]. The mean age of menopause is 49.22 y in Japanese women, and because the mean (SD) age of women that participated in the present study was 61.2 (11.9), one of the reasons for the absence of a sex interaction may have been due to the age of the target population [47]. However, the underlying mechanisms were not examined in the present study.

Several limitations of the present study need to be acknowledged. Because this was a single-center study, an unintentional selection bias for patients cannot be fully excluded. Furthermore, participants in the present study were applicants for medical examinations; therefore, the ratio of health-conscious individuals may have been high among participants. Moreover, the generalizability of the present study is limited because participants were not representative of the general Japanese population. Furthermore, dietary data was obtained from BDHQ; we did not examine actual diets. Although the validity of BDHQ has already been demonstrated, we need to carefully interpret dietary data. We also need to consider that it was not possible to assess causality because of the cross-sectional design of the present study. A treatment-effect bias needs to be considered. Although patients being treated for diabetes, dyslipidemia, CAD, and cerebrovascular disease were excluded from the present analysis and the use of antihypertensive medication was adjusted for (Table 4), patients receiving medication for hypertension may also have been receiving lifestyle guidance from their doctors.

Conclusion

We performed a cross-sectional study with Japanese representatives to examine the relationship between the intake of SFA and hypertension. A high intake of SFA was inversely associated with hypertension, and this relationship was stronger for elderly participants. We also found a correlation between the intake of SFA, particularly SCFAs and MCFAs, and decreases in urinary 8-OHdG levels. The regular consumption of SFA may contribute to the prevention and treatment of hypertension in elderly patients.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2018.10.020.

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