Table 1. Characteristics of study population

Characteristics	Total	Hypertension	
		No	Yes
No.	1,643	865	778
Age, years	66.6±7.9	64.6±7.9	68.8±7.3**
Male, %	43.4	39.9	47.3**
Body mass index, kg/m^2	22.7±3.2	21.9±2.9	23.6±3.3**
Diabetes, %	10.6	5.4	16.3**
Dyslipidemia, %	38.2	30.2	47.2**
Antihypertensive medication, %	30.1	0	36.4**
Systolic blood pressure, mm Hg	128±20	116±13	142±17**
Diastolic blood pressure, mm Hg	78±11	72±9	84±10**
Heart rate, bpm	69±11	68±10	70±12**
Triglycerides, mmol/L[a]	1.20±0.69	1.11±0.62	1.30±0.73**
HDL cholesterol, mmol/L	1.60±0.42	1.64±0.42	1.57±0.41**
Blood glucose level, mmol/L[a]	5.79±1.07	5.77±0.77	6.03±1.29**
Hemoglobin A1c, %[a]	5.47±0.64	5.37±0.52	5.58±0.73**
eGFR, ml/min/1.73 m^2	75.0±11.0	77.3±8.5	72.5±12.8**
CPITN stage, %			
0	35.4	37.8	32.8*
1	0.9	0.7	1.0
2	11.5	12.7	10.2
3	32.2	32.0	32.5
4	20.0	16.8	23.5**
Gingival bleeding +, %	35.6	32.7	38.8**
Number of remaining teeth	21.8±7.7	22.6±7.4	20.9±7.9**
Eichner index, %			
A	60.4	65.8	54.3**
B	28.1	24.9	31.8**
C	11.5	9.3	13.9**
Maximum bite force, no.	502±310	504±296	501±325
Smoking status (never/former/current), %	61.4/27.8/10.8	62.7/24.7/12.6	60.0/31.1**/8.9**
Daily alcohol intake, %	54.8	56.5	52.8
Daily fruit intake, %	53.6	53.3	53.9
Daily sugar-sweetened soft drink intake ≥3 cups/day, %	7.7	9.7	5.5**
Physical activity ≥1 hour/day, %	40.4	40.5	40.2
Nocturnal sleep duration, hours	6.55±1.10	6.46±1.04	6.66±1.15**

Values are mean ± SD or frequency (%).

Abbreviations: CPITN, Community Periodontal Index of Treatment Needs; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

[a]Values were log-transformed for analysis.

*P < 0.05 and **P < 0.01 vs. patients without hypertension.

On the other hand, except for prevalence of smoking habit or daily sugar-sweetened soft drink intake, no significant graded relationship between the number of components present and the corresponding prevalence of poor lifestyle, including smoking habit, prevalence of daily alcohol consumption, daily fruit intake, daily sugar-sweetened drink intake, physical activity, and nocturnal sleep duration, was found (Table 4).

Table 2. Associations between markers of oral health disorders

Variables	CPITN stage 0	CPITN stage 1 or 2	CPITN stage 3	CPITN stage 4	P_{trend}
Gingival bleeding*, %	26.3	28.1	42.8**	45.1**	<0.01
Remaining tooth number, no.	22.6±6.4	24.7±4.8**	23.4±5.6	16.0±10.8**	<0.01
Remaining tooth number ≤18 in men, ≤21 in women, %	26.5	11.3**	20.4	48.5**	<0.01
Eichner index, %					
A	62.7	76.4**	66.4	36.6**	<0.01
B	29.4	18.7*	28.7	30.8	0.01
C	7.9	4.9	4.9	32.6**	<0.01

Variables	Remaining tooth number: 1st quartile (≤18 in men, ≤21 in women)	2nd quartile (19–25 in men, 22–25 in women)	3rd quartile (26–27 in men, 22–25 in women)	4th quartile (28 in men, 27–28 in women)	P_{trend}
Gingival bleeding*, %	37.4	40.2	33.0	30.5	0.02
CPITN stage, %					
Stage 0	34.7	33.2	37.1	37.2	0.56
Stage 1 or 2	5.2	12.9**	13.5**	19.7**	<0.01
Stage 3	24.3	34.5*	39.3**	31.1	<0.01
Stage 4	35.8	19.4**	10.1**	12.0**	<0.01
Eichner index, %					
A	5.2	51.7**	96.1**	100**	<0.01
B	52.2	48.3	3.9**	0**	<0.01
C	42.6	0**	0**	0**	<0.01

Variables	Eichner index A	Eichner index B	Eichner index C	P_{trend}
Gingival bleeding*, %	33.1	44.6**	27.0	<0.01
Remaining tooth number, no.	26.3±2.0	19.2±4.8**	4.5±4.4**	<0.01
Remaining tooth number ≤18 in men, ≤21 in women, %	2.3	50.2**	100.0**	<0.01
CPITN stage, %				
Stage 0	36.8	37.0	24.3**	<0.01
Stage 1 or 2	15.6	8.2**	5.3**	<0.01
Stage 3	35.5	32.9	13.8**	<0.01
Stage 4	12.1	21.9**	56.6**	<0.01

Values are mean ± SD or frequency (%).
Abbreviation: CPITN, Community Periodontal Index of Treatment Needs.
*$P < 0.05$, and **$P < 0.01$ vs. patients with CPITN stage 0, lowest quartile in remaining tooth number, or Eichner index A, respectively.

Relations of oral health disorders to blood pressure

The influence of these additive effects of oral health markers on blood pressure was examined in the subpopulation of 1,148 subjects (687 women) not taking antihypertensive medication. In the model including CPITN stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C, SBPs/DBPs (±SDs) in subjects with 0 (n = 190 men; n = 331 women), 1 (n = 142 men; n = 236 women), 2 (n = 72 men; n = 77 women), and ≥3 (n = 57 men; n = 43 women) components of oral health disorders were 123±20/76±11, 125±18/76±11, 129±20/78±12,

Table 3. Associations of markers of oral health disorders with diagnosis of hypertension

	Age- and sex-adjusted			Multivariable-adjusted[a]		
Variables, unit of increase	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
CPITN stage 4	1.27	0.99–1.64	0.07	1.05	0.96–1.16	0.27
Gingival bleeding +	1.25	1.01–1.54	0.04	1.17	0.94–1.47	0.16
Remaining tooth number ≤18 for men, ≤21 for women[b]	1.16	0.92–1.48	0.21	1.17	0.90–1.51	0.24
Eichner index C	1.17	0.85–1.61	0.33	1.09	0.78–1.55	0.62
CPITN stage 4 and gingival bleeding +	1.83	1.03–2.63	<0.01	1.71	1.17–2.50	<0.01
CPITN stage 4 and tooth number ≤18 for men, ≤21 for women[b]	1.34	0.95–1.91	0.10	1.34	0.92–1.94	0.13
CPITN stage 4 and Eichner index C	1.45	0.98–2.17	0.06	1.44	1.02–2.02	0.04
Gingival bleeding + and tooth number ≤18 for men, ≤21 for women[b]	1.94	1.37–2.77	<0.01	1.63	1.07–2.47	0.01
Gingival bleeding + and Eichner index C	2.26	1.22–4.40	<0.01	2.51	1.30–5.00	<0.01
Tooth number ≤18 for men, ≤21 for women[b] and Eichner index C	1.24	0.90–1.71	0.18	1.23	0.91–1.69	0.08

Abbreviation: CPITN, Community Periodontal Index of Treatment Needs.
[a]Multivariable-adjusted model included age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.
[b]Sex-specific lowest quartile of remaining tooth number.

and 132 ± 22/79 ± 12 mm Hg, respectively (P_{trend} < 0.01, respectively). Age- and sex-adjusted SBPs (±SEs) in subjects with 0, 1, 2, and ≥3 components of oral health disorders were 124 ± 1, 125 ± 1, 128 ± 2, and 131 ± 2 mm Hg (p for trend <0.01), and DBP (±SE) was 76 ± 1, 76 ± 1, 78 ± 1, and 79 ± 1 mmHg (P_{trend} = 0.04), respectively. Multivariable linear regression analysis revealed that SBP significantly differed among groups, with the highest SBP in the subgroup with ≥3 components (130 ± 2 mmHg) (Table 5; Figure 2).

DISCUSSION

Our study identified an additive relationship between oral health disorders and risk of hypertension. Worse occlusal status was suggested to be responsible in these relationships. Our findings were noteworthy because they were based on a large, representative sample of the Japanese general urban population. In addition, careful measures of study exposure and outcome variables allowed precise estimation of the association.

Our results showed that the associations between individual oral health markers (CPITN stage 4, presence of gingival bleeding, lowest quartile of remaining tooth number, and Eichner index C) and risk of hypertension did not remain significant after adjustment for several potential confounding factors. Although previous investigations identified that periodontal disease, as well as lower tooth number, was independently associated with risk of hypertension,[1–5,7–9] we could not confirm these associations in this study. Alternatively, we examined the combined effects of oral health markers on hypertension. Combinations of oral health markers—that is, severe periodontal disease and presence of gingival bleeding, severe periodontal disease and worse occlusal status, presence of gingival bleeding and lower tooth number, and presence of gingival bleeding and worse occlusal status—were each independently associated with risk of hypertension. Our results suggested that worse occlusal status, which was assessed by Eichner index, was responsible for the relationship between oral health disorders and hypertension. Occlusal status may better reflect chewing status than does tooth number, which may lead to alterations not only in food selection and dietary quality but also in masticatory performance. This, in turn, would affect body composition and nutritional status,[11] both of which are causal factors in the development of hypertension. Apart from masticatory performance, dental malocclusion may lead to mandibular malposition, which induces narrowing of the upper airway, resulting in obstructive breathing disorders. Mandibular position has been implicated in nocturnal oxygenation and pharyngeal collapsibility,[27] and in healthy subjects with obstructive sleep apnea, treatment with an oral jaw-positioning appliance has been reported to improve cardiac autonomic modulation.[28] Of the combinations of oral health disorders, in this study, the strongest risk of hypertension was observed with the combination of the presence of gingival bleeding and Eichner index. The mechanism by which the concomitance of gingival

Table 4. Characteristics of study population by number of oral health disorder components: Community Periodontal Index of Treatment Needs stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C

Characteristics	0	1	2	3	4	P_{trend}
No.	703	527	241	151	21	NA
Age, years	64.4±7.9	66.5±7.8**	69.7±6.7**	72.0±5.5**	69.7±7.0*	<0.01
Men, %	40.0	41.6	48.6	58.3**	38.1	<0.01
Body mass index, kg/m²	22.4±3.0	23.0±3.2*	22.9±3.5	23.2±3.6*	22.8±3.0	<0.01
Diabetes, %	7.0	12.3	12.5	19.9**	0	<0.01
Dyslipidemia, %	34.3	38.3	41.9	48.3*	52.4	<0.01
Hypertension, %	42.7	44.6	53.9*	66.2**	61.9	<0.01
Antihypertensive medication, %	25.9	28.3	38.2*	44.4**	23.8	<0.01
Systolic blood pressure, mm Hg	126±20	128±19	132±20**	134±20**	139±19	<0.01
Diastolic blood pressure, mm Hg	77±11	78±11	79±11	80±11	83±12	<0.01
Heart rate, bpm	69±11	69±10	70±11	69±11	71±11	0.43
Triglycerides, mmol/L[a]	1.16±0.65	1.21±0.70	1.24±0.68	1.28±0.77	1.26±0.63	0.08
HDL cholesterol, mmol/L	1.68±0.43	1.58±0.40**	1.54±0.38**	1.45±0.41**	1.53±0.46	<0.01
Blood glucose level, mmol/L[a]	5.68±0.89	5.85±1.24	5.82±0.96	6.08±1.38**	5.56±0.47	<0.01
Hemoglobin A1c, %[a]	5.41±0.55	5.51±0.68	5.50±0.60	5.62±0.82**	5.25±0.67	<0.01
eGFR, ml/min/1.73m²	76.1±10.9	76.1±10.5	72.6±11.6**	70.2±11.2**	73.9±7.8	<0.01
CPITN stage, %						
Stage 0	45.8	33.8**	29.5**	7.3**	0**	<0.01
Stage 1 or 2	18.5	11.4**	3.7**	2.7**	0	<0.01
Stage 3	35.7	40.2	21.6**	9.9**	0*	<0.01
Stage 4	0	14.6**	45.2**	80.1**	100**	<0.01
Gingival bleeding +, %	0	62.1**	71.4**	43.1**	100**	<0.01
Remaining tooth number ≤18 in men, ≤21 in women, %	0	23.3**	61.8**	100.0**	100**	<0.01
Eichner index, %						
A	85.2	60.2**	30.7**	1.3**	0**	<0.01
B	14.8	39.9**	47.7**	21.9	0	<0.01
C	0	0	21.6**	76.8**	100**	<0.01
Maximum bite force, *N*	609±297	495±298**	404±290**	229±172**	191±134**	<0.01
Smoking status (never/former/current), %	65.9/25.2/9.0	63.0/25.4/11.6	55.2/33.2/11.6	46.4**/37.8*/15.9	52.4/38.1/9.5	<0.01
Daily alcohol intake, %	52.5	57.7	51.9	59.6	57.1	0.23
Daily fruit intake, %	54.3	51.6	56.9	53.6	38.1	0.40
Daily sugar-sweetened soft drink intake ≥3 cups/day, %	6.3	7.8	9.5	8.6	28.6**	<0.01
Physical activity ≥1 hour/day, %	38.3	40.2	46.1	38.4	61.9	0.07
Nocturnal sleep duration, hours	6.5±1.1	6.5±1.1	6.7±1.2	6.7±1.3	6.6±1.2	0.11

Values are mean ± SD or frequency (%).

Abbreviations: CPITN, Community Periodontal Index of Treatment Needs; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NA, not applicable.

[a]Values were log-transformed for analysis.

*$P < 0.05$ and **$P < 0.01$ vs. subgroup with no component.

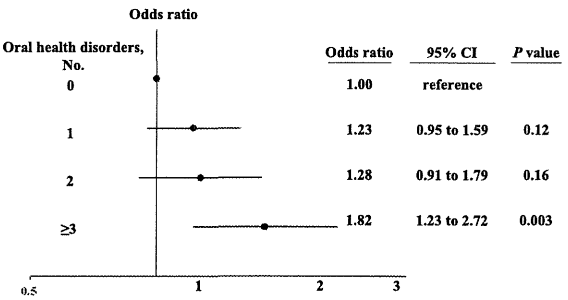

Figure 1. Odds ratios for hypertension by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C. Data are adjusted odds ratio (95% confidence interval). Analyses were controlled for age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, physical activity, daily sugar-sweetened soft drink intake, and nocturnal sleep duration.

bleeding and malocclusion is a strong risk for hypertension remains hypothetical, but activation of inflammation, worse masticatory performance, and breathing disorders may be present and thus increase the risk of hypertension.

In this study, adjusted R^2 values in the model after adding the number of oral health components were higher than without including oral markers or after adding individual oral health markers, suggesting that the concomitance of these oral health disorders seems to jointly contribute to the risk of hypertension. The precise mechanism by which the concomitance of several oral health disorders is an independent risk for hypertension remains hypothetical but is likely multifactorial. In this study, a significant graded relationship between the number of components present and the corresponding body mass index, as well as bite force, was found. Worse masticatory performance, obstructive breathing disorders, periodontal inflammation, and obesity may be present in the case of concomitant oral health disorders and thus enhance the risk of hypertension. On the other hand, in this study, 42.6% of subjects with the lowest quartile of remaining tooth number corresponded to Eichner index C. Although these two oral health markers essentially do not mean the same thing, the remaining tooth number and Eichner index influenced each other. More generally, all of the oral health disorders examined in this study are relatively interrelated. Therefore, our results should be also interpreted as indicating that moderately or severely impaired, but not mildly impaired, oral health is associated with increased risk of hypertension.

Lifestyle changes are widely recognized to lower blood pressure or to reduce the risk of developing hypertension.[29] Of these, the lifestyle variables reported in this study have been suggested to be important factors modulating blood pressure.[29–31] Except for daily sugar-sweetened soft drink intake, we did not find a significantly worse lifestyle in the groups with a higher number of components of oral health

Table 5. Association between number of oral health disorder components—Community Periodontal Index of Treatment Needs stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C—and differences in blood pressure in subjects not taking antihypertensive medication (n = 1,148)

Models	0	1			2			≥3			
		β	95% CI	P value	β	95% CI	P value	β	95% CI	P trend	P_{trend}
Systolic blood pressure											
Age- and sex-adjusted	Reference	0.77	−1.81 to 3.34	0.56	2.79	−0.82 to 6.40	0.13	5.36	1.07 to 9.66	0.01	<0.01
Multivariable-adjusted[a]	Reference	0.24	−2.30 to 2.78	0.85	2.98	−0.55 to 6.51	0.10	5.41	1.16 to 9.66	0.01	0.03
Diastolic blood pressure											
Age- and sex- adjusted	Reference	0.16	−1.32 to 1.64	0.83	1.46	−0.62 to 3.54	0.17	2.51	0.04 to 4.98	0.047	0.04
Multivariable-adjusted[a]	Reference	−0.16	−1.61 to 1.29	0.83	1.41	−0.60 to 3.42	0.17	2.36	−0.06 to 4.78	0.06	0.046

[a]Multivariable-adjusted model included age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.

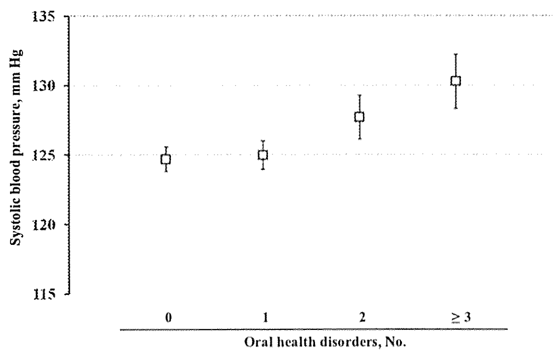

Figure 2. Adjusted mean systolic blood pressure by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C in subjects not taking antihypertensive medication (n = 1,148). Data are adjusted mean ± SE. The *P* value for trend was 0.03. Analyses were controlled for age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, physical activity, daily sugar-sweetened soft drink intake, and nocturnal sleep duration.

disorders; rather, significantly lower prevalences of current smoking, daily sugar-sweetened soft drink intake, and longer nocturnal sleep duration were found in hypertensive subjects than in those without, suggesting that some hypertensive subjects in this study had already instituted lifestyle changes. Modification of lifestyle as a result of oral health disorders has been speculated to be another possible cause of development of hypertension;[9,13] however, our results may support the existence of a direct association of oral health disorders with hypertension.

Our analysis has several limitations. First, the design of this study does not allow us to clarify the underlying mechanism. Indeed, reverse causality whereby hypertension leads to oral health disorders cannot be excluded. Another recent study showed a negative association between periodontal disease and incident hypertension.[32] Second, several important inflammatory and metabolic markers, such as C reactive protein and insulin, were not measured in our study. Unmeasured variables, such as salt intake and sleep disorders, may affect the observed results. Nonetheless, the use of 4 oral health markers that refer to different manifestations of oral disease and cover both the presence and the extent of disease indicates that the results are not coincidental, hence limiting any bias resulting from using only 1 oral health disorder variable.

In conclusion, there is an additive relationship between oral health disorders and increased odds of hypertension and raised SBP in the Japanese urban population. Our results also suggest that moderately or severely impaired oral health—that is, several concomitant oral health disorders—is associated with risk of hypertension. Our findings emphasize that poor oral health might have a direct relationship with hypertension, and this might have important implications for public health. The next crucial step is to investigate whether oral health disorders are causally linked to hypertension in a longitudinal setting. If so, dental therapy might be used in clinical practice to reduce the development of hypertension.

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DISCLOSURE

The authors declared no conflict of interest.

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Original Contribution

Modification of the Excess Risk of Coronary Heart Disease Due to Smoking by Seafood/Fish Intake

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Seafood/fish intake has been regarded as a protective factor for coronary heart disease (CHD), while smoking is a strong risk factor. To examine whether associations between smoking and risk of CHD are modified by seafood/fish intake, we studied 72,012 Japanese men and women aged 45–74 years who completed 2 food frequency questionnaires, 5 years apart, during the period 1995–2009. After 878,163 person-years of follow-up, 584 incident cases of CHD (101 fatal and 483 nonfatal), including 516 myocardial infarctions, were documented. There was a clear dose-response association between smoking and CHD risk among subjects with a low seafood/fish intake (<86 g/day) but not among those with a high seafood/fish intake (≥86 g/day). Compared with never smokers, the multivariable hazard ratios in light (1–19 cigarettes/day), moderate (20–29 cigarettes/day), and heavy (≥30 cigarettes/day) smokers were 2.39 (95% confidence interval (CI): 1.60, 3.56), 2.74 (95% CI: 1.90, 3.95), and 3.24 (95% CI: 2.12, 4.95), respectively, among low seafood/fish eaters and 1.13 (95% CI: 0.64, 1.99), 1.29 (95% CI: 0.95, 2.04), and 2.00 (95% CI: 1.18, 3.51), respectively, among high seafood/fish eaters. Compared with heavy smokers with a low seafood/fish intake, light smokers with a high seafood/fish intake had substantially reduced risk of CHD (hazard ratio = 0.57, 95% CI: 0.32, 0.98). High seafood/fish intake attenuated the positive association between smoking and risk of CHD.

coronary heart disease; fish intake; follow-up studies; seafood intake; smoking

Abbreviations: CHD, coronary heart disease; CI, confidence interval; FFQ, food frequency questionnaire; JPHC, Japan Public Health Centre-based Prospective Study on Cancer and Cardiovascular Disease.

Fish intake, in both small (1, 2) and large (3–5) amounts, is inversely associated with risk of coronary heart disease (CHD). Regarding both the exposure variable (seafood/fish intake) and the outcome (CHD), Japan is unique; it has a very high seafood/fish intake (>3 times that of Western populations (6)) and a very low incidence of CHD (3–5 times lower than that of Western populations (7)).

Compared with Western countries, Japanese men had a high proportion of current smokers (47%) in 2000, while Japanese women had a low proportion (11%) (8). However, the proportion of current smokers among Japanese women aged 20–49 years has increased since 1990 (8). The epidemiologic evidence supporting a positive association between cigarette smoking and CHD is very strong (9). Smoking is common in Japan, but the Japanese population has low rates of CHD, which suggests that high fish intake may account for the lower CHD rates observed relative to other populations (5, 10, 11). A prospective study in middle-aged Japanese-American men showed that high fish intake may limit the increase in risk of CHD morbidity and mortality among heavy smokers (≥30 cigarettes/day) (12). However, a case-control study among Greeks showed that moderate fish consumption but not high fish consumption was inversely associated with CHD risk among smokers (13). To our knowledge, no other published data about a joint association or interaction between seafood/fish intake and smoking status in the risk of CHD have been released. Using data from a nationwide study, the Japan Public Health Centre-based Prospective

Study on Cancer and Cardiovascular Disease (JPHC Study), we examined whether the association between smoking and risk of CHD was modified by seafood/fish intake. We hypothesized that a high seafood/fish intake may limit the increase in risk of CHD, even among smokers.

METHODS

Study population

The JPHC Study, a large, nationwide Japanese prospective cohort study, was launched in 2 phases at a number of public health centers: 5 public health centers for cohort I (in 1990) and 6 public health centers for cohort II (in 1993). The study design has been described in detail previously (14). Three questionnaire surveys were conducted: at baseline in 1990 (cohort I) and 1993 (cohort II) and at 5- and 10-year follow-ups. Because the 5-year follow-up survey included a more comprehensive food frequency questionnaire (FFQ) than the baseline surveys, the 5-year survey was used as the baseline (starting point) for the present study. At the time of the 5-year survey, subjects were aged 45–64 years in cohort I and aged 45–74 years in cohort II. Information on medical histories and health-related lifestyle factors, such as smoking, alcohol drinking, and dietary habits, was obtained. This study was approved by the institutional review board of the National Cancer Centre of Japan.

We excluded subjects at 2 public health centers because of differences in recruitment criteria. After exclusion of 5,681 persons who had died, moved out of a study area, or were lost to follow-up before the starting point, the remaining 92,900 subjects were eligible for participation. Of these, 80,964 subjects responded (response rate = 87.2%) and were included in the present study. We excluded subjects who reported a history of myocardial infarction, cerebrovascular disease, or cancer ($n = 3,398$) before the starting point. Based on the 5-year FFQ assessment, an additional 5,203 subjects with missing information about seafood/fish intake and/or smoking habits and 351 subjects who reported extreme total energy intakes (outside the range of the mean ± 3 standard deviations) were excluded, which left a total of 72,012 subjects (32,982 men and 39,030 women) who were ultimately included in our analysis.

Dietary assessment

The FFQs administered during the 5- and 10-year surveys assessed the average intake of 147 food and beverage items, including 19 seafood/fish items (7 types of fresh fish (salmon, skipjack/tuna, cod/flatfish, sea bream, horse mackerel/sardine, saury/mackerel, and eel), 5 seafoods other than fish (squid, octopus, shrimp, clam, and pond snail), 4 salted and dried fish products (salted fish, dried fish, dried whitebait, and salted fish roe), and 3 other fish products (canned tuna and 2 fish-paste products, chikuwa and kamaboko)), over the previous year. For most food items, 9 response options were available to describe consumption frequency, ranging from rarely to 1–3 times/month; 1–2, 3–4, or 5–6 times/week; and 1, 2–3, 4–6, or ≥7 times/day. A standard portion size was specified for each food. The daily intakes of seafood/fish and all food items were calculated by multiplying daily consumption frequency by the typical portion size (14).

For different seafood/fish intakes, the Spearman correlation coefficients for correlation between 2 administrations of the 5-year FFQ, 1 year apart, among 244 men and 254 women ranged from 0.50 to 0.73 in men and from 0.52 to 0.69 in women, and those for correlation between the 5-year FFQ and four 1-week dietary records ranged from 0.20 to 0.57 in men and from 0.25 to 0.49 in women. The mean intakes of seafood/fish were 102 g/day in men and 87 g/day in women according to the 5-year FFQ and were 99 g/day in men and 73 g/day in women according to the dietary records (14). Web Figure 1 (available at http://aje.oxfordjournals.org/) shows the distribution of daily seafood/fish consumption in our subjects, represented by the mean value and interquartile range.

In the second and third survey questionnaires, the questions were about current smoking status, average number of cigarettes smoked per day for current smokers, and reasons for cessation of smoking for former smokers.

Endpoint assessment

CHD events were included in the study if they occurred between the return of the 5-year questionnaire and the end of 2009 in cohort I or the end of 2007 in cohort II. Seventy-eight major hospitals with the capacity to treat patients for CHD were registered within the administrative districts of the JPHC cohorts. Physicians, unaware of the patients' lifestyle data, reviewed the medical records at each hospital. Myocardial infarction was confirmed in the medical records according to the criteria of the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Project (7), which requires evidence from electrocardiograms, cardiac enzymes, or autopsy. Subjects who moved away from their original residential areas (2% of the subjects), identified through the residential registry, were treated as censored at that time.

Statistical analysis

Statistical analyses were based on incidence rates of CHD during the follow-up period. For each individual, person-months of follow-up were calculated from January 1, 1995 (in cohort I) or January 1, 1998 (in cohort II) onward, until one of 4 endpoints had been achieved: incidence of the first CHD event, death, emigration, or December 31, 2009 (in cohort I) or December 31, 2007 (in cohort II), whichever came first. We tested for effect modification by seafood/fish intake in the association between smoking status (never smokers; former smokers; and current light smokers (<20 cigarettes/day), moderate smokers (20–29 cigarettes/day), or heavy smokers (≥30 cigarettes/day)) and risk of CHD. Hazard ratios and 95% confidence intervals were calculated after adjustment for age, sex, and other potentially confounding factors with time-dependent Cox proportional hazards models. We updated the information on dietary intake, smoking status, and the confounding factors listed below (except for age, sex, and public health center) from the 10-year follow-up survey, to which 88.7% of the subjects responded. Accordingly, dietary intakes and smoking status at the time of the 5-year survey were related to the incidence of CHD that occurred during the time period between the 5- and 10-year surveys, and dietary intakes and smoking status at the time of the 10-year survey were related to the incidence of CHD that occurred from the time of the 10-year survey to the end of the study. For subjects who had not responded to the 10-year survey and had incident CHD afterwards, smoking status and intakes reported on the 5-year survey were used. Potentially confounding factors included for statistical adjustment were age (5-year categories); sex; public health center; alcohol intake (nondrinkers; occasional drinkers; and weekly ethanol intake of <150 g/week, 150–<300 g/week, 300–<450 g/week, or ≥450 g/week); body mass index (weight (kg)/height $(m)^2$); histories of hypertension and diabetes (yes or no); medication use for hypercholesterolemia (yes or no); sports during leisure time (<1 day/month, 1–3 days/month, and ≥1 day/week); and quintiles of dietary intake of fruits, vegetables, saturated fat, monounsaturated fat, *n*-6 polyunsaturated fat, cholesterol, and total energy.

There was no evidence that proportional hazards assumptions were violated, as indicated by the lack of significant interaction between the predictors and a function of survival time in the model. Two different sex interaction terms were generated and tested by means of the Wald test; seafood/fish consumption (continuous) × sex (0, 1) and smoking stratum (0, 1, 2) × sex (0, 1); neither term was significant ($P > 0.05$ for all CHD events). Another interaction term was generated for seafood/fish consumption (continuous) × smoking stratum (0, 1, 2); the *P* value for interaction was less than 0.05 for all CHD events, except fatal coronary events. The analyses were conducted with SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). All *P* values presented are 2-sided, and $P < 0.05$ was regarded as statistical significance.

RESULTS

Table 1 shows updated information on cardiovascular disease risk factors and intakes of selected nutrients and foods according to smoking status, stratified by dietary intake of seafood/fish. The prevalence of current smoking was 41% for men, 4% for women, and 21% for all subjects. In both low and high seafood/fish eaters, compared with never smokers, former smokers were more likely to be hypertensive and diabetic and to consume more alcohol. Compared with never smokers, subjects across increasing strata of current smoking (light, moderate, and heavy) were on average 4–5 years younger and less likely to practice sports, to be hypertensive, and to use lipid-lowering drugs but were more likely to be diabetic and to consume more alcohol and total energy. Increasing number of cigarettes smoked per day was associated with less consumption of fatty acids, cholesterol, fruits, and vegetables. Seafood/fish intake decreased across the smoking strata in subjects with low seafood/fish intake, whereas it increased across the smoking strata in those with high seafood/fish intake.

During 878,163 person-years of follow-up, we documented 584 incident cases of CHD (428 men and 156 women). There were 101 (74 men and 27 women) fatal coronary events and 483 (354 men and 129 women) nonfatal coronary events, including 516 (376 men and 140 women) myocardial infarctions.

The multivariable-adjusted hazard ratio for total CHD risk in the highest quintiles of seafood/fish intake versus the lowest quintiles were 0.83 (95% confidence interval (CI): 0.61, 1.17; *P*-trend = 0.25) for all subjects, 1.28 (95% CI: 0.78, 1.79; *P*-trend = 0.42) for never smokers, 0.90 (95% CI: 0.69, 2.06; *P*-trend = 0.67) for former smokers, and 0.63 (95% CI: 0.39, 1.02; *P*-trend = 0.05) for current smokers. Among current smokers, the reduced risk of CHD observed in the highest quintiles of seafood/fish intake compared with the lowest quintiles was primarily observed for nonfatal coronary events (hazard ratio = 0.55, 95% CI: 0.36, 0.92), not for fatal coronary events (hazard ratio = 1.62, 95% CI: 0.59, 2.51) (not shown in tables).

Table 2 shows the multivariable hazard ratio for CHD risk according to smoking stratum in all subjects and in subjects with low and high seafood/fish intakes. A positive dose-response association between cigarette smoking and risk of CHD was evident in all subjects and in subjects with a low seafood/fish intake (less than the median of 86 g/day). On the other hand, among subjects with a high seafood/fish intake (median or more; ≥86 g/day), the association between smoking and risk of CHD was attenuated and modified in light and moderate smokers; hazard ratios were 1.13 (95% CI: 0.64, 1.99), 1.29 (95% CI: 0.95, 2.04), and 2.00 (95% CI: 1.18, 3.51) in light, moderate, and heavy smokers with a high seafood/fish intake, respectively, compared with never smokers with a high seafood/fish intake. Similar associations were found for myocardial infarction and nonfatal coronary events, while no difference between low and high seafood/fish consumers was found for risk of fatal coronary events.

Sex-specific analysis (Web Table 1) revealed no difference in the association between smoking status and risk of CHD in all men and women. Because of the small number of female smokers and the very small numbers of cases among light, moderate, and heavy female smokers, the attenuated risk of CHD in female smokers with a high seafood/fish intake was still observed, but the confidence intervals were widened.

The highest age-adjusted incidence rate for CHD (0.16 cases per 1,000 person-years) was observed in heavy smokers who consumed less seafood/fish; therefore, we used this group as our reference group in Figure 1 and Web Table 2, to evaluate risk in the other 9 combination groups of seafood/fish intake and smoking status. The risk of CHD was lower in subjects with a high seafood/fish intake across the different current smoking strata (light, moderate, and heavy) but did not reach the lower risk observed in never or former smokers. Compared with heavy smokers with a low seafood/fish intake, heavy smokers with a high seafood/fish intake had a 23% reduction in the risk of CHD. In addition, compared with that in heavy smokers, the reduced risk of CHD varied in light and moderate smokers according to their seafood/fish intake, with a significant reduction in light smokers with a high seafood/fish intake; the multivariable-adjusted hazard ratios for CHD were 0.74 (95% CI: 0.48, 1.15) and 0.85 (95% CI: 0.57, 1.26), respectively, in light and moderate smokers with low seafood/fish intake and 0.57 (95% CI: 0.32, 0.98) and 0.70 (95% CI: 0.48, 1.20),

Table 1. Updated Lifestyle, Health, and Dietary Characteristics of Participants According to Smoking Status and Seafood/Fish Intake, Japan Public Health Centre-based Prospective Study on Cancer and Cardiovascular Disease, 1995–2009

	Smoking Status[a]									
	Never Smoker		Former Smoker		Light Smoker		Moderate Smoker		Heavy Smoker	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Low Seafood/Fish Intake[b]										
Male sex		26		96		81		94		98
Age, years	57 (8)		57 (8)		56 (8)		54 (7)		52 (6)	
Body mass index[c]	23.8 (3.2)		23.9 (3.0)		22.9 (3.0)		23.2 (3.0)		23.6 (3.1)	
History of hypertension		26		30		21		18		17
History of diabetes mellitus		5		9		7		7		9
Alcohol consumption, g/week	221 (267)		317 (271)		326 (272)		377 (288)		446 (386)	
Sports ≥1 day/week		29		29		24		22		18
Hyperlipidemia treatment		9		7		4		4		3
Daily dietary intake										
Total energy, kcal	1,919 (890)		2,132 (829)		2,083 (863)		2,182 (854)		2,252 (814)	
Saturated fats, g	18 (8)		15 (8)		15 (9)		14 (9)		14 (8)	
Monounsaturated fats, g	22 (10)		18 (10)		18 (10)		17 (11)		16 (10)	
n-3 fatty acids, g	2.3 (0.8)		1.9 (0.8)		2.0 (0.8)		1.8 (0.8)		1.7 (0.8)	
n-6 fatty acids, g	11.6 (4.3)		9.5 (3.9)		9.7 (4.6)		8.9 (4.4)		8.3 (4.1)	
Cholesterol, g	264 (164)		234 (159)		239 (178)		230 (176)		224 (190)	
Seafood/fish, g	53 (29)		47 (28)		48 (27)		46 (28)		44 (28)	
Meat, g	65 (78)		66 (88)		66 (63)		71 (89)		72 (69)	
Fruits, g	247 (225)		176 (167)		166 (173)		142 (171)		123 (150)	
Vegetables, g	592 (438)		479 (361)		457 (390)		404 (329)		365 (346)	
High Seafood/Fish Intake[b]										
Male sex		15		94		73		90		96
Age, years	57 (7)		58 (8)		57 (8)		55 (7)		53 (6)	
Body mass index	23.7 (3.2)		23.7 (3.0)		22.9 (3.1)		23.1 (3.0)		23.7 (3.1)	
History of hypertension		27		32		24		19		16
History of diabetes mellitus		6		11		7		10		11
Alcohol consumption, g/week	168 (222)		294 (249)		302 (238)		334 (254)		403 (309)	
Sports ≥1 day/week		30		30		27		23		19
Hyperlipidemia treatment		12		9		6		5		3
Daily dietary intake										
Total energy, kcal	1,981 (1,046)		2,210 (967)		2,210 (1,218)		2,355 (1,142)		2,410 (1,024)	
Saturated fats, g	18 (7)		15 (7)		17 (9)		15 (7)		14 (7)	
Monounsaturated fats, g	24 (9)		20 (9)		22 (11)		20 (9)		19 (9)	
n-3 fatty acids, g	3.5 (1.7)		3.2 (1.7)		3.3 (1.7)		3.4 (2.3)		3.2 (1.7)	
n-6 fatty acids, g	12.1 (3.9)		10.3 (3.8)		10.8 (4.6)		10.1 (4.3)		9.3 (3.9)	
Cholesterol, g	331 (160)		314 (180)		327 (196)		335 (273)		321 (209)	
Seafood/fish, g	136 (96)		137 (108)		143 (94)		151 (153)		145 (102)	
Meat, g	65 (75)		66 (67)		73 (76)		74 (76)		75 (70)	
Fruits, g	262 (196)		190 (180)		182 (192)		163 (169)		138 (160)	
Vegetables, g	624 (391)		507 (340)		515 (408)		468 (333)		419 (312)	

Abbreviation: SD, standard deviation.

[a] Light smoking was defined as <20 cigarettes/day, moderate smoking as 20–29 cigarettes/day, and heavy smoking as ≥30 cigarettes/day.

[b] Low seafood/fish intake was defined as less than the median intake (<86 g/day); high seafood/fish intake was defined as the median intake or more (≥86 g/day).

[c] Weight (kg)/height (m)^2.

respectively, in those with high seafood/fish intake. Risk of CHD in subjects who had never smoked or had quit smoking was much lower but did not vary according to seafood/fish intake; the multivariable-adjusted hazard ratios for CHD were 0.32 (95% CI: 0.22, 0.48) and 0.39 (95% CI: 0.26, 0.59), respectively, in those with low seafood/fish intake and 0.32 (95% CI: 0.19, 0.55) and 0.44 (95% CI: 0.29, 0.69), respectively, in those with high seafood/fish intake. Similar associations were observed for myocardial infarction and nonfatal coronary events (Web Table 2).

DISCUSSION

In this large cohort study of the Japanese general population, high seafood/fish intake attenuated the excess risk of CHD among current smokers. Light smokers with high seafood/fish intake had a substantially reduced risk, but it did not reach the lower risk of never or former smokers. High seafood/fish intake added little to the risk of CHD among never and former smokers. That observed association was independent of other measured risk factors.

The responses to endothelial injury caused by smoking (15) may be counteracted by effects of n-3 fatty acids from seafood/fish intake (3, 5, 12). This makes sense given the multiple biological pathways that are affected by n-3 fatty acids. They include the lowering of blood pressure levels and dyslipidemia, especially high levels of triglycerides, improvement of vascular function, inhibition of inflammatory responses and platelet aggregation, and reduction of low-density lipoprotein uptake in the aorta (16–19). Furthermore, the associations of n-3 fatty acids with reduced cardiac arrhythmias (20) and reduced inflammation within advanced atherosclerotic plaques (21, 22) and maintained heart rate variability (23) would be expected to promote secondary prevention. One of these biological pathways is the alteration of arachidonic acid metabolism, leading to the following: inhibition of leukotriene B_4 syntheses (a chemoattractant), syntheses of the physiologically inactive thromboxane A_3 instead of thromboxane A_2 (a potent vasoconstrictor and pro-aggregator of platelets), and syntheses of prostaglandin I_2 (a vasodilator and platelet anti-aggregator) (24).

In JPHC Study cohort I, Iso et al. (5) demonstrated an inverse association between fish intake and risk of CHD in 41,578 middle-aged subjects (40–59 years) during 11 years of follow-up. The present analysis extended the follow-up time for cohort I to 15 years, with the addition of subjects from cohort II ($n = 72,012$ for both cohorts combined), and revealed that high seafood/fish intake may limit the adverse effects of smoking among current smokers, especially light smokers.

Our results among subjects with low seafood/fish intake are consistent with the findings by Rodriguez et al. in the Honolulu Heart Program (12) showing a positive dose-response association between smoking and risk of CHD. However, in the study by Rodriguez et al. (12), the inverse association between high fish intake and CHD risk was observed only in heavy smokers, whereas in the current study a decreased risk of CHD associated with high seafood/fish intake was observed for all of the current smoking strata and reached a level of significance in light smokers. Our results suggest that the positive dose-response association between smoking and risk of CHD could be interrupted by increasing seafood/fish intake, especially in lighter smokers; this is supported by the lack of excess CHD risk in light-to-moderate smokers with a high seafood/fish intake (compared with never smokers) and by the reduced CHD risk in light, moderate, and heavy smokers with a high seafood/fish intake (compared with heavy smokers with a low seafood/fish intake). On the other hand, Rodriguez et al. did not explain why the inverse association between high fish intake and CHD risk in their study was evident only in subjects who smoked ≥30 cigarettes/day, not in those who smoked <30 cigarettes/day (12). Rodriguez et al. claimed that random error explained the higher CHD risk found in light smokers with a high fish intake compared with light smokers with a low fish intake (12).

In the current study, the risk of fatal coronary events did not vary according to seafood/fish intake in current smokers or nonsmokers. Previously, Iso et al. (5) found no association between fish intake and risk of fatal coronary events among subjects in JPHC cohort I. These findings contrast with the results reported by many Western investigators (25) but agree with those of other Japanese investigators (3, 26). One of the reasons for the lack of a significant association with fatal coronary events may be low statistical power (40%) to detect an association. Another reason is potential misdiagnosis of fatal coronary events. In the present study, only 27% of fatal coronary events were confirmed by laboratory findings or autopsy, whereas 98% of nonfatal coronary events were confirmed clinically and by investigative tests. It is possible that almost every subject in the present study population was above a threshold of seafood/fish intake for prevention of fatal coronary events. In our study, the lowest seafood/fish intake was 44 g/day in heavy smokers with a low seafood/fish intake and the highest intake was 151 g/day in moderate smokers with a high seafood/fish intake. One potential reason why a strong inverse association with nonfatal coronary events was seen in this cohort but is not generally seen in Western populations is that seafood/fish intake may affect coronary risk only at very high levels of intake. Here, it seems to contradict the findings obtained among Greeks by Panagiotakos et al. (13), who reported a J-shaped association between fish intake and CHD risk among smokers, showing that only moderate fish intake (not high fish intake) was associated with reduced risk of CHD. However, the Greek study was a case-control study and was liable to have contained recall bias; furthermore, high-risk subjects may have attempted to eat more fish or may have overestimated their real intake, because self-reported fish intake in that study showed a cross-validation concordance of 88% for patients and 95% for controls (13).

The strengths of the current study include its large sample size, the population-based prospective design, the inclusion of both men and women, and the use of validated FFQs. The analyses performed in the present study were based on energy-adjusted measures of fish intake. We considered changes in seafood/fish intake and smoking habits over time by updating the data from the 10-year follow-up questionnaire. Furthermore, our study of the Japanese population allowed us to assess any potential association between smoking and risk of CHD at relatively high levels of seafood/fish intake.

Table 2. Hazard Ratio for Coronary Heart Disease According to Smoking Status, Overall and by Seafood/Fish Intake, Japan Public Health Centre-based Prospective Study on Cancer and Cardiovascular Disease, 1995–2009[a]

Endpoint and Smoking Status[b]	No. of Subjects	No. of Cases	HR[c]	95% CI	HR[d]	95% CI
Total (All Seafood/Fish Intakes)						
Coronary heart disease						
Never smoker	46,747	234	1.00	Referent	1.00	Referent
Former smoker	10,179	106	1.04	0.79, 1.32	1.09	0.83, 1.43
Light smoker	5,182	79	1.89	1.33, 2.61	2.01	1.50, 2.67
Moderate smoker	6,457	105	2.26	1.67, 3.01	2.37	1.80, 3.10
Heavy smoker	3,429	60	2.42	1.77, 3.36	2.56	1.83, 3.59
Myocardial infarction						
Never smoker	46,747	206	1.00	Referent	1.00	Referent
Former smoker	10,179	91	1.05	0.77, 1.42	1.10	0.81, 1.50
Light smoker	5,182	70	1.82	1.25, 2.51	1.99	1.52, 2.62
Moderate smoker	6,457	92	2.19	1.59, 2.94	2.26	1.66, 3.18
Heavy smoker	3,429	57	2.31	1.71, 3.12	2.59	1.91, 3.51
Nonfatal coronary events						
Never smoker	46,747	202	1.00	Referent	1.00	Referent
Former smoker	10,179	85	1.15	0.84, 1.57	1.20	0.88, 1.64
Light smoker	5,182	62	1.77	1.27, 2.40	2.00	1.54, 2.61
Moderate smoker	6,457	87	1.99	1.49, 2.86	2.12	1.55, 3.10
Heavy smoker	3,429	47	2.49	1.83, 3.38	2.77	2.02, 3.78
Fatal coronary events						
Never smoker	46,747	32	1.00	Referent	1.00	Referent
Former smoker	10,179	21	0.50	0.23, 1.07	0.55	0.25, 1.18
Light smoker	5,182	17	1.15	0.64, 2.07	1.26	0.69, 2.28
Moderate smoker	6,457	18	1.28	0.75, 2.19	1.44	0.83, 2.51
Heavy smoker	3,429	13	1.26	0.58, 2.71	1.41	0.64, 3.07
Low Seafood/Fish Intake[e]						
Coronary heart disease						
Never smoker	26,127	117	1.00	Referent	1.00	Referent
Former smoker	6,581	70	1.25	0.85, 1.82	1.24	0.85, 1.81
Light smoker	3,247	55	2.12	1.34, 3.15	2.39	1.60, 3.56
Moderate smoker	4,292	73	2.34	1.69, 3.48	2.74	1.90, 3.95
Heavy smoker	2,358	40	2.97	1.96, 4.52	3.24	2.12, 4.95
Myocardial infarction						
Never smoker	26,127	107	1.00	Referent	1.00	Referent
Former smoker	6,581	59	1.10	0.74, 1.65	1.05	0.70, 1.60
Light smoker	3,247	48	2.06	1.37, 3.09	2.45	1.60, 3.76
Moderate smoker	4,292	67	2.37	1.64, 3.44	2.63	1.78, 3.90
Heavy smoker	2,358	37	2.86	1.86, 4.41	3.08	1.94, 4.88
Nonfatal coronary events						
Never smoker	26,127	100	1.00	Referent	1.00	Referent
Former smoker	6,581	55	1.14	0.70, 1.60	1.05	0.68, 1.56
Light smoker	3,247	47	2.19	1.40, 3.40	2.33	1.49, 3.66
Moderate smoker	4,292	60	2.34	1.60, 3.31	2.55	1.70, 3.71
Heavy smoker	2,358	32	2.80	1.81, 4.28	2.89	1.89, 4.59

Table continues

Table 2. Continued

Endpoint and Smoking Status[b]	No. of Subjects	No. of Cases	HR[c]	95% CI	HR[d]	95% CI
Fatal coronary events						
Never smoker	26,127	17	1.00	Referent	1.00	Referent
Former smoker	6,581	15	1.88	0.76, 2.24	1.70	0.74, 2.00
Light smoker	3,247	8	2.17	0.53, 4.14	2.04	0.52, 3.97
Moderate smoker	4,292	13	2.97	0.89, 6.81	2.54	0.81, 6.17
Heavy smoker	2,358	8	2.26	0.50, 4.44	1.99	0.44, 3.88
High Seafood/Fish Intake[e]						
Coronary heart disease						
Never smoker	20,620	117	1.00	Referent	1.00	Referent
Former smoker	3,616	36	0.80	0.47, 1.34	0.67	0.40, 1.14
Light smoker	1,935	24	1.25	0.72, 1.97	1.13	0.64, 1.99
Moderate smoker	2,165	32	1.34	1.01, 2.12	1.29	0.95, 2.04
Heavy smoker	1,071	20	2.05	1.21, 3.46	2.00	1.18, 3.51
Myocardial infarction						
Never smoker	20,620	99	1.00	Referent	1.00	Referent
Former smoker	3,616	32	0.92	0.53, 1.62	0.79	0.44, 1.39
Light smoker	1,935	22	1.40	0.77, 2.55	1.33	0.72, 2.44
Moderate smoker	2,165	25	1.63	1.02, 3.18	1.50	0.94, 3.10
Heavy smoker	1,071	20	2.25	1.30, 4.19	2.13	1.21, 4.04
Nonfatal coronary events						
Never smoker	20,620	102	1.00	Referent	1.00	Referent
Former smoker	3,616	30	0.86	0.50, 1.46	0.82	0.47, 1.34
Light smoker	1,935	15	0.95	0.70, 1.99	1.12	0.66, 1.78
Moderate smoker	2,165	27	1.66	1.04, 2.84	1.60	0.98, 2.69
Heavy smoker	1,071	15	1.99	1.19, 3.93	2.08	1.23, 4.18
Fatal coronary events						
Never smoker	20,620	15	1.00	Referent	1.00	Referent
Former smoker	3,616	6	1.03	0.25, 1.78	1.10	0.25, 1.98
Light smoker	1,935	9	3.03	0.78, 5.02	2.77	0.71, 4.10
Moderate smoker	2,165	5	1.09	0.21, 3.26	1.37	0.45, 4.26
Heavy smoker	1,071	5	2.07	0.13, 4.15	2.37	0.12, 5.08

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The *P* value for interaction between seafood/fish intake and smoking stratum (Wald test) was less than 0.05 for all endpoints except fatal coronary events.

[b] Light smoking was defined as <20 cigarettes/day, moderate smoking as 20–29 cigarettes/day, and heavy smoking as ≥30 cigarettes/day.

[c] Adjusted for age and sex.

[d] Adjusted for age; sex; alcohol intake; body mass index; histories of hypertension and diabetes; use of medication for hypercholesterolemia; sports during leisure time; public health center; and dietary intake (in quintiles) of fruits, vegetables, saturated fat, monounsaturated fat, *n*-6 polyunsaturated fat, cholesterol, and total energy.

[e] Low seafood/fish intake was defined as less than the median intake (<86 g/day); high seafood/fish intake was defined as the median intake or more (≥86 g/day).

As for limitations, we excluded 5,554 subjects with implausible energy intakes or missing information on seafood/fish intake or smoking status. Although these exclusions were necessary for the current analysis, we could not rule out the possibility of selection bias resulting from these exclusions. The moderate-to-weak correlations for reproducibility of some types of seafood/fish is another limitation. Lastly, we adjusted for a variety of potential confounders; however, we cannot rule out the possibility of unmeasured and residual confounding.

In conclusion, in this prospective study of Japanese populations with different smoking habits (never, former, light, moderate, and heavy smokers), who were unique in having a very high intake of seafood/fish and a very low incidence

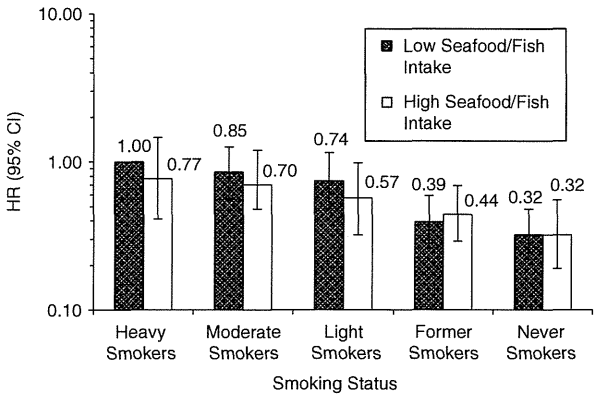

Figure 1. Hazard ratios (HRs) and 95% confidence intervals (CIs; T-shaped bars) for coronary heart disease (CHD) according to smoking status and seafood/fish intake, Japan Public Health Centre-based Prospective Study on Cancer and Cardiovascular Disease, 1995–2009. Dark columns, low seafood/fish intake (less than median; <86 g/day); white columns, high seafood/fish intake (median or more; ≥86 g/day). The *y* axis is set to a logarithmic scale. Results were adjusted for age; sex; alcohol consumption; body mass index; histories of hypertension and diabetes; use of medication for hypercholesterolemia; sports during leisure time; public health center; and dietary intake (in quintiles) of fruits, vegetables, saturated fat, monounsaturated fat, *n*-6 polyunsaturated fat, cholesterol, and total energy. Heavy smokers with a low seafood/fish intake had the highest age-adjusted incidence of CHD per 1,000 person-years and therefore were used as the reference group. Never and former smokers with low or high seafood/fish intakes had a significantly reduced risk of CHD ($P < 0.0001$), and light smokers with a high seafood/fish intake also had a reduced risk ($P < 0.05$). P for interaction = 0.06 (Wald test).

of CHD, we investigated the impact of seafood/fish intake on the associations between smoking and CHD risk in both men and women combined and sex-specifically. To our knowledge, this was the first study of its kind. Our results support a public health message suggesting a reduction of CHD risk among current smokers through an increase in seafood/fish intake. We are not recommending eating seafood/fish as an antidote to smoking, because smoking cessation is one of the best ways to prevent CHD. However, the recommendation of increasing seafood/fish intake is an alternative in the prevention of CHD when the subject is resistant to quitting smoking. Nonsmokers still have the lowest risk of CHD, regardless of their seafood/fish intakes.

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Brief Review

Prevention of Hypertension and Cardiovascular Diseases

A Comparison of Lifestyle Factors in Westerners and East Asians

Yoshihiro Kokubo

Appropriate lifestyle modifications are a fundamental step to prevent hypertension, which is the strongest risk factor for cardiovascular disease (CVD).[1,2] However, the slope of the association between blood pressure (BP) and stroke is steeper among Asians than Westerners.[3,4] This result is partly explained by the higher proportion of strokes that are hemorrhagic in Asian compared with Western populations and the steeper association of BP with hemorrhagic stroke as compared with ischemic stroke.[5] The population-attributable fractions of hypertension for ischemic stroke in men and women have been reported as 40% and 36% in China, 34% and 35% in South Korea, 37% and 39% in Japan (East Asian), 15% and 44% in Australia, and 18% and 43% in New Zealand (Western), respectively.[6] These differences between Westerners and East Asians depend on both genetic (racial) and lifestyle factors.

A schema of the progression from lifestyle behaviors to the onset of stroke and coronary heart disease (CHD) is shown in the Figure. Lifestyle (modifiable) and genetic (unmodifiable) factors are key cardiovascular risk factors, especially higher BP (the primary stage of CVD prevention). Furthermore, cardiovascular risk factors, especially hypertension, are key factors for the prevention of CVD (the secondary stage of CVD prevention). To prevent CVD, it is important to improve lifestyle and reduce cardiovascular risk factors in the early stage. The health behaviors appearing in recent guidelines for the management of hypertension are also important for the primary prevention of stroke.

The guidelines put out by the United States,[7] Europe,[8] China,[9] and Japan[10] for lifestyle modifications for prevention of hypertension are similar, namely: (1) salt restriction, (2) high consumption of vegetables and fruits, (3) increased intake of fish and reduced content of saturated/total fat, (4) appropriate weight control, (5) regular physical exercise, (6) moderate alcohol consumption, and (7) quitting smoking. These factors are also considered as important stroke-prevention guidelines.[11,12]

In this review, I compare finding from studies on lifestyle status in Westerners and East Asians in relation to these basic hypertension guidelines (Table).

Salt Restriction

Many epidemiological studies have shown that reduced salt intake is directly related to decreased BP.[13–15] The Dietary Approaches to Stop Hypertension (DASH) diet, which was a randomized trial comparing the effects on BP of 3 total salt intake levels (8.3, 6.2, and 3.8 g/d for high, intermediate, and low salt intakes), showed significantly lower systolic (SBP, −5.9, −5.0, and −2.2 mm Hg) and diastolic BPs (DBP, −2.9, −2.5, and −1.0 mm Hg) at each salt level, respectively.[14] The DASH diet and salt reduction independently lowered SBP and DBP.

In a Chinese study that included a 7-day low-salt intervention (51.3 mmol/d), a 7-day high-salt intervention (307.8 mmol/d), and a 7-day high-salt plus potassium supplementation (60 mmol/d), the correlation coefficients of the SBP responses to low-sodium and high-sodium intervention were −0.47 and that to high-sodium intervention and potassium supplementation was −0.52.[16] These correlation coefficients were greater than those reported by the DASH-Sodium trial.[17]

The Intersalt Study[13] and the INTERMAP (International Study of Macro-/Micronutrients and Blood Pressure) Study[18] reported medium values of urinary salt excretion of 5.9 to 8.0 and 8.3 to 10.7 g/d in the United States, 8.8 and 7.5 to 9.4 g/d in the United Kingdom, 11.5 to 14.2 and 14.6 to 17.2 g/d in Northern China, 9.2 and 7.5 to 8.8 g/d in Southern China, and 10.2 to 11.8 and 10.9 to 12.3 g/d in Japan, respectively. Salt intake by East Asians is higher than that by Westerners. This tendency was more remarkable 50 years ago. Dahl[19] showed a positive linear relationship between the prevalence of hypertension and mean salt intake across 5 population groups in the 1950s: 4 g/d among Alaskan Eskimos, 7 g/d in Marshall Islanders (Pacific Ocean), 10 g/d in the United States (Brookhaven), 14 g/d in Hiroshima (South Japan), and 27 g/d in Akita (Northeast Japan). Dahl[19] also noted a strong north–south trend in death rates of stroke in Japan.

The salt intake of North Japan is among the highest in East Asia. This extremely high sodium intake is attributable to higher consumption of tsukemono (Japanese pickles), soy sauce (seasoning), and miso soup. Higher carbohydrate intake (rice) and lower saturated fat and animal protein intakes (meat) are also observed in North Japan. These dietary patterns do not maintain adequate arterial walls and may lead to intracerebral hemorrhage.[20]

Asians are likely to have a genetically high salt sensitivity.[21,22] The Gly460Trp variant of the *α-adducin* gene has been associated with renal sodium retention and salt-sensitive hypertension through enhancement of the activity of the

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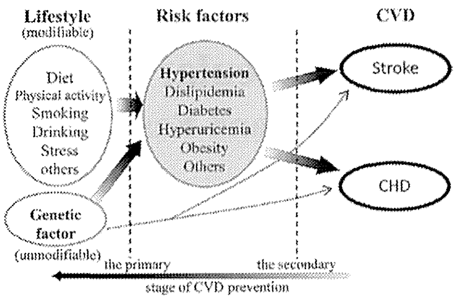

Figure. Schema of the progression from lifestyle changes to the incidence of hypertension and cardiovascular disease (CVD). CHD indicates coronary heart disease.

sodium pump. A meta-analysis showed a statistically significant association between salt sensitivity and *α-adducin* Gly460Trp polymorphism in Asians (odds ratio, 1.33; 95% confidence intervals [CIs], 1.06–1.69), but not in whites, indicating that the BP response to sodium varies among ethnic groups.[23] The frequencies of a common variant at codon 235 of the angiotensinogen gene with methionine-to-threonine amino acid substitution, the T235 allele of M235T, were 81% in Japanese[24] and 42% in whites.[25] The frequencies of the T(-344) allele of the T(-344)C polymorphism of the aldosterone synthase gene were 69% in Japanese[26] and 53% in whites.[27] The frequencies of the T825 allele of the C825T polymorphism for the G-protein β3 subunit were 52% in Japanese[28] and 25% in whites.[29]

High Consumption of Vegetables and Fruits

Dietary fiber, potassium, magnesium, and antioxidant vitamins are abundant in vegetables and fruits. In the Health Professionals Follow-Up Study, dietary fiber, potassium, and magnesium were inversely related to baseline SBP and DBP and to changes in BP during a 4-year follow-up among US men.[30] For men with a fiber intake of <12 g/d, the hazard ratio of hypertension was 1.57 (95% CIs, 1.20–2.05) compared with a fiber intake of >24 g/d. Fruit fiber but not vegetable or cereal fiber was inversely associated with incidence of hypertension.[30] On the contrary, the Nurses' Health Study has shown an inverse association between intakes of fruits and vegetables and SBP and DBP among 41 541 white US female nurses without diagnosed hypertension, cancer, or CVD.[31] Meanwhile, the Chicago Western Electric Study demonstrated that vegetable protein, total carbohydrate, β-carotene, and an antioxidant vitamin score based on vitamin C and β-carotene were inversely and significantly related to average annual change of SBP in men for an 8-year follow-up period.[32] During 7 years of follow-up, compared with the <0.5 cups/d group, the annual changes of SBP were −0.40 and −0.32 mm Hg for 0.5 to 1.5 cups/d of vegetables and fruits in men.[33] Therefore, diets higher in fruits and vegetables may reduce the risk of developing hypertension.

The Ohasama study has shown that higher intake of fruit is associated with a lower risk of future home hypertension.[34] During a 4-year follow-up, the highest quartile of fruit intake was associated with a significantly lower risk of future home

Table. Comparison Between Western and East Asian Studies According to the Lifestyle in the Hypertension Guidelines

Lifestyle Modification	Epidemiological Findings	Comparison Between Westerners and East Asians
Salt restriction	Reduced salt intake is related to decreasing BP.	Salt intake: Westerners<East Asians
		Salt sensitivity: Westerners<<East Asians
High consumption of vegetables and fruits	Diets higher in vegetables and fruits may reduce the risk of developing HT.	
Increased intake of fish, reduced content of saturated/total fat, and other type of diet		
Fish	Fish (n-3 PUFA) is a weak but significantly inversely associated with BP.	Westerners, Chinese<Japanese
Soy*	Soy intake reduces risk of CVD and may reduce BP. However, more evidence needs to accumulate.	Westerners, Chinese<Japanese
The DASH diet*†	Salt reduction lowered systolic and diastolic BP.	
The Mediterranean diet*	The Mediterranean diet associated with moderate but significant reduction of systolic and diastolic BP.	
Appropriate weight control	Obesity and overweight are risk factors for CVD and HT.	Obesity: Westerners>>East Asians
Regular physical exercise	Physical inactivity is a risk factor of HT.	
Moderate alcohol consumption	Excessive drinking is a risk factor for increased BP.	Drinking rate: Westerners<Japanese (men), Westerners>East Asians (women)
		ALDH deficient: Westerners<<East Asians
Quitting smoking		Smoking rate: Westerners<East Asians
		Population-attributable fraction for CVD: Westerners<East Asians (men)

ALDH indicates aldehyde dehydrogenase; BP, blood pressure; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; HT, hypertension; and PUFA, polyunsaturated fatty acid.

*Appeared in 2013 European Society of Hypertension/European Society of Cardiology Guidelines.[8]

†Appeared in Seventh report of the Joint National Committee.[7]

< indicates less than; >, greater than; <<, much less than; and >>, much greater than.

hypertension (odds ratio, 0.40; 95% CIs, 0.22–0.74). However, there was no association between higher vegetable intake and future home hypertension. The Shibata study demonstrated that serum vitamin C concentration was inversely associated not only with SBP and DBP, but also with incident stroke (*P* for trend=0.017).[35] These studies suggest that a plant-based dietary pattern including fruits and vegetables benefits BP control in both Western and East Asian countries.

Increased Intake of Fish, Reduced Content of Saturated/Total Fat, and Other Types of Diet

Epidemiological studies show that dietary n-3 polyunsaturated fatty acids (PUFAs) and fish oil had a weak but significantly inverse association with BP.[36,37] Even a small amount of fish intake (30–60 g/d) reduces the risk of CHD and sudden cardiac death in Western countries.[38] In a large cohort study, a high consumption of fish (180 g/d) was associated with an ≈40% reduced risk of CHD, compared with low fish consumption (<23 g/d).[39] This means that higher intake of fish can further reduce the risk of initial CHD events. The WHO-CARDIAC (WHO Cardiovascular Diseases and Alimentary Comparison) Study revealed an inverse relationship between the age-adjusted CHD mortality rate and the plasma levels of n-3 PUFAs worldwide.[40] East Asians had lower averages of saturated fatty acid than Westerners.[15] Mean dietary n-3 PUFAs in Japan is higher than those in Western countries and China.[15] Japanese have among the highest n-3 PUFA intakes and one of the lowest CHD mortalities worldwide. However, Japanese have higher salt intake and higher BP, counterbalancing their high fish intake.

As another significant characteristic of Japanese food, many studies on soy intake have reported that a higher dietary intake of soy reduced the risks of cardiovascular risk factors, notably on intermediate end points such as hyperlipidemia.[41] Higher soy and isoflavone intakes were associated with reduced risks of ischemic stroke and CHD in Japanese women. The risk reduction was accentuated for postmenopausal women.[42] The WHO-CARDIAC Study showed an inverse relationship between age-adjusted CHD mortality rate and 24-hour urinary isoflavone excretion in men worldwide. Japan and Taipei have some of the highest soy intakes and some of the lowest CHD mortality rates in men worldwide.[40] Both the higher fish intake and high soy intake among Japanese may contribute to its status as the country with the lowest CHD mortality worldwide. However, the evidence of association between soy and BP has been limited.[43]

The Mediterranean diet, with its higher contents of fruits, vegetables, legumes, nuts, cereals, fish, and olive oil, has been shown to be associated with a moderate, but significant, reduction of 3.1/1.9 mm Hg in SBP/DBP during a median 4.2-year follow-up.[44] These results are consistent with those of the DASH study.[16]

Appropriate Weight Control

Obesity and overweight have been rapidly increasing throughout the world in recent decades. The mean body mass index (BMI) levels (kilograms per meter squared) in men and women from East Asia (23.7 and 23.2 in Japan and 22.4 and 23.9 in China) are generally much lower than those of Westerners (27.7 and 27.2 in the United Kingdom and 29.1 and 28.7 in the United States).[15] Obesity and overweight are established risk factors for CVD, hypertension, dyslipidemia, diabetes mellitus, and metabolic syndrome.[45] The Framingham Heart Study showed that hypertension is approximately twice more prevalent in obese individuals than in nonobese individuals.[46] The study demonstrated that the highest quintile of the BMI group exhibited 16/9 mm Hg higher SBP/DBP than those in the lowest quintile (increase in 4 mm Hg SBP per 4.5 kg increased weight).[47] A meta-analysis of 25 studies has estimated that BP reductions were −1.05 mm Hg systolic and −0.92 mm Hg diastolic when expressed per kilogram of weight loss.[48]

In Japanese male office workers, BMI was shown to be a strong risk factor for incidence of hypertension in a 4-year follow-up.[49] Compared with BMI <18.5 kg/m^2, the hazard ratios of hypertension were 2.0, 2.3, and 2.3 for BMIs of 22.0 to 24.9, 25.0 to 25.9, and ≥30 kg/m^2, respectively. Weight gains (>2 kg) increased the risk of hypertension by 1.2 times.

Regular Physical Exercise

Many prospective cohort studies have demonstrated that physical inactivity is associated with an increasing risk of hypertension,[50–52] metabolic syndrome, diabetes mellitus,[53] CHD,[54] stroke,[51,54,55] cancer,[56] and all-cause mortality.[54,56] In a longitudinal study during 4-year follow-up in 1970, the relative risk for hypertension among the low-fitness group (72% of the group) was 1.5 times that of the high-fitness group.[57] Subjects who moved from the low-fitness to the high-fitness group during the follow-up period had approximately half the risk of developing hypertension compared with those whose fitness levels remained low.[57] In another study, normotensive subjects conducted cardiorespiratory fitness at the baseline, and each maximal metabolic equivalent unit was associated with a 19% lower risk (95% CIs, 12%–24%) during an 8.7-year follow-up period.[58]

In the Shibata study, heavy physical activity was a risk factor for incidence of stroke (hazard ratio, 3.3; 95% CIs, 1.2–9.5) during 1977 to 1992.[59] In the 1970s, most residents engaged in agricultural work, usually by hand, and had no exercise or sports. Although mechanization has gradually reduced their amount of physical labor, they still work much harder than urban or sedentary populations. In the Osaka Health Survey, in 59 784 person-years of follow-up, durations of subjects' walk to work of 11 to 20 and ≥21 minutes were associated with 0.88 and 0.71 times reduced risk of progressive hypertension (*P* for trend=0.02).[52]

In a meta-analytic study, the studies reviewed demonstrated a robust protective effect of active commuting on cardiovascular outcomes (hazard ratio, 0.89; 95% CIs, 0.81–0.98).[51] In another meta-analysis study using pedometers, 8 randomized controlled trials showed that pedometer users significantly increased their physical activity by 2491 steps/d more than controls.[50] Participants in this intervention significantly decreased their SBP by 3.8 mm Hg.

Moderate Alcohol Consumption

Alcohol consumption is higher in Japanese men (ethanol, 26.7 g/d) than in men in the United States (10.1 g/d) and United

Kingdom. (16.6 g/d). However, for women, consumption in Westerners is higher than in East Asians.[15] Nearly 50% of Koreans, Chinese, and Japanese are found to be aldehyde dehydrogenase (ALDH) deficient, the most frequent manifestation of which is called the Oriental flushing syndrome. ALDH deficiency is a risk factor for increased BP,[60] as is excessive drinking.[61] The high alcohol intake and high rate of ALDH deficiency among Japanese men may contribute to their elevated BP.

In a systematic review, an overall odds ratio for hypertension in 2*2 homozygotes of ALDH2 was 2.4 times higher than in wild-type homozygotes (*1*1).[62] This has turned out to be the case with a locus associated with BP-related traits that has recently been identified near the *ALDH2* gene at 12q24.13 in East Asians. Eight common single-nucleotide polymorphisms seem to identify a common ancestral haplotype (H3). Haplotype H4 is common in East Asians (frequency, 38%) but is absent in Europeans and is rare in Africans (4%).[63] Haplotype H5 is common in East Asians (29%) but is absent in Europeans and Africans. Haplotype H7 is common in Europeans (36%) but is absent in East Asians and Africans.

Quitting Smoking

Both normotensive and untreated hypertensive smokers present higher daily BP levels than nonsmokers.[64,65] Epidemiological data have shown that the smoking rates in East Asian men remain high at 40% to 60%, although this is after declining substantially for the past 20 years. The smoking rates were lower in East Asian women at 3% to 15% compared with Western women.[66] Another epidemiological study demonstrated that the prevalences of smoking in men were higher in East Asian (68% in South Korea, 63% in China, and 47% in Japan) region than in the Western Pacific region (16% in Australia and 26% in New Zealand).[67] The population-attributable fractions of CHD caused by smoking men and women were higher in the East Asian region (29% and 23% in South Korea, 27% and 22% in China, and 22% and 17% in Japan, respectively) than in the Western Pacific region (10% and 8% in Australia and 13% and 10% in New Zealand, respectively). Australia and New Zealand, with predominantly white populations, had relatively low smoking prevalences and therefore low population-attributable fractions for CVD. In a Japanese cohort study, the population-attributable fraction for CVD among men without metabolic syndrome who smoke (21.8%) was approximately the same as that among men with metabolic syndrome (19.4%).[68]

Conclusions and Perspectives

Appropriate lifestyle modifications are the first step of preventive hypertension. Official recommendations regarding lifestyle changes to improve hypertension are similar in East Asian and Western countries. However, the contributions of BP to stroke are different for Westerners and East Asians, attributable to differences in genetics and lifestyle. High consumption of fruits and vegetables, regular physical exercise, and maintaining appropriate body weight are all beneficial for BP control in both Western and East Asian populations. Fish and n-3 PUFA have a weak but significantly inverse association with BP. East Asians have the benefit of diets higher in fruits and vegetables and fish and less incidence of obesity. On the contrary, East Asians have a genetically higher salt sensitivity and a greater salt intake than Westerners. Excessive alcohol intake contributes to the increased BP in Japanese men, especially given their high rate of ALDH deficiency. The smoking rates in East Asian men are also higher than that in Western countries. To maintain an appropriate BP, East Asians should pay particular attention to quitting smoking and reducing salt and alcohol intake, whereas Westerners need to pay attention to weight control including regular exercise and consider replacing dietary meat high in saturated fat with fish. Further comprehensive prospective studies are anticipated to show how each factor contributes to BP control and a reduced risk of CVD in Westerners and East Asians.

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Disclosures

None.

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